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Consolidating Molecular Logic with New Solid-bound YES and PASS 1 Gates and their Combinations
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**Abstract:** H+–driven YES and PASS 1 molecular logic gates based on anthracene and 4-aminophthalimide fluorophores emitting blue and green, respectively, are employed on amino-terminated polyethyleneglycol-polystyrene and aminopropyl silica particles. The (YES + PASS 1) logic combination is also a distinguishable tag in both colours. The scope of such tags is delineated.

**Introduction**
Following humble beginnings,[i] molecular logic-based computation is now in a phase of consolidation as evidenced by 500 laboratories contributing to the movement (Figure 1). Additional evidence of this consolidation can be found in a dedicated conference series,[ii] a real-life medical application,[iii] a number of dedicated books and reviews,[iv] besides sections of others,[v] and several dedicated special issues and article collections such as this one.[vi] Other evidences are the extension of Boolean principles to molecular versions of arithmetic,[vii] ID tagging,[viii] cryptography,[ix] arrayed logic,[x] in situ imaging,[xi] conditional photodynamic therapy,[xii] intracellular logic,[xiii] multi-valued logic,[xiv] human-level computing,[xv] among others. Extending the principles learned with molecules in solution to those on solids would be one general avenue of this consolidation scenario. The current work takes some steps in this direction.

Transplanting molecular logic onto solids might appear counter-productive at first sight, since the solid object tends to be far larger than the molecular device so that space-resolution is sacrificed. A strength of molecular logic devices is their general avenue of this consolidation scenario. The current work takes some steps in this direction.

The first molecular logic tags were H+–driven YES gate 1 and PASS 1 gate 2 covalently bound to amino-terminated polyethyleneglycol-polystyrene (APEG-PS) beads (average diameter ~100 μm).[vii] We now present new data on these and related new systems in order to better understand the scope of molecular computational identification[viii] (MCID). The initial logic-tagged objects 3 and 4 consisted of an organic polymer particle and a blue-emitting hydrocarbon...
fluorophore with a more-or-less pure $\pi\pi^*$ excited state\(^8\) (Figure 2). Logically, at least two avenues open up for extending the MCID concept. First, inorganic polymer particles such as aminopropyl silica (APS)\(^{18}\) deserve attention. Second, heteroaromatic fluorophores with internal charge transfer (ICT) excited states\(^{19,20}\) e.g. green-emitting 4-aminonaphthalimide\(^{21}\) will be examined. The receptor module necessary for the expression of some logic types, e.g. H$^+$-binding tertiary amine, is carried forward from the initial study.\(^8\) A pyridine receptor for H$^+$ and a benzocrown ether receptor for Na$^+$ have also been used in previous studies.\(^8,22\)

**Results and Discussion**

Starting materials 1 and 2 were available from the initial study.\(^8\) These are attached to APS particles (average diameter ~50 $\mu$m) via dicyclohexylcarbodiimide-type coupling to create amide bonds and to produce 5 and 6. The green-emitting H$^+$-driven PASS 1 tag 7 is easily accessible by reacting 4-chloro-1,8-naphthalic anhydride 22 with glycine t-butylester, followed by a nucleophilic aromatic substitution of the halogen by 1-butylamine and a final step of ester hydrolysis (Figure 3). A similar route, but with 2-(diethylamino)ethylamine replacing 1-butylamine in the second step, yields the green-emitting H$^+$-driven YES logic tag 8. 7 and 8 are connected via amide bonds to APEG-PS and APS to produce 9, 10, 11 and 12. When a more water-compatible PASS 1 logic tag became necessary, ester-protected 8, 13, was quaternized with iodomethane followed by ester hydrolysis. 14 and 15 are the resulting tagged polymer particles.

![Figure 2](image)

Figure 2. Chemical structures of the blue-emitting anthracene-related compounds used in this study and some of their precursors. Reagents for the conversions are given under Figure 3.

A powerful feature of logic tagging arises through non-Boolean multi-valued logic.\(^4\) Such examples are built by double-tagging the polymer particles with 1 and 2 or with 8 and 16. (YES + PASS 1) logic-tagged APS 17 emits blue and 18 emits green (Figure 4). Although double (or multiple)-tagging can be carried out in various tag molar ratios,\(^8\) only 1:1 versions are studied here.
Figure 3. Chemical structures of the green-emitting 4-aminonaphthalimide-related compounds used in this study and some of their precursors. Reagents for the various conversions are: i. glycine t-butylester, ii. N-butylamine, iii. formic acid, iv. N,N-diethylaminoethylamine, v. APEG-PS or APS, Diiisopropylcarbodiimide, hydroxybenzotriazole, vi. Mel.

Comparison of the emission spectra of 19,[9] 3 and 5 at acidic pH (Figure 5) shows the occurrence of self-absorption as the anthracene fluorophores are anchored on APEG-PS and, even more so, on APS at 5% loading. The well-known smallness of the Stokes shift in ππ* emission spectra[23] leads to self-absorption of the 0-0 vibrational band of the emission spectrum and, to a lesser extent, the 0-1 band, when these fluorophores are present at a high effective local concentration. The linear and flexible PEG chains on APEG-PS spread out since they are rather well-solvated in methanol:water (1:1, v/v). Hence the fluorophores are comparatively further apart and suffer less self-absorption than that seen when they are anchored with a short propyl chain to the silica core of APS. The same trend is seen from the I00/I02 and I01/I02 values (Table 1) for the anthracene-based PASS 1 logic cases 20,[8] 4 and 6. Such self-absorption issues do not arise in the emission spectra of 4-aminonaphthalimides 7 - 12, 14 - 16 and 18 with ICT excited states owing to their substantial Stokes shifts in polar media.[23]

Figure 4. Chemical structures of the blue- and green-emitting (YES + PASS 1) logic tagged objects used in this study. The gate loading is 2.5% each in each case.

The fluorescence emission wavelengths due to the ππ* excited states of the anthracene-based YES gates 19, 3 and 5 are essentially constant (Table 1) since the emissive protonated forms are hydrophilic enough to take up positions in the mixed aqueous medium further from the polymer surface. A slight ICT character induced in the anthracene excited state by the electron-withdrawing protonated aminomethyl substituent puts the wavelengths at 400, 425 and 445 nm. All corresponding wavelengths of the uncharged PASS 1 gate 20 are blue-shifted about 10 nm due to the lack of such an ICT contribution. The hydrophobic fluorophores within 4 and 6 are held close to the polymer surface and hence the observable emission wavelengths are shifted back into the range observed for the YES logic-tagged cases 3 and 5. Such near coincidence of the 0-1 vibrational bands of polymer-bound PASS 1 and YES gates is vital for the near-ideal operation of gate combinations (see below).

Where observable, the absorption and emission wavelengths of ICT-based fluorophores within the protonated YES gates 8, 9 and 10 are blue-shifted about 18 nm when compared to the corresponding PASS 1 logic systems 7, 11 and 12, due to an electrostatic destabilization of the excited state by the protonated amine two methylene groups away.[24] The more water-compatible PASS 1 logic systems 16, 14 and 15, which carry a quaternary ammonium centre near the fluorophore, naturally have wavelengths nearly identical to the YES gates.

Figure 5. Fluorescence emission spectra of 19 (full line), 3 (dotted line) and 5 (dashed line) in methanol: water (1:1, v/v) at pH 2.5 and normalized at the 0-2 band maximum. The excitation wavelength is 368 nm.
Figure 6. Family of fluorescence emission spectra of 8 in methanol:water (1:1, v/v) as a function of pH. The excitation wavelength is 432 nm. pH values in order of increasing intensity: 11.0, 10.4, 9.9, 9.4, 8.9, 8.5, 7.9, 7.5, 7.0 and 2.5.

It is clear from Figure 6 and the large H⁺-induced fluorescence intensity enhancement factors (FEH⁺ values, Table 1) that excellent H⁺-driven YES logic behaviour is seen in the fluorescence 'off-on' action. Aminoalkyl appended fluorescent dyes are prototypical ‘fluorophore-spacer-receptor’ systems[19,24-26] where photoinduced electron transfer (PET) occurs from the amino group to the fluorophore across the spacer until it is arrested by protonation of the amine. It is gratifying to see the fluorescence switching action observed for the dissolved compounds, e.g. 19 and 8, carrying through when they are anchored at the polymer-liquid interface (e.g. 9 and 10, Figures S1 and S2 and Table 1).

Although PET switching thermodynamics in homogeneous solution is reasonably predictable from measured redox potentials[27] or from calculated frontier orbital energies,[28] it is more difficult to assess in the polymer environment. This is specially relevant since lower polarity media are known to retard PET,[29] which would reduce the FEH⁺ values to what is observed here.

Table 1. Optical properties of the logic tags and tagged polymer particles in methanol:water (1:1, v/v).

<table>
<thead>
<tr>
<th>Case</th>
<th>λex (nm)</th>
<th>λem (nm)</th>
<th>I00/I02a</th>
<th>I01/I02a</th>
<th>pKα*</th>
<th>g</th>
<th>FEH⁺b</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>368</td>
<td>400, 425, 443</td>
<td>1.34</td>
<td>1.66</td>
<td>5.3</td>
<td>0.93</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>368</td>
<td>400, 425, 445</td>
<td>0.64</td>
<td>1.38</td>
<td>3.9</td>
<td>0.70</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>368</td>
<td>427, 445</td>
<td>0.16</td>
<td>1.08</td>
<td>5.2</td>
<td>0.45</td>
<td>77</td>
</tr>
<tr>
<td>20</td>
<td>368</td>
<td>390, 410, 436</td>
<td>1.86</td>
<td>2.07</td>
<td>n/a</td>
<td>n/a</td>
<td>1.1</td>
</tr>
<tr>
<td>4</td>
<td>368</td>
<td>401, 420, 442</td>
<td>0.82</td>
<td>1.70</td>
<td>n/a</td>
<td>n/a</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>368</td>
<td>419, 440</td>
<td>0.25</td>
<td>1.30</td>
<td>n/a</td>
<td>n/a</td>
<td>1.0</td>
</tr>
<tr>
<td>21</td>
<td>368</td>
<td>400, 420, 440</td>
<td>0.73</td>
<td>1.54</td>
<td>4.1</td>
<td>0.78</td>
<td>2.0c</td>
</tr>
<tr>
<td>17</td>
<td>368</td>
<td>422, 440</td>
<td>0.35</td>
<td>1.12</td>
<td>5.2</td>
<td>0.38</td>
<td>2.0c</td>
</tr>
<tr>
<td>8</td>
<td>432</td>
<td>525</td>
<td>n/a</td>
<td>n/a</td>
<td>8.7</td>
<td>0.75</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>432</td>
<td>523</td>
<td>n/a</td>
<td>n/a</td>
<td>8.2</td>
<td>0.62</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>432</td>
<td>529</td>
<td>n/a</td>
<td>n/a</td>
<td>9.7</td>
<td>0.48</td>
<td>99f</td>
</tr>
</tbody>
</table>

a; I00 is the emission intensity observed for the 0-0 transition etc. b; IF pH2.5/IF pH11.0; c; Measured at λem = 422 nm; d; IF pH13.0; e; Apparent pKα* = 8.2; f; Measured at λem = 530 nm.

The pH dependence of the fluorescence intensity (IF) is analyzed according to a generalized version of the Henderson-Hasselbalch equation (1),

$$\log[(IF_{\text{max}} - IF)/(IF - IF_{\text{min}})] = g \cdot \text{pH} - g \cdot pKα^*$$

(1)

where IFmax and IFmin are measured at pH values of 2.5 and 11.0 respectively and where g is ideally unity. Although this last condition is commonly approached in homogeneous mixed aqueous solution,[30,31] e.g. 19 and 8, it is not obvious at polymer-liquid interfaces. Indeed, the well-solvated termini of the APEG-PS are seen to approach the conditions...
contributor to this drop in pKa* is the repulsion of H+ from the protonated amine terminals of the polymer particles.

a more polar environment for the tag in chains, as compared to methanol-water, in a ternary logic device. Such action is facilitated by the long, flexible and rather hydrophilic PEG chains. The APS counterpart the hydrolysis of the amide bond anchoring the tag, catalyzed by the exposed tertiary amine nucleophile of an adjacent PS particles tagged with 4-aminonaphthalimide carrying a quaternary ammonium side-chain, separation of the H+ receptor from the fluorophore and the lack of a significant dipole in the excited state of due to the reduced polarity of the APEG-PS environment and the H+ repulsion effect of the partially protonated amine is the major cause of equation (2).

Such deviation from ideality can be understood in terms of the fluorophores being held closer to the APS surface, e.g. in 18 and in 10, which reduces their solvation. A range of individual pK* values are expressed by different sub-populations of tags present in environments of varying polarities due to the restricted solvation. Different domains of tags on the polymer surfaces are also probably involved. The reduced g values indicate the widths of the pK* distribution. The pK* values also throw light on the effect of translocating the ‘fluorophore-spacer-receptor’ system from homogeneous mixed aqueous solution to the polymer-solution interface. The rather apolar environment created by PEG chains, as compared to methanol-water, in 3 lowers its pK* value to 3.9 as compared to 5.3 seen in 19. Another contributor to this drop in pKa* is the repulsion of H+ from the protonated amine terminals of the polymer particles.

Figure 7. Physical electronic representation of (YES + PASS 1) logic. It is noted that binary logic symbols are employed as starting points to depict a ternary logic device.

Although the environment near APS is apolar too, its Si-O- moieties electrostatically concentrate H+ locally so that the effective pK* value (5.2) for 5 approaches that found in homogeneous solution. This effect dominates over the H+ repelling effect of the partially protonated amine termini since the latter are less numerous than the Si-O- moieties. Similar arguments hold true in the (YES + PASS 1) logic cases 21 and 17. In the 4-aminonaphthalimide series, the APEG-PS YES logic case 9 has a pK* value of 8.2, which is noticeably lower than that found in homogeneous solution for 8 (8.7) due to the reduced polarity of the APEG-PS environment and the H+ repulsion effect of the partially protonated amine termini. Again, the electrostatic effect of the Si-O- groups raises the pK* value of 10 to 9.7. Such a high value suggests a more polar environment for the tag in 10 than in 5. This is to be expected given the lower Hansch hydrophobicity of 4-aminonaphthalimide as compared to anthracene.

FEH+ values for all the PASS 1 logic gates studied here are close to ideal value of unity, with one exception. APEG-PS particles tagged with 4-aminonaphthalimide carrying a quaternary ammonium side-chain, 14, show a FEH+ value of 1.6, alongside an apparent pK* value of 8.2. This is due to the amino terminals of the polymer particle causing an intraparticle but interchain PET from the primary amino groups to the fluorophore aided by its cationic side-chain.

pK* = pK* (2)

This is also true for 8, in spite of its excited state dipole of 11D, suggesting that the fluorophore-receptor separation is the major cause of equation (2).

Some complications which occurred during this study need to be noted and lessons learned. YES logic-tagged APEG-PS particles 9 display the expected H+-induced fluorescence switching ‘on’, but leaching of fluorescent species occurs in mixed aqueous solutions over a period of several hours. Eventually the tags are lost. This behaviour can be ascribed to the hydrolysis of the amide bond anchoring the tag, catalyzed by the exposed tertiary amine nucleophile of an adjacent tag. Such action is facilitated by the long, flexible and rather hydrophilic PEG chains. The APS counterpart 10 is stable under similar conditions because of the shortness of the hydrophobic propyl chain. We also note that the APEG-PS based 3 is stable because its non-terminal tertiary amine unit is flanked by the bulky anthracene fluorophore so that its nucleophilicity is suppressed. The stability of 3 also provides evidence that terminal primary amines of APEG-PS do not contribute to nucleophilic catalysis of tag hydrolysis.

PASS 1 logic-tagged APS particles 12 display weak emission, presumably due to the surface Si-OH/Si- causing intraparticle hydrogen bonding with the excited fluorophore. Related fluorescence quenching due to intramolecular hydrogen bonding is known. This problem was solved by employing a more hydrophilic version of 12, 15, so that the better solvation of the ICT fluorophore takes it to an average position which is further from the surface groups and closer to the bulk liquid. Intraparticle hydrogen bonding-based quenching effects on ICT excited states by surface Si-OH/Si- could also have occurred in the case of YES-tagged material 10. However, such issues were not visible at basic pH since intramolecular PET-based quenching within the aminoethylaminonaphthalimide moiety is faster. Similarly, no intraparticle quenching by Si-OH is seen at acidic pH because the hydrophilic protonated receptor pulls the fluorophore away from the APS surface towards the bulk liquid.
Table 2. Ideal logic table for a H⁺-driven (YES + PASS 1) logic gate with fluorescence output. The fluorescence intensities from two binary logic gates are observed as a sum total.

<table>
<thead>
<tr>
<th>Input [H⁺]</th>
<th>YES</th>
<th>PASS 1</th>
<th>(YES + PASS 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Output Fluorescence</td>
<td>Output Fluorescence</td>
<td>Output Summed Fluorescence</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3. Observed logic table for H⁺-driven (YES + PASS 1) logic gates 17 and 18 with fluorescence output, measured as the total emission from both logic components in each case.

<table>
<thead>
<tr>
<th>Input [H⁺]</th>
<th>17</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Output Fluorescence</td>
<td>Output Fluorescence</td>
</tr>
<tr>
<td></td>
<td>λex 368 nm, λem 422 nm</td>
<td>λex 429 nm, λem 530 nm</td>
</tr>
<tr>
<td>0 (10⁻¹¹ M)</td>
<td>1.0²</td>
<td>1.0²</td>
</tr>
<tr>
<td>1 (10⁻⁵ M)</td>
<td>2.0¹</td>
<td>1.5¹</td>
</tr>
</tbody>
</table>

a; Normalized value, b; Observed pK⁺* = 5.2; c; Observed pK⁺* = 9.8

These complications are avoided by 18, where 8 and 16 are used to double-tag APS. The same holds true for 17, where 1 and 2 are the two tags on APS and for 21, where 1 and 2 are the two tags on APEG-PS. As mentioned earlier, double-tagging leads to significant strengthening of the MCID approach by increasing the number of distinguishable objects. The physical electronic representation of the (YES + PASS 1) logic case is illustrated in Figure 7 and the ideal logic table is given in Table 2. Table 3 gives the observed behaviour of 17 and 18. The FE⁺ value for 17 is the ideal value of 2.0 while that for 18 is 1.5. The lower value seen for 18 is because its F₁₉₅ value is measured at pH 11.0 which is not far enough away from the pK⁺* value of 9.8. Fluorescence measurements on 4-aminonaphthalimides at pH > 11.0 are not suitable for PASS 1 logic behaviour, due to excited state deprotonation.[24] Another indication of ideal (YES + PASS 1) logic behaviour is found in the measured pK⁺* value in each case being essentially identical to the corresponding value for the case tagged with YES logic alone.

Conclusion
Molecular logic identification tags emitting blue and green have been synthesized and evaluated on organic and inorganic polymer particles. H⁺-controlled fluorescence switching abilities of the logic tags are translatable to polymer particle surfaces, in spite of the lower polarities of these surfaces. The approach of employing tertiary amines as H⁺ receptors on H⁺-driven YES logic tags works well, as long as rather nucleophilic terminal amines are not combined with long, flexible and rather hydrophilic linkers on the particle surface. Some degree of hydrophilicity is also necessary for H⁺-driven PASS 1 logic tags of the ICT type to be strongly emissive on APS surfaces. Pure ππ*-based PASS 1 tags function well even when they are rather hydrophobic. Once the above caveats are respected, ternary logic tags of the (YES + PASS 1) type are successfully demonstrated. Further extensions of molecular computational identification to other emission colours, other logic types,[22] and other objects are awaited.

Experimental section
See supporting information for detailed synthetic procedures and for pH-dependent fluorescence spectra of 9 and 10.

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Keywords: molecular logic • molecular computation • molecular computational identification • photoinduced electron transfer (PET) • fluorescent PET switches

