An Optoelectronic Nose: "Seeing" Smells by Means of Colorimetric Sensor Arrays

Kenneth S. Suslick

Abstract

A new approach to general sensors for odors and volatile organic compounds (VOCs) using thin films of chemically responsive dyes as a colorimetric sensor array is described. This optoelectronic "nose," by using an array of multiple dyes whose colors change based on the full range of intermolecular interactions, provides enormous discriminatory power among odorants in a simple device that can be easily digitally imaged. High sensitivities (ppb) have been demonstrated for the detection of biologically important analytes such as amines, carboxylic acids, and thiols. By the proper choice of dyes and substrate, the array can be made essentially nonresponsive to changes in humidity.

***Keywords**: optical materials, optical spectroscopy, sensor technology, thin films, volatile organic compounds.*

Introduction

Devices designed for the identification of volatile organic compounds (VOCs) are generally termed electronic noses. The multiple, cross-reactive sensors used in such devices have been based primarily on property changes (e.g., mass, volume, conductivity) in some set of polymers or on electrochemical oxidations at heated metal oxide surfaces.[1,2] Despite some success with such systems, their ability to detect compounds at low concentrations relative to vapor pressures and to discriminate between compounds within a similar chemical class is limited. In addition, interference from large environmental changes in humidity remains problematic. We have previously reported a general approach to an optoelectronic nose based on the colorimetric array detection of a range of odorants using metalloporphyrins.[3-6] The importance of including metal-ion–containing sensors in such an array is confirmed by recent indications that mammalian olfactory receptors are, in fact, metalloproteins.[7] Here, we review extensions of our colorimetric sensor array and its success in addressing many of the current problems with electronic nose technology.

Colorimetric Sensor Array

The detection and identification of chemicals is a fundamental aspect of the area of supramolecular chemistry known as molecular recognition. Intrinsically, such processes involve the interactions between molecules. The classification of intermolecular interactions is well established (Table I) and involves bond formation and coordination; acid–base interactions; hydrogen bonding; charge transfer and $\pi-\pi$ molecular complexation; dipolar and multipolar interactions; and last (and least), van der Waals interaction and physical adsorption.

Remarkably, nearly all prior electronic nose technology relies almost exclusively on van der Waals and physical adsorption, the weakest and least selective of forces between molecules. We believe this is a fundamental flaw in the development of sensors with high sensitivity and high selectivity. In many ways, our colorimetric sensor array revisits the earlier, pre-electronic era of analytical chemistry,[8] updated by the addition of modern digital imaging and pattern recognition techniques.

In addition, new sensor technology development faces the dilemma of creating sensors that are both increasingly sensitive and increasingly robust. Just as position and momentum are canonical variables, one may argue that beyond a certain point, the more sensitive a sensor becomes, the less robust it inherently can be. The path around this dilemma is the development of disposable sensors, thus unlinking the opposing demands. Colorimetric sensor arrays provide one successful method of doing so.

There are two fundamental design requirements for a colorimetric sensor array: (1) the chemoresponsive dye must contain a center to interact strongly with analytes, and (2) this interaction center must be strongly coupled to an intense chromophore. The first requirement implies that the interaction must *not* be simple physical adsorption, but rather must involve other stronger chemical interactions (e.g., Table I).

Chemoresponsive dyes are those dyes that change color, in either reflected or absorbed light, upon changes in their chemical environment. The consequent dye classes from these requirements are (1) Lewis acid/base dyes (i.e., metal-ion–containing dyes), (2) Brønsted acidic or basic dyes (i.e., pH indicators), and (3) dyes with large permanent dipoles (i.e., zwitterionic solvatochromic dyes) (Figure 1 and Chart 1). In addition, we have incorporated our own bis-pocketed metalloporphyrins,[9] which have bulky protecting groups on both faces of the porphyrin, to provide an aspect of shape-selective sensing to the array.

Using simple printing technology, colorimetric arrays of chemoresponsive dyes

Table I: Classes of Intermolecular Interactions.

Stronger (>100 kJ/mol)	
↑	• Lewis (e^- pair) donor/acceptor
↑	• Brønsted (proton) acid–base
↑	• Hydrogen bonding
↑	• Charge-transfer & $\pi-\pi$ delocalization
↑	• Dipole–dipole, quadrupole–dipole, …
↑	• van der Waals (physisorption, absorption)
Weaker (<5 kJ/mol)	

have been created on a variety of inert solid supports, such as reverse-phase silica gel plates, acid-free paper, and porous membranes of various polymers such as nylon and poly(vinylidene fluoride), as shown in Figure 1.

For recognition of analytes with Lewis acid/base capabilities, the use of porphyrins and their metal complexes are a natural choice. Metalloporphyrins are nearly ideal for the detection of metal-ligating vapors because of their open coordination sites for axial ligation (i.e., above and below the porphyrin plane) to the central metal atom, their large spectral shifts upon ligand binding, and their intense coloration. A series of metalated tetraphenylporphyrins (TPPs) was used to provide differentiation based on metal-selective coordination.

Common pH indicator dyes change color in response to changes in the proton (Brønsted) acidity or basicity of their environment. Solvatochromic dyes change color in response to changes in the general polarity of their environment, primarily through strong dipole–dipole interactions. To some extent, all dyes inherently are solvatochromic, although some are much more responsive than others; among the most responsive are Reichardt's dye and Nile red.

In addition, our array incorporates a series of Zn-substituted, bis-pocketed porphyrins, based on ortho-substitution of the TPP core to differentiate analytes based on size and shape. These compounds include a family of silylether porphyrins with large, medium, and small pockets on both faces of the porphyrin (Figure 2). These have been previously shown to exhibit extremely selective binding of organic ligands.[9]

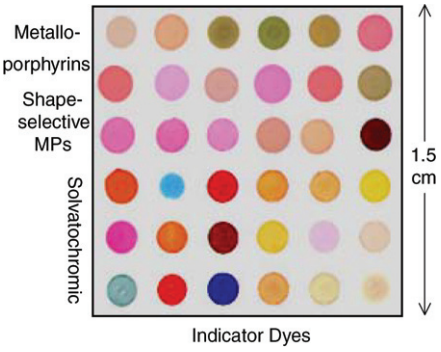

Figure 1. Colorimetric sensor array containing 36 chemically responsive dyes on a hydrophobic membrane; the array was prepared using split-pin contact printing, as originally developed for DNA array printing. MPs = metalloporphyrins.

Discrimination of VOCs

The colorimetric sensor array is a digitally imaged two-dimensional extension of litmus paper. For any volatile analyte, odorant, or complex mixture of odorants, a difference map is easily generated by digital subtraction, pixel by pixel, of the image of the array before and after exposure: red value after exposure minus red value before, green minus green, blue minus blue. Averaging of the centers of the spots (~200 pixels) avoids artifacts from non-uniformity of the dye spots, especially at their edges. Although the resulting data are inherently digital (simply a vector of 3*N* dimensions, where *N* is the total number of spots), it is convenient to represent the changes in RGB (red–green–blue) values using a difference map whose color values are the absolute values of the changes in color of each dye spot (Figure 3).

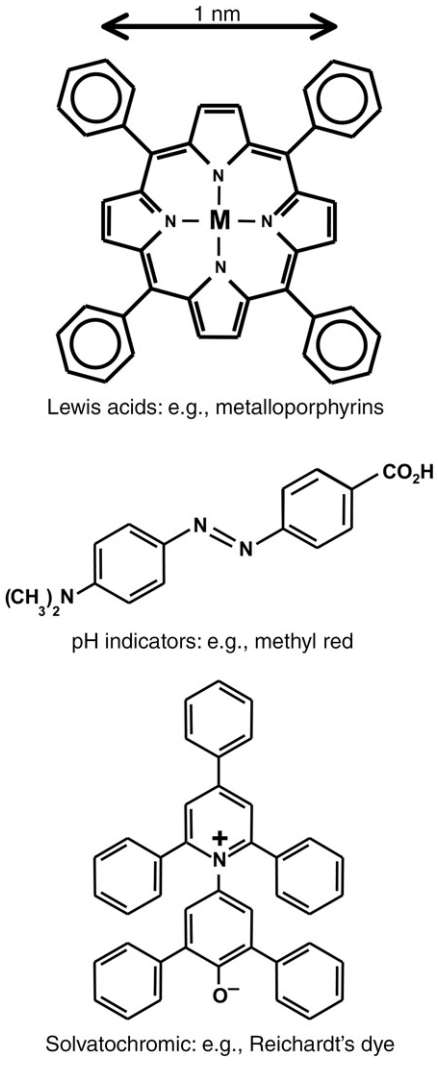

Chart 1. The components of colorimetric sensor arrays are inherently nanoscale.

We determined the sensor array responses for a series of different VOCs representing the common organic functionalities:[4] amines, arenes, alcohols, aldehydes, carboxylic acids, esters, halocarbons, ketones, phosphines, sulfides, and thiols. These patterns are shown in Figure 4 for a 24-dye array. Excellent discrimination among these analytes is observed even without any statistical analysis. This is in keeping with Brauman's second law:[10] If one needs complex statistics to answer a simple question, one has done the *wrong* experiment.

Each analyte response is represented as the change in the red, green, and blue values of each of the 24 dyes (i.e., a 72-dimensional vector). To examine the multivariate distances between the analyte responses in this 72-dimensional RGB color space, a hierarchical cluster analysis was performed; this analysis makes use of only the digital data representing the observed difference maps—no specific chemical information is included. The resulting dendrogram for the responses to saturated analyte vapors is shown in Figure 5. The dendrogram relates the color differences associated with each odorant; the closer the odorants are to one other in the dendrogram, the closer their difference maps and the more similar their chemical properties are (or, at least, the properties being probed by the dyes). Remarkably, the clusters formed are in keeping with the qualitative structural and electronic properties of the VOCs. The familial similarities among compounds of the same functionality are exceptional: amines, alcohols, aldehydes, esters, etc., are all easily distinguished from each other. The only exception to this appears to be the pair of ketones—methyl ethyl ketone and 4-heptanone—which overlap into the ester and ether subgroups, respectively. This slight intergroup confusion may reflect the inclusion of too few ketones (i.e., two) to form a recognizable class out of a sample of 32 VOCs.

A principal component analysis (PCA) finds the independent linear combinations of the changes in RGB values of the 24 dyes (i.e., 72 dimensions) that change the most for the analytes tested. The PCA of a full set of VOC patterns reveals a surprisingly high degree of dispersion among the independent dimensions created by linear combinations of the RGB responses of the 24 dyes used in these arrays. The PCA shows that 95% of the discriminatory range requires 12 dimensions (out of the possible 72 dimensions) and 99% requires 20 dimensions. This extremely high dispersion (i.e.,

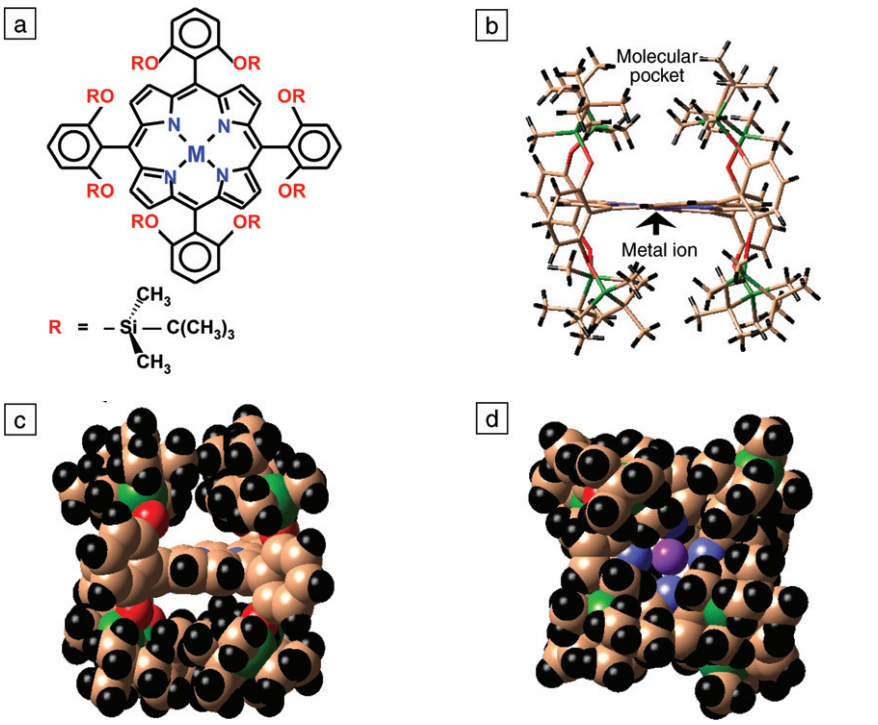

Figure 2. Molecular models of a very sterically hindered bis-pocket porphyrin from the single-crystal x-ray diffraction structure of Zn(Si$_6$PP). (a) Chemical structure, (b) cylinder side view, (c) space-filled side view, and (d) space-filled top view; space-filling is shown at 70% van der Waals radii. Porphyrin carbon atoms are shown in tan, oxygen atoms in red, hydrogen atoms in black, silicon atoms in green, and Zn in purple.[9] For Zn(Si$_6$PP), an energy-minimized structure was obtained using Cerius^2 software from MSI.

high dimensionality) reflects the very wide range of chemical-property space being probed by our choice of chemoresponsive dyes. In comparison, most prior electronic nose technology is dominated by only two or three independent dimensions, one of which—hydrophobicity—often accounts for >90% of the discrimination;[1,2] this is the inherent result of relying on van der Waals interactions for molecular recognition.

With a 24-dye array, each of the 72 dimensions can take on one of 256 possible values (for inexpensive 8-bit scanners or digital cameras). The theoretical limit of discrimination, then, would be the number of possible patterns (i.e., 256^{72}). Realistically, however, the RGB vector components do not range over the full 256 possible values; we do observe that R, G, and B values vary over a range of 40. To discriminate patterns, let us assume a change of at least 4 is needed in the R, G, or B value (we can actually easily discriminate with changes of 2). From the PCA, not all of the 72 dimensions are equally important. In fact, roughly 95% of all information is contained in ~12 specific dimensions (i.e., linear combinations of the 72 different R, G, and B values). This implies a practical limit of discrimination that is still immensely large: $(40/4)^{12} = 10^{12}$ distinct patterns should be recognizable in a 24-dye colorimetric sensor array.

Interference from Humidity

Physisorption of molecules on surfaces is dominated by the relative hydrophobicity of the adsorbate and adsorbent. It should be no surprise, therefore, that a serious weakness in current electronic nose technology is sensitivity to changes in humidity. Water vapor ranges in the environment from <2000 to >20,000 ppm; if one is interested in a VOC concentration of a few parts per million, or worse, a few parts per billion, then even a very low level of interference from water is intolerable.

The dyes in our colorimetric sensor array, however, have been selected from hydrophobic, water-insoluble dyes, and the substrates on which the dyes are printed are also highly hydrophobic. As a consequence, these arrays are essentially impervious to changes in relative humidity. As shown in Figure 6, the dyes are essentially unresponsive to water vapor. The water vapor insensitivity of our technology provides a substantial advantage in the analysis of real-world samples.

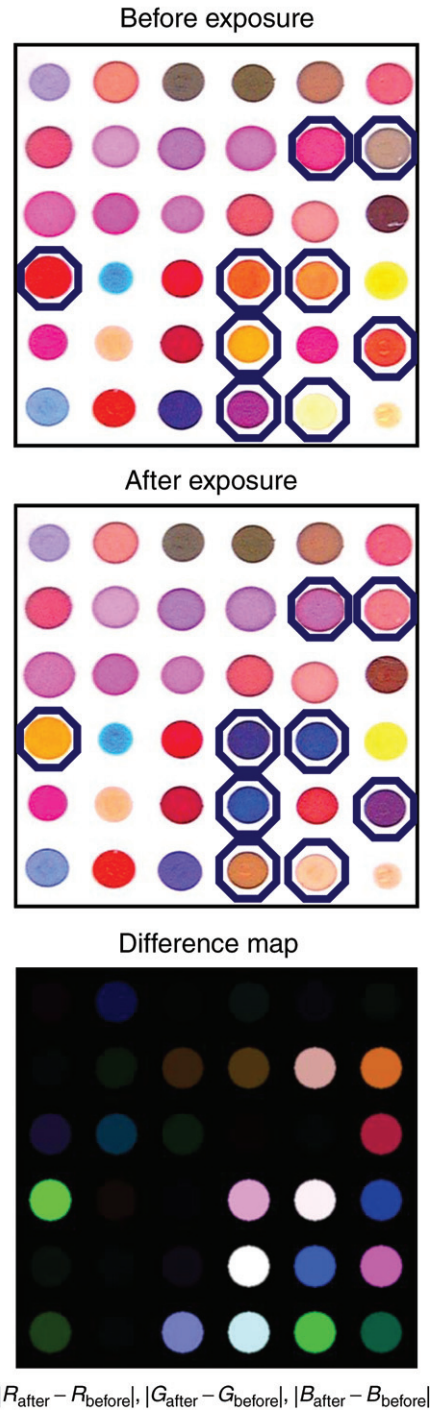

Figure 3. A difference map of a colorimetric array can be generated for any odorant by digital subtraction, pixel by pixel, of the image of the array before and after exposure. The circled spots are those whose color changes are the biggest. The difference map shows the absolute value of the red (R) value after exposure to the analyte, minus the red value before exposure to the analyte, $|R_{after} - R_{before}|$. The same holds for the green (G) and blue (B) values.

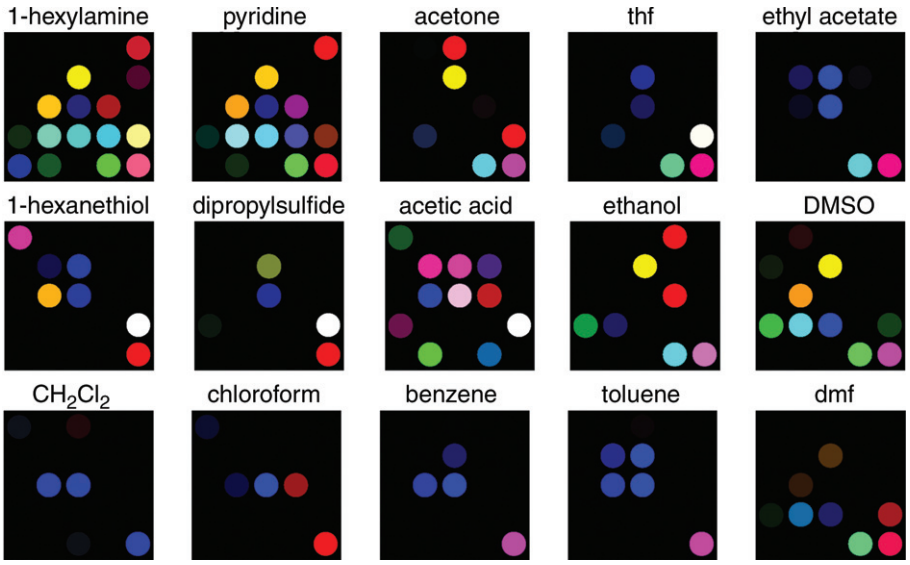

Figure 4. Colorimetric array responses for some common volatile organic compounds at full vapor pressure at 300 K. Abbreviations: thf = tetrahydrofuran, DMSO = dimethylsulfoxide, and dmf = dimethylformamide.

Sensitivity

In marked contrast with most prior electronic nose technology, our colorimetric array sensor technology is based on strong and relatively specific interactions between the analytes and a chemoresponsive dye library. The prior use of adsorption into polymer arrays (e.g., conductive polymer arrays, quartz microbalance or surface acoustic wave detectors coated with a variety of polymers, or polymers doped with a *single* indicating fluorophore) depends upon weak matrix–analyte interactions to provide limited selectivity and relatively poor sensitivity. A major advantage of our sensor arrays is that they are able to provide unique patterns for the identification of odors even at extremely low vapor concentrations of many analytes, because we rely on *strong* (but still reversible) interactions between analyte and sensor dyes for molecular recognition.

Metal–ligand (i.e., metal–analyte) bonds range in their bond enthalpies from ~40 kJ/mol to ~200 kJ/mol. In noncoordinating solvents (e.g., alkanes), equilibrium binding constants are often $>10^6\ M^{-1}$. For pyridine, the vapor pressure is 0.02 atm at room temperature, so we have a Raoult's constant of $\sim 2 \times 10^{-3}$ atm M^{-1}. For a binding constant of $\sim 10^6\ M^{-1}$, this is equivalent to ~2 ppb vapor. In contrast, the enthalpy of physical adsorption (e.g., into polymers) is only ~5–20 kJ/mol (i.e., roughly a tenth of a metal bond). Therefore, the equilibrium constant for adsorption will typically be only about 5×10^{-5} as large as that for ligation to metal ions. Therefore, ligation is *intrinsically* ~20,000-fold more sensitive than adsorption into polymers. Differences in the sensitivity of detection techniques, of course, can either enhance or diminish this intrinsic advantage of ligation and other strong interactions over physical adsorption and other weak interactions (e.g., van der Waals).

As shown in Figure 7 for a 24-dye array, this expectation of improved sensitivities is realized experimentally. Even gas chromotography/mass spectrometry (GC/MS) achieves typically only parts per million to 100 ppb sensitivities for VOCs in the absence of pre-concentration. Figure 7 shows, however, that sub-ppm discrimination is not a problem with our colorimetric array detection for functionalized analytes such as thiols, amines, and carboxylic acids.

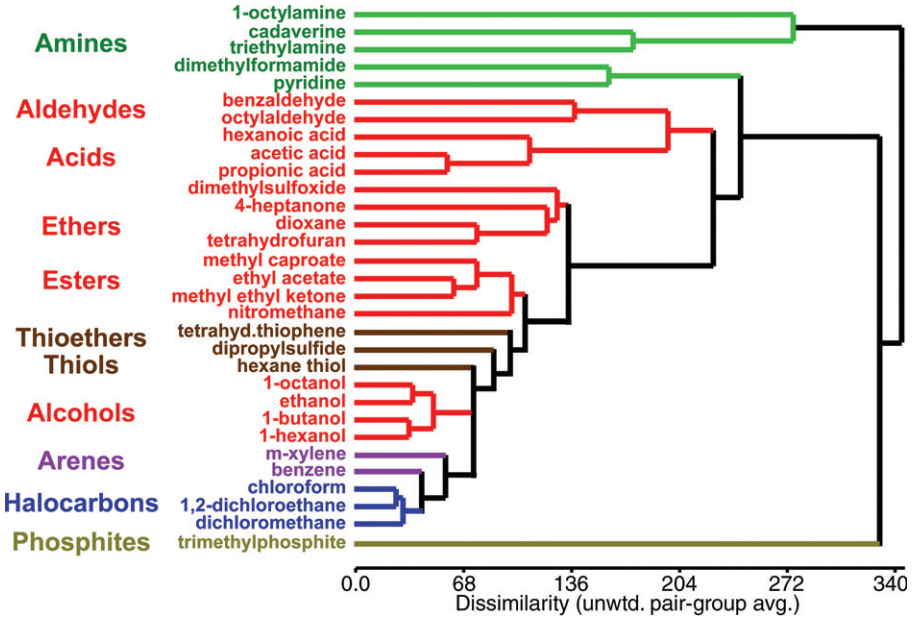

Figure 5. Dendrogram of the colorimetric array responses to 32 common organic compounds at full vapor pressure at 300 K (XLStat analysis package v.5.1, unweighted pair-group average agglomerative hierarchical cluster analysis). The x axis represents distance in the 72-dimensional Euclidean space.

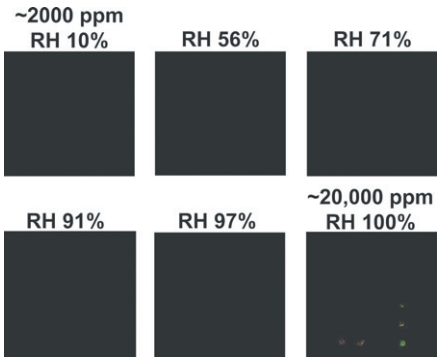

Figure 6. Difference maps upon exposure to relative humidity (RH). As can be seen by the lack of variation in the maps, the colorimetric array is insensitive to changes in RH. Similarly, changes in humidity do not significantly affect the color fingerprints of other analytes.

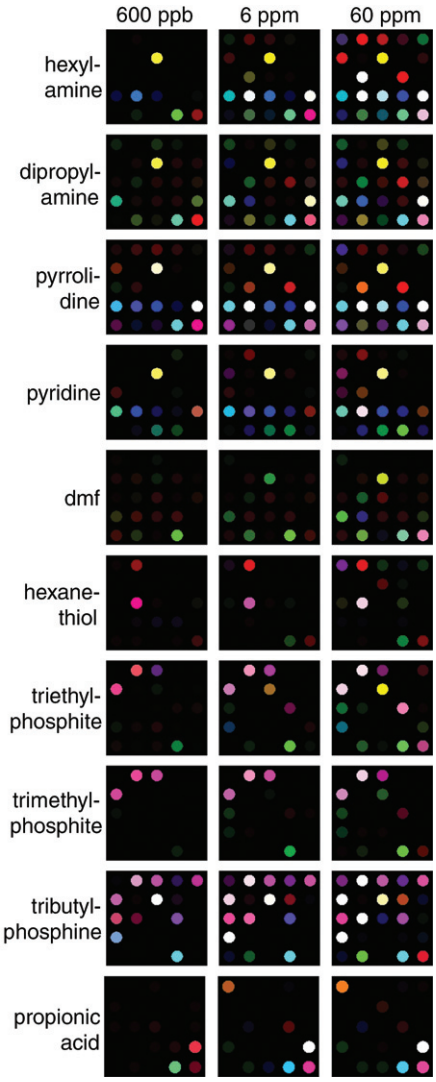

Figure 7. A colorimetric array sensitivity with limits of recognition well below 1 ppm.

In fact, we can extend our sensitivities down to the low ppb regime for many such analytes. Extension of sensitivity by improved imaging technology (e.g., true 16-bit or 24-bit color resolution in place of our currently used 8-bit scanners) may improve our sensitivity by a thousandfold.

For quantitative analysis of analyte concentrations, every analyte at a different concentration is best thought of as a different analyte for the colorimetric array. For each analyte, a specific dye will begin to change color at some concentration, and as the analyte concentration increases, the color change will asymptotically saturate; some dyes change at low concentrations of any given analyte, some only at very high concentrations. Quantitative analysis of single analytes (or of a single analyte changing in a constant background) can be easily done by comparison to a pattern library of analyte concentration.

Analysis of Complex Mixtures

Both the mammalian olfactory system and electronic nose techniques, in general, give a composite response to complex mixtures. It is a natural tendency to assume that for any complex mixture, the single analytical goal is a complete component-by-component analysis. But in fact, multiple analytic goals for complex mixtures are conceivable: comparison to a standard (e.g., quality control, counterfeit detection), identification of chemical class or family of an unknown VOC, correlation of odors to properties (e.g., "good-smelling," as determined by a human sensory evaluation panel), changes in concentrations of a few components against a constant background, and of course, a complete component-by-component (CBC) analysis. Separation techniques (e.g., GC, high-performance liquid chromatography, cluster expansion) excel at CBC analyses. For many other applications, however, a composite response may be not only sufficient, but actually preferred. Too much data is often only slightly better than not enough.

For rapid comparisons among complex mixtures, for example, we find that colorimetric array sensors can fill an important niche. As a closing example, consider the results of Figure 8 as an interesting comparison among complex odorants of some importance to those of us with a caffeine addiction!

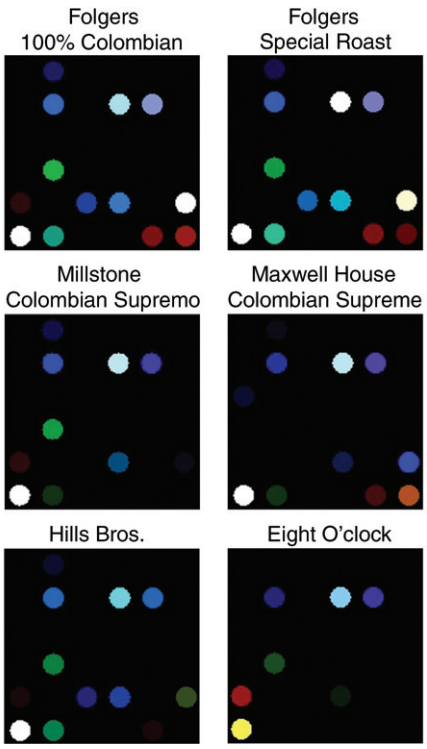

Figure 8. Colorimetric array analysis of a complex mixture: headspace analysis of various ground coffees. A selection of the best coffees, as determined by Consumer Reports,[11] *are readily distinguishable, even without detailed chemometric analysis.*

Conclusions

Most chemical sensing technology currently used in "electronic noses" relies on the weakest of intermolecular interactions, van der Waals and physical adsorption, for their detection and identification of analytes. By greatly expanding the nature of chemical interactions to include far stronger forces, including dipolar, proton acid–base, and Lewis acid–base interactions, we have greatly increased both sensitivity to and discrimination among analytes. In many ways, we have simply extended litmus paper into a digital multidimensional space. We resurrect the analytical chemistry of a century ago by using arrays of colorimetric sensors combined with modern digital imaging and thereby create a new technological approach that has much promise for the detection and identification of odorants and the fingerprinting of complex mixtures of odorants.

Acknowledgments

This work was supported by the U.S. National Institutes of Health (HL 25934) and in part by the U.S. Department of Energy Seitz Materials Research Laboratory under grant DEFG02-91-ER45439. The author is particularly grateful to the students and co-workers who have contributed to development of this work: Neal A. Rakow, Avijit Sen, William B. McNamara III, Margaret A. Kosal, Jennifer Wilson, Shirley Nakagaki, Chen Zhang, Ming Fang, Michael Janzen, and Daniel Bailey.

References

1. K.J. Albert, N.S. Lewis, C.L. Schauer, G.A. Sotzing, S.E. Stitzel, T.P. Vaid, and D.R. Walt, *Chem. Rev.* **100** (2000) p. 2595.
2. J.W. Gardner and P.N. Bartlett, *Electronic Noses: Principles and Applications* (Oxford University Press, New York, 1999).
3. N.A. Rakow and K.S. Suslick, *Nature* **406** (2000) p. 710.
4. N.A. Rakow and K.S. Suslick, *Artificial Chemical Sensing: Olfaction and the Electronic Nose*, edited by J.R. Stetter and W.R. Pensrose (Electrochemical Society, Pennington, NJ, 2001) p. 8.
5. K.S. Suslick and N.A. Rakow, "Colorimetric artificial nose having an array of dyes and method for artificial olfaction," U.S. Patent 6,368,558 (April 9, 2002).
6. K.S. Suslick, N.A. Rakow, and A. Sen, "Colorimetric artificial nose having an array of dyes and method of artificial olfaction," U.S. Patent 6,495,102 (December 17, 2002).
7. J. Wang, Z. Luthey-Schulten, and K.S. Suslick, *Proc. Natl. Acad. Sci. U.S.A.* **100** (2003) p. 3035.
8. I.M. Kolthoff, *Acid Base Indicators*, translated by C. Rosenblum (MacMillan, New York, 1937).
9. A. Sen and K.S. Suslick, *J. Am. Chem. Soc.* **122** (2000) p. 11565.
10. J.I. Brauman, personal communication (1972).
11. *Consumer Reports* (January 2000) p. 29. □