

Fluorescent Molecular Logic Gates Driven by Temperature and by Protons in Solution and on Solid

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Dedicated to Professor Vincenzo Balzani on the occasion of his 85th birthday.

Abstract: Temperature-driven fluorescent NOT logic is demonstrated by exploiting predissociation in a 1,3,5-trisubstituted Δ^2 -pyrazoline on its own and when grafted onto silica microparticles. Related Δ^2 -pyrazolines become proton-driven YES and NOT logic gates on the basis of fluorescent photoinduced electron transfer (PET) switches. Additional PASS 1 and YES + PASS 1 logic gates on silica are also demonstrated within the same family. Beside these small-molecule systems, a polymeric molecular thermometer based on a benzofurazan-derivatized *N*-isopropylacrylamide copolymer is attached to silica to produce temperature-driven fluorescent YES logic.

Introduction

The appeal of molecular logic-based computation^[1-22] is now spreading beyond chemistry laboratories into the molecular biology community.^[23-31] Molecular logic systems are being applied increasingly in cell physiology.[32-40] As the interest grows, it behoves us as chemists to strengthen the foundations of the field by exploring its scope. Being the key driver of chemical processes,^[41] temperature deserves to be explored as an input for molecular logic,^[42] especially in a solid-bound context. When outfitted with fluorescent tags, solid microparticles^[43-54] can be identified in populations if molecular logic is built-in. Two separate examples employing thermal input and fluorescent output are presented. Arising from the first of these, we develop a set of proton-driven gates. Although many such gates are known, we are unaware of any example of thermal- and proton-driven devices emerging from the same structural family.

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This family arises from 1,3,5-triaryl- Δ^2 -pyrazolines which have a history of use as optical brighteners.^[55] So they attracted attention for co-option into fluorescent sensors of the "offon"[56-63] and "on-off"[64,65] types based on the fluorescent PET (photoinduced electron transfer) switching/sensing principle.^[66-70] This was done by exploiting the 5-substituent to serve as an electron donor or acceptor under certain conditions. These were subsequently recognized as YES and NOT logic gates respectively.^[1] Recently, Magri et al have used their experience with Δ^2 -pyrazolines to construct "off-on-off"^[71-73] and INHIBIT^[74,75] logic systems using this motif^[76,77] and to immobilize them on organic polymeric microparticles as well.[53] studies with 1,3,5-trisubstituted Δ^2 -Durina our pyrazolines,^[64,78–80] found examples we where predissociation^[78,79,81] of the C(5)–N(1) bond controlled the fluorescence in nonpolar solvent, where detailed analysis allowed the determination of its bond dissociation energy in solution.^[82] Shifting to aqueous media and anchoring on solids will not allow such detailed analysis, but the phenomenon will hopefully be preserved to permit the construction of temperature-driven gates in a very applicable milieu for use in future molecular computational identification (MCID) schemes.[45,48-53]

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Molecular thermometers^[83–87] are proving to be popular devices for monitoring cell function.^[88–91] Although many twostate systems which are in a Boltzmann distribution can serve this purpose,^[86] the random coil-to-globule transition of certain polymers^[92,93] in water are particularly sensitive to temperature owing to cooperativity between the polymer segments. Now we show that this phenomenon is preserved upon transplantation to a microparticle surface contacting an aqueous solution.

MCID schemes were introduced in 2006 to exploit the nanometric size of molecular logic gates.^[45] Although continuing developments in semiconductor logic gates have now brought them into the molecular size range,^[94] their wireless operation requires antennas which need to be as long as their operating wavelengths.^[95] So, radiofrequency identification (RFID) chips are still operating in the submillimetre range. Thus, molecular logic gates retain their advantage in the tagging of micrometric objects. The diversity of MCID tags depends on characteristic wavelengths of excitation and emission, the nature of the input, the logic type of the input-output function, besides parallel combination of individual tags. So far, only a few fluorophores have been co-opted, and there is a need for more.^[45,48–53]

Results and Discussion

1,3,5-triaryl- Δ^2 -pyrazolines are conveniently synthesized from aromatic aldehyde, methyl ketone and hydrazine components. A carboxylic acid substituent present in either of the latter two precursors enables these Δ^2 -pyrazolines to be attached to γ aminopropylsilica microparticles (1–10). The tag is applied at 10% loading on silica, unless otherwise noted. Our study



focusses on 1–10, although 1a and b–10a and b will serve as controls in some of these instances. 1a-10a are *N*-methylcarboxamides, whereas 1b-10b are the parent carboxylic acids. 7-Chloro-4-*N*,*N*-dimethyl aminosulfonyl-2,1,3-benzoxadiazole was the starting point for preparation of silica-bound polymer 11 and its control carboxylic acid 11b. Detailed synthetic procedures and characterization (m.p., NMR, HR-MS) are described in the Supporting Information.

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The 1,3-diaryl- Δ^2 -pyrazoline fluorophore possesses an internal charge transfer (ICT) excited state.^[55] Electron-withdrawing substituents placed on the 3-aryl moiety cause substantial redshifts of the emission, which would allow the construction of logic tags of different colours. Diversity in emission wavelength as well as in logic characteristics augment the distinguishability of MCID tags. Regiochemical effects on photochemical phenomena^[96] can be conveniently studied with various permutations of substituents in the three aryl rings of the Δ^2 -pyrazoline. Regarding the stimulated fluorescence of these compounds and others in this work, our logic convention will consistently be of the positive variety where "high" signal levels are taken as "1" and "low" signal levels are taken as "0".

Silica-bound YES gate 1 is designed to operate with H⁺ input and fluorescence output, since 1,3-diiaryl- Δ^2 -pyrazoline fluorophores,^[76] especially those carrying electron-withdrawing substituents in the 1- and 3-aryl rings,^[56,58] are known to undergo PET with aniline derivatives in the 5-position. PET thermodynamics are known to be favourable in those cases.^[56,58,76] Indeed, an appropriate control **1 a** shows a huge H⁺ -induced fluorescence enhancement (FE_{H+}) factor of 210 and a pK_a value of 4.3 for its green emission at 505 nm when dissolved in methanol/water (1:1, v/v; Table 1). Another control 1 b exhibits similar behaviour. Still, the case of 1 is not easily predicted due to its local environment being determined both by the silica surface and the mixed aqueous solvent. In the event, 1 produces excellent H⁺-driven YES logic behaviour with $FE_{H^+} = 73$ and $pK_a = 4.4$ (Figure 1). In terms of predictability, it is gratifying that the pK_a values agree, the FE_{H^+} values are all large



Figure 1. Family of fluorescence emission spectra of 1 in MeOH/H₂O (1:1, v/v) as a function of pH, excited at 404 nm. pH values (in order of decreasing intensity at 508 nm): 3.0, 3.5, 4.1, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5 and 8.0.



Table 1. Spectral and acidity data for H ⁺ -driven gates. ^[a,b]								
Case	$\lambda_{e_{\mathrm{X}}}$ [nm]	$\lambda_{em.acid}$ [nm]	$\lambda_{e{ m m.base}}$ [nm]	ϕ_{max}	FE _{H+}	p <i>K</i> _a		
1	404	508	_[c]	_ ^[d]	73	4.4		
1a	404	505	_[c]	0.51	210	4.3		
1b	396	490	_[c]	0.33	180	4.1		
2	395	506	508	_[d]	1.5	_[e]		
2b	395	500	514	0.35	6.0	4.2		
4	376	486, 580	493– ^[c]	_[d]	65, 19	4.6, 5.1		
4a	376	445	470	0.37	2.0	5.7		
4b	386	468, 506	_[c]	0.46	140	3.5, 5.0		
5	379	482	482	_[d]	1.15	_[e]		
5a	379	477	482	0.38	1.5	7.2		
5 b	374	502	461	0.48	0.5	4.5		
6	364	483, 446	483	_[d]	2.5, 0.13	4.6, 2.2		
6b	364	449	461	0.30	40	4.5		
7	364	454	454	_[d]	0.85	[e]		
7a	364	454	450	0.26	1.5, 0.6	7.1, 2.7		
7b	367	454	473	0.35	2.0	4.9		
8	356	449, 455	455	_[d]	0.4	4.5		
8b	356	455, 440	469	0.24	0.04, 1.25	4.1, 6.2		
9	366	454	454	_[d]	_[e]	_[e]		
9b	366	436	442	0.04	_[e]	_[e]		
10	356	455	455	_[d]	1.1	_[e]		
10b	356	455	470	0.16	2.0	5.6		

[a]. Gates in MeOH/H₂O (1:1, v/v), 20 °C. Silica-bound versions have 10% loading on γ -aminopropyl silica particles (50 µm). Soluble versions are used at 5 × 10⁻⁶ M. Silica-bound versions are excited at the excitation wavelength determined for their soluble controls from their absorption spectra. pK_a values are determined by analysis of pH-dependent fluorescence intensities according to the equation log[(I_{max} -I)/(I- I_{min})] = pH-pK_a and variants.^[102] [b]. **2a**, **6a** and **8a**-10**a** are not available due to unsuccessful synthesis. [c]. Immeasurable due to weak signal. [d]. Not determined due to the difficulty of fluorescence quantum yield measurement of solids in contact with liquids. [e]. Immeasurable due to near-unity or ill-defined FE_{H⁺} values.

a)

and the emission wavelengths are reasonably close for 1, 1 a and 1 b.

MCID schemes are enriched when the same fluorophore can be embedded in multiple logic gates.^[45] To this end, silicabound 2 is examined for PASS 1 logic activity. The most appropriate control 2a resisted our efforts at synthesis. A related structure 2b was not a suitable control in this case as it did not display H⁺-independent emission. Its ionizable carboxylic acid group leads to a rather large FE_{H^+} value of 6.0 at 500 nm. One of the deactivation pathways of a Δ^2 -pyrazoline ICT excited state involves water-coupling to the N(2) lone electron pair.^[80] The negative pole of the ICT state partly locates on N(2) while the positive pole locates on N(1). $^{\scriptscriptstyle [55]}$ So, the donor in the ICT state is weakened in the carboxylic acid form of 2b (c.f. the carboxylate form) leading to less electron density being transferred to N(2) and less coupling to water. 2, being a carboxamide, does not possess a similar difficulty. It is gratifying to find only a small, linear rather than sigmoidal, pH-dependence in the emission of 2. When compared with the large FE_{H^+} value displayed by YES gate 1, 2 can be employed as a PASS 1 logic gate with fluorescence output at 510 nm while being driven by H⁺ input.

As both YES gate 1 and PASS 1 gate 2 contain the same fluorophore, it is no surprise that they both emit at 506–508 nm. This should allow observation of their summed emissions as output during the parallel running of these two logic gates immobilized at equal loading on the same silica particle, when excited at 397 nm (Figure 2). Any H⁺ input will impact each of the gates equally. Thus, we can expect YES + PASS 1 logic behaviour.^[6] **3** is such a doubly labelled system



Figure 2. a) Physical electronic representation of a YES + PASS 1 logic gate. b) Its logic table. c) Family of fluorescence emission spectra of 3 in MeOH/ H₂O (1:1, v/v) as a function of pH, excited at 397 nm. pH values (in order of decreasing intensity at 508 nm): 1.9, 2.5, 3.0, 3.5. 4.0, 4.6, 5.0, 5.6, 6.1, 6.5, 7.0, 7.5 and 8.0.

which displays ternary logic action where $FE_{H^+} = 1.6$ at 504 nm, which is close to 2 (the value expected from an ideal YES +





PASS 1 gate^[6]). Comfortingly, the pH-dependence is sigmoidal and the pK_a value is found to be 4.1, which is within experimental error of the corresponding value of the parent YES gate **1** (4.3).

Silica-bound 4 is a regioisomer of YES gate 1. Soluble 4a would be an appropriate control for 4, but 4a does not show convincing YES logic behaviour. Instead of the hoped-for simple H⁺-induced "off-on" switching of fluorescence, we only have a more modest enhancement of emission along with a 20 nm blue-shift as the pH is dropped. It appears that aggregation is interfering. Aggregation has recently been found to interfere with another system designed on the basis of PET-fluorescence competition.^[97] The carboxylic acid version **4b** has the complication of an ionizable acid moiety, but its ionized form is soluble without aggregation so that excellent "off-on" switching of blue fluorescence with $FE_{H^+} = 140$ at 468 nm is found upon protonation of the aniline unit. However, carboxylate protonation kicks-in as lower pH values are traversed and causes a 38 nm red-shift. Some aggregation effects are therefore to be expected in the emission behaviour of silica-bound 4 and are signalled by the extreme broadening and red-shifting of the band(s) to produce a whitish colour (Figure S1 in the Supporting Information). Although excellent "off-on" switching is observed befitting a YES logic gate, the deviation from the predicted emission band position and shape precludes the use of 4 for MCID purposes. 4 tells a cautionary tale regarding MCID tags on solid surfaces despite the reliably predictive nature of "fluorophore-spacer-receptor" systems at the molecular level.[67]

In contrast to the problems presented by **4**, PASS 1 logic shows up clearly in the case of silica-bound **5** owing to its pHindependent emission at 482 nm. Its appropriate control **5a** shows a small extent of H^+ -induced fluorescence enhancement at the same wavelength. The control **5b** with an ionizable carboxylic acid moiety naturally displays a more complicated response, with a 41 nm red-shift upon acidification, when the 3aryl group becomes electron deficient to encourage the internal charge transfer in the excited state.

All the cases discussed so far involve an electron-withdrawing substituent in the 3-aryl ring under many conditions which leads to preferential stabilization of the ICT excited state. Now we turn our attention to examples carrying 1,3-diaryl- Δ^2 pyrazoline fluorophores where a 3-phenyl ring is employed instead, so that a blue-shifted emission is anticipated. Such expectations are generally borne out, but silica-bound 6 does not. Also, it does not display a pronounced H⁺-induced fluorescence enhancement befitting a YES logic gate. $\mathsf{FE}_{\mathsf{H}^+}$ is only 2.5, suggesting that PET is not efficient from the dimethylaniline unit to the fluorophore in the silica surface environment. On the other hand, control 6b is an excellent example of a H⁺-driven YES gate. Logic applications of **6b** have been studied previously by Magri's laboratory with wider pH excursions,^[53] as has a version of **6** involving polystyrenepolyoxyethylene instead of silica. Corresponding PASS 1 logic gate 7 emits at 460 nm with no dependence on pH. The emission intensity of control 7a at the same wavelength has a small pH-dependence, while control 7b with its ionizable carboxylic acid shows some pH dependence in both fluorescence wavelength and intensity.

Reasonable H⁺-driven NOT logic behaviour emerges in the emission at 449 nm of silica-bound **8**, where a PET process occurs from the fluorophore to the benzoic acid moiety.^[64] Its synthetic precursor **9** has a weak but pH-independent emission at 454 nm, which is reasonably close to expectation for a PET process occurring from the fluorophore to the benzoic acid ester unit. The structural relationship between **8** and **9** is maintained within controls **8b** and **9b**. Carboxylate **8b** is much more emissive around 455 nm than carboxylic acid ester **9b** in the non-acidic range, since only the latter possesses an electron-deficient aryl unit in the 5-position under these conditions to permit a PET process.

The versatility of Δ^2 -pyrazolines as fluorescent logic gates demonstrated in the previous paragraphs can be extended further to include temperature as an input. Temperature-driven logic gates arrived rather late during the growth of Boolean chemistry^[42] and examples are still scarce.^[98] Δ^2 -pyrazolines carrying groups which can preferentially stabilize a radical centre at the 5-position have weakened fluorescence,^[99] which is weakened further at higher temperatures.^[82] The initially populated excited state can fluoresce or cross into a repulsive state which leads to C(5)-N(1) bond dissociation. Such predissociation is usually seen in small diatomics in the gas phase^[81] but are rarely identified in solution phase for larger molecules such as 1,3-diphenyl-5-styryl- Δ^2 -pyrazoline.^[82] The well-defined lines usually seen in gas-phase absorption spectra of diatomics can broaden into diffuse regions when the residence time in the excited state is shortened because of crossing into the repulsive state. Heisenberg's uncertainty principle demands that the energy of a very short-lived state would be less welldefined. Additionally, diatomics lose their fluorescence when excited at these diffuse regions. The line broadening criterion cannot be applied for larger polyatomic molecules in the solution phase owing to their intrinsically broad absorption bands. However, predissociation remains detectable since the collisions in the solution phase forces excited states to be vibrationally equilibrated so that extra thermal activation is required to cross into the repulsive state.

We have now outfitted 1,3-diphenyl-5-styryl- Δ^2 -pyrazoline with a carboxylic acid group in the 1-aryl unit to produce 10b, which serves as a control for silica-bound 10. An increase of temperature is expected to cause quenching of fluorescence in 10b, due to the predissociation mentioned above. A similar effect is hoped for in 10, although its more complex environment makes prediction more hazardous. In the event, both cases show substantial effects in-line with temperature-driven fluorescent NOT logic gates (Table 2. The fluorescence intensities at 60 $^{\circ}$ C (I_{60}) are smaller by factors of up to 3 when compared to those at 10 °C (I_{10}). Silica-bound 10 produces a usable I₁₀/I₆₀ ratio (Figure 3) although it is reduced somewhat from the solution phase value displayed by 10b. Now that thermally-driven logic on solid particles has been introduced, many available cases of temperature-dependent luminescence, for example, tris(bipyridine)Ru^{II} derivatives,^[100] might be coopted for similar purposes.

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Table 2. Spectral data for temperature-driven gates. ^[a,b]							
Case	$\lambda_{ex}/{ m nm}$	λ_{em}/nm	I ₁₀ /I ₆₀				
10	356	455	2.0				
10b	356	470	3.0 ^[c]				
7	364	454	1.7				
7b	367	473	1.2				
11	444	560	2.6				
11b	444	557	24				

[a]. 5×10^{-6} M gates in MeOH/H₂O (1:1, v/v; pH 7), except for 11 and 11 b which are in H₂O (pH 7). [b]. **10a** is not available due to unsuccessful synthesis. [c] Fluorescence quantum yield (ϕ) = 0.08 at 20 °C. This allows calculation of the activation energy (E_a) as 29 kJ mol⁻¹ using the equation $\log[(\phi_0/\phi)-]=E_a/2.3 RT + \log[A/(k_F + k_D)]$, where ϕ_0 is fluorescence quantum yield of **7 b**, *R* is the gas constant, *T* is absolute temperature, *A* is a pre-exponential factor, k_F is rate constant of fluorescence and k_D is rate constant of excited-state deactivation other than bond dissociation.^[82]



Figure 3. Family of fluorescence emission spectra of 10 in MeOH/H₂O (1:1, v/v; pH 7) as a function of temperature, excited at 356 nm. Temperature values (in order of decreasing intensity at 455 nm): 11, 22, 33, 41, 50 and 62 °C.

It is important to test related structures where the radical stabilizing effect is less, so that predissociation is disfavoured. Excising the ethene unit in **10** and **10b** would achieve this end,^[101] and produce the structures **7** and **7b** respectively. The latter cases indeed show smaller I_{10}/I_{60} ratios. Although, the silica-bound cases show smaller differences in I_{10}/I_{60} ratios when the alkene unit is removed.

We turn to polymeric systems to add more logic tags with thermal input and fluorescence output. *N*-Isopropylacrylamide polymers show a lower critical solution temperature in water due to a chain folding transition.^[83] Suitable copolymers of these will hide a fluorophore from water at higher temperatures but expose it in the cold, so that a fluorescence signal change would result. Push–pull benzofurazans with amino and sulfonamide terminals are such fluorophores,^[83] which interact with water to result in a quenched and red-shifted emission under these conditions. Random co-polymer **11b** also contains free carboxylic acids for coupling to aminopropyl silica microparticles to result in silica-bound **11.** Compound **11b** displays a high I_{10}/I_{60} ratio of 24 at 525 nm (Figure 4). This is excellent temperature-driven YES logic behaviour for the fluorescence output. However, the polymer segmental motions required for





Figure 4. Family of fluorescence emission spectra of 11 b in H_2O (pH 7) as a function of temperature, excited at 444 nm. Temperature values (in order of decreasing intensity at 455 nm): 18, 32, 33, 35, 36, 37, 40, 43, 47 and 51 °C.



Figure 5. Family of fluorescence emission spectra of 11 in H_2O (pH 7) as a function of temperature, excited at 444 nm. Temperature values (in order of decreasing intensity at 455 nm): 9, 19, 28, 37, 45 and 55 °C.

the chain-folding transition would be restricted somewhat when it is anchored to the silica surface by the carboxamide groups. Thus, a smaller, but still useful, I_{10}/I_{60} ratio of 2.6 at 525 nm is observed in silica-bound 11 (Figure 5).

Conclusions

A set of H⁺-driven fluorescent tags on silica microparticles display YES, PASS 1, YES+PASS 1 and NOT logic functions in multiple emission colours despite being based on a single family of 1,3,5-triaryl- Δ^2 -pyrazolines. Some of them also serve as temperature-driven fluorescent logic tags on silica, while being augmented with versions employing benzofurazan-derivatized polyacrylamides. In each case, studies with soluble control compounds shed light on the mode of operation. The competition of fluorescence with photoinduced electron transfer, predissociation or water-coupling are the three modes concerned (Scheme 1). These tags widen the scope of molecular computational identification of small objects in populations.



Scheme 1. The range of excited state mechanisms that come into effect for the discussed cases.

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Conflict of Interest

The authors declare no conflict of interest.

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

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FULL PAPER

A single family of compounds, 1,3,5triaryl- Δ^2 -pyrazolines, produces fluorescent logic gates in aqueous solution and on solid silica microparticles with H⁺ and temperature as inputs. H⁺-driven YES, PASS 1, YES + PASS 1, NOT, as well as temperature-driven NOT gates are demonstrated. H⁺-driven logic gates are based on photoinduced electron transfer (PET), whereas the temperature-driven cases depend on C(5)-N(1) predissociation. Temperature-driven YES logic gates based on polyacrylamide polymers alongside push-pull benzofurazans are also introduced for tagging solid particles.



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Fluorescent Molecular Logic Gates Driven by Temperature and by Protons in Solution and on Solid