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Analog Parallel Processing of Molecular Sensory Information

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Molecular devices[1] lie at the smaller size-range of nanoscience and nanotechnology.[2] Molecular processing of digital information now has many examples, especially regarding diverse logic operations.[3] Some of these digital devices require parallel operation to achieve their function.[4] However analog information remains a substantial part of our world, for example, many sensors for chemical species deal with analog information[5] since they must produce a measurable change in signal in response to small changes of analyte concentration. Molecular sensors fall far short of the ideal response which should occur uniformly over a large range of analyte concentration. We now show a simple but predictive way of running molecular analog devices[6] in parallel so that they emulate the response function of the glass pH electrode[7]—the workhorse of many scientific laboratories and the basis of several industries—though operating wireless at a far smaller size-scale, along with an imaging capability in real time.

While there have been several admirable efforts to develop molecular-level systems to address this problem,[8] a predictive approach to attaining a wide quasilinear dynamic range has remained elusive. Classical "universal indicators"[9] cannot provide a high degree of quantitation under simple monitoring conditions. Molecular optical sensors on/within bulk materials naturally give wide, but unpredictable, dynamic ranges and also sacrifice space resolution.[10]

Our design is summarized in Figure 1. This approach remained inaccessible until fluorescent photoinduced electron transfer (PET) sensors became available.[5,11,12] Unlike other fluorescent sensor designs,[12−16] these possess the following set of features:[17] (a) all the absorption spectral parameters (wavelengths, intensities, and shapes) of each member of a family based on the same fluorophore are virtually independent of pH as also are all the emission spectral parameters (wavelengths and shapes), except for the fluorescence quantum yield (or intensity), (b) all members have essentially identical absorption and emission spectral parameters which are largely predictable from those for the fluorophore module, for example, 9,10-disubstituted anthracenes, (c) all members can be arranged to have their emission switched "off" at pH $\gg$ pK_{ai}; that is, $\phi_{min} \rightarrow 0$ when compared to ϕ_{max}. In common with other fluorescent sensor designs,[12−16] all members have the pH dependence of fluorescence intensity (I_F) well described by the equation $\log[(I_{F_{max}}/I_F) - 1] = \text{pH} - \text{p}K_{ai}$, that is, the dynamic range of each member is the classical value of ca. 2 pH units.[5] The overall dynamic range can now be hugely extended by running a judiciously chosen 1:1:1:1 weighted set of members **1a**−**d**[18] in parallel, where the observed response function is given by

$$\sum I_F = I_{F_{max}} \sum \{1/[1 + 10^{(\text{pH}-\text{p}K_{ai})}]\} \qquad (1)$$

This equation is evaluated numerically to maximize the linearity of the response function. For instance, the pK_{ai} values of the members must belong to the arithmetical progression 1.3, 3.6, 5.9, and 8.2 (i.e., with a spacing of 2.3 pH units) if the maximum linearity is to be attained by four members over the pH range 0−9.5. Set **1a**−**d** is a convenient compromise, though more accurate matching to the optimum theoretical prediction can be done by considering linear free-energy relationships of substituted amines[21] or by exploring their large diversity, including those with very high pK_a values.[22] The key parameters of set **1a**−**d** are given in Table 1. All the conditions mentioned above are clearly met for this set.

The 1:1:1:1 parallel operation of set **1a**−**d** is easily accomplished by measuring the fluorescence emission spectra as a function of pH for an equimolar mixture of these compounds (Figure 2). The summed 0−1 band fluorescence intensity (I_F)−pH profile in Figure

Table 1. Optical and Proton-Binding Properties of **1a**−**d**[a]

case	absorption[b] λ (log ϵ)	emission[c] λ (ϕ_{max}, ϕ_{min})	pK_a[d]
1a	393(4.03), 372(4.02), 353(3.81)	405, 427, 445 (0.59, 0.004)	8.1
1b	395(4.10), 374(4.09), 355(3.87)	405, 427, 445 (0.56, 0.005)	6.1
1c	395(4.03), 374(4.03), 355(3.81)	404, 426, 443 (0.55, 0.014)	4.1
1d	393(4.01), 372(4.01), 353(3.76)	404, 426, 443 (0.56, 0.008)	1.4

[a] Contains 10 μM of each sensor in aerated methanol/water (1:4, v/v). ϕ_F obtained by comparison with **1b** (ϕ_F = 0.66 in deaerated methanol/water (1:4, v/v) at pH 3.5).[20] [b] Essentially independent of pH. [c] Excitation at 372 nm. [d] Obtained by employing $\log[(\phi_{F_{max}} - \phi_F)/(\phi_F - \phi_{F_{min}})] = \text{pH} - \text{p}K_a$.[20]

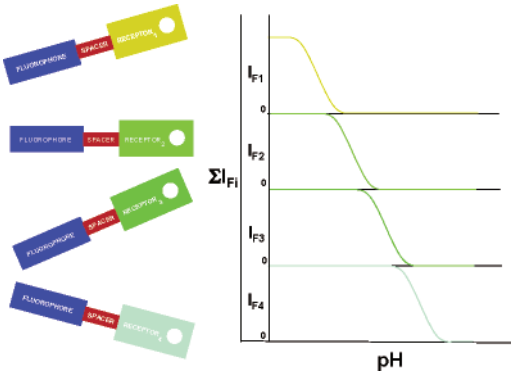
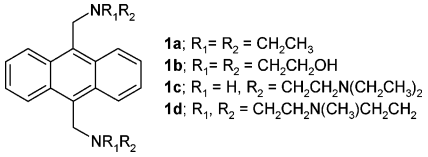


Figure 1. Four members of a fluorescent PET sensor family, of the "fluorophore−spacer−receptor$_i$" format, with identical fluorophores and spacers but different receptors with carefully chosen proton-binding strengths are chosen and run in parallel so that the sensing range of one member lies adjacent to that of another. The nett result is that the summed fluorescence intensity becomes quasilinear with pH. Thus the sensor family has a greatly extended sensing range in a quantitatively predictive manner.



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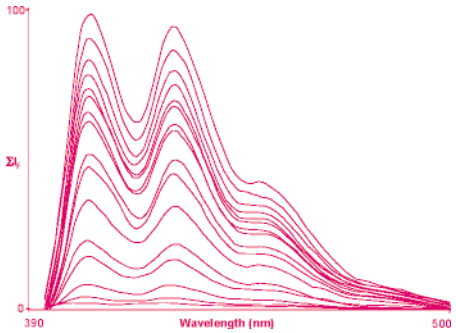

Figure 2. Representative fluorescence spectra of the sensor set **1a**−**d** (10 μM each) in methanol/water (1:4, v/v): The excitation is 372 nm. The pH values (in order of decreasing intensity at 427 nm) are 0.74, 1.46, 1.91, 2.39, 2.90, 3.25, 3.74, 4.14, 4.79, 5.26, 6.37, 7.25, 7.90, 8.42, 8.88, and 9.44.

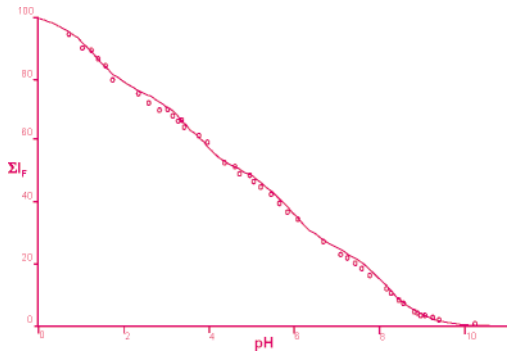

Figure 3. The summed 0−1 band (427 nm) intensity−pH profile of the sensor set **1a**−**d** (open circles). The full line is the optimum theoretical curve obtained from eq 1.

3 is the major result, with the wide-range quasilinear response being clear to see. Additionally, it is close to the optimum theoretical curve predicted by eq 1.

This work opens the way to intracellular applications by the appending of sets related to **1a**−**d** onto short chain polymers.[23] The construction of sensors with extended dynamic range for other species of chemical and biological interest also comes into view since the fluorescent PET sensor principle[6,12] is rather general.

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Supporting Information Available: Outline derivation of eq 1; FORTRAN program for the numerical evaluation of the optimum set of sensors. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) **1a**[17,19] and **1b**[20] are known. **1c** and **1d** are prepared by analogous procedures.[19] Characterization of **1c**·2HCl: pale yellow crystals; mp 257−258 °C. ^{1}H-NMR (d_6-DMSO) δ: 8.61 (4H, m, ArH), 7.70 (4H, m, ArH), 5.13 (4H, bs, ArCH_2N), 3.70−3.43 (12H, m, HN(CH_2)$_2$NH), 3.12 (8H, q, (CH$_3$CH_2)$_2$N), 1.22 (12H, t, CH_3). EI-MS m/z: 434 (M$^+$, 1), 319(15), 318(44), 100(12), 87(13), 86(100). LSI-MS calcd for $C_{28}H_{42}N_4$, 434.3409; found, 434.3409. **1d**: yellow crystals; mp 240−241 °C. ^{1}H-NMR (CDCl$_3$) δ: 8.52 (4H, m, ArH), 7.52 (4H, m, ArH), 4.48 (4H, s, ArCH_2N), 2.72 (8H, bt, N(CH_2)$_2$), 2.43 (8H, bt, (CH_2)$_2$NCH$_3$), 2.28 (6H, s, CH_3). EI-MS m/z: 402 (M$^+$, 3), 302(100), 204(16), 191(10). Anal. Calcd for $C_{25}H_{34}N_4$: C, 77.56; H, 8.51; N, 13.92. Found: C, 77.03; H, 8.57; N, 13.39.

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