

Structural and mechanistic insights into an Fe³⁺-triggered quinazoline based molecular rotor†

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Highly fluorescent, multifunctional and thermoreversible conformational switching (1) has been designed and developed by embedding two imidazo[1,2-*c*]quinazoline (IQ) units in the pyridyl scaffold. The origin of the conformational and optical switching of 1 to 1' has been established by various studies and by developing a model compound.

Research pertaining to the conformational relay of small molecules has fascinated chemists for many years and has emerged as an important area in chemistry, biology and medicine.¹ Elegant design of the molecules capable of converting photochemical or chemical energy into circular motion can lead to the development of molecular rotors.² In this context, stimulus dependent molecular switches are exciting because of their potential application in molecular machines/motors and spring-like devices.³ A better understanding of the conformational switching can be achieved by developing a fluorescent molecular rotor considering the high sensitivity of fluorescence techniques.⁴ In contrast, pH responsive conformational dynamics is an essential process in biological systems.^{5,6}

Also, metal ion induced molecular motions involved in several biological events are of particular interest.⁷ Amongst the recognized metal triggered systems, the metal ion is held by the ensuing conformer that complicates the evaluation of their reciprocal properties.^{5,8} A metal ion induced molecular rotor exclusive of metal in both the conformers is yet to be explored. Further, reports on dynamic control in small molecular rotors

via intermolecular H···bonding are rather scarce.^{6c,9} Conversely, an apparent effect of the conformational changes on optical behaviour can be established only by achieving their crystal structures. The origin of the molecular switching induced by pH/cation/anion often remains indistinct if the resulting conformer is merely hypothetical.

To overcome these inadequacies, through this work we have designed and synthesized a highly fluorescent (Φ , 100%) molecule 6-methyl-6-pyridin-2-yl-5,6-dihydrobenzo[4,5]imidazo[1,2-*c*]quinazoline (1) and demonstrated that it acts as a Fe³⁺-triggered molecular rotor, in turn, as an optical switch. Further, we have strived to elucidate all the mechanistic ambiguities by various studies. To assess the molecular changes by fluorescence tuning rotor 1 was designed by introducing two imidazoquinazoline (IQ) fluorophores as flexible frameworks into a rigid pyridyl ring core (Fig. 1).¹⁰ The C–C single bonds connecting IQ arms with the pyridyl ring can freely rotate, but in a restricted fashion to maintain the T_d geometry about sp³-carbon centres (Fig. 1). The results showed that 1 serves as a Fe³⁺-selective molecular rotor and the ensuing conformation 1' lacks Fe³⁺ in its structure and controlled *via* weak interactions.

Rotor 1 was synthesized by condensation of 2,6-diacetylpyridine with 2-aminophenyl benzimidazole in an appreciable yield (92%) and characterized by elemental analyses, FTIR, NMR (¹H and ¹³C) and ESI-MS techniques (Scheme S1, ESI†). The ¹H NMR spectrum of 1 showed a singlet at δ 7.44 ppm assignable to quinazoline –NH

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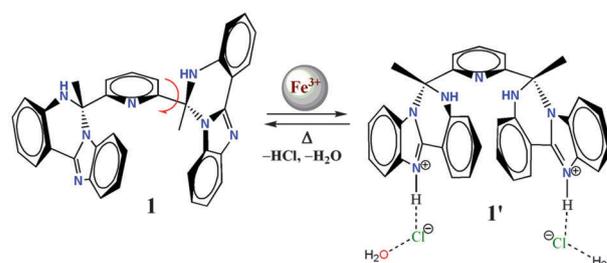


Fig. 1 Fe³⁺-mediated conformational switching of 1 to 1' (thermoreversible).

(H1) protons and two sets of methyl singlets (H12) at 2.12 and 2.05 ppm (Fig. S1a, Table S1, ESI[†]). Aromatic protons H4 and H7 resonated at 7.88 ppm, while H9–H11 in the range of 6.80–6.91 ppm. The molecular ion peak [M+H] at m/z 546.2323 (55%) and a vibration at 3260 cm^{-1} strongly suggested the successful synthesis of **1** (Fig. S1b and S1c, ESI[†]).

The cation selective conformational switching ability of **1** was assessed by the addition of various metal ions (2.0 equiv., see ESI[†]) to a solution of **1** (c , $10\text{ }\mu\text{M}$; $\text{H}_2\text{O}:\text{MeOH}$, 80:20). Notably, only Fe^{3+} led to a sharp colour change (light yellow, Fig. S2, ESI[†]) indicating some sort of interaction between **1** and Fe^{3+} . To gain deep insight, **1** was reacted with FeCl_3 and the ensuing product **1'** isolated and thoroughly characterized by various techniques (see ESI[†]). The ^1H NMR spectrum of **1'** displayed broad and downfield signals for all the protons relative to **1** (Fig. S3, Table S1, ESI[†]). Proton H1 shifted towards the downfield side and appeared at δ , 8.21, while methyl protons resonated as singlets at 2.18 and 2.11 ppm. H4 and H7 appeared as multiplets at $\sim\delta$ 7.96–8.02 and H9–H11 at \sim 6.87–7.08 ppm (ESI[†]).

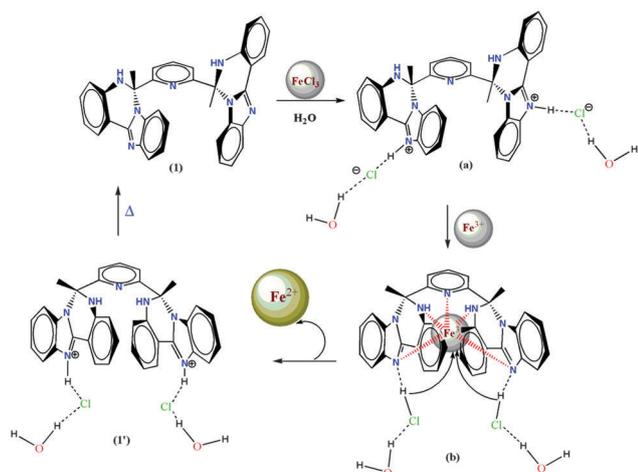
FeCl_3 upon dissolution in water generates HCl and it may be the driving force for conversion of **1** into **1'**. To verify this, **1** was treated with conc. HCl (\sim 3.0 equiv.) and the isolated product was analysed by various techniques. Notably, its ^1H NMR displayed a quite different pattern (Fig. S4a, Table S1, ESI[†]) and a vigilant examination (Fig. S1–S6, ESI[†]) indicated that lowering the pH leads to a downfield shift for all the protons due to protonation of **1**. Large downfield shift and multiplicity changes for **1'** may be attributed to the Fe^{3+} -triggered conformational change. Unlike **1** (Fig. S1c, ESI[†]), the IR spectrum of **1'** showed three vibrations at 3517, 3428 and 3260 cm^{-1} indicating the presence of water and secondary as well as quaternary -NH groups (Fig. S7a, ESI[†]). ESI-MS of **1'** exhibited an $\text{M} + \text{H}$ peak at m/z 654.1609 and a 100% peak at 581.2323 [**1'** – ($\text{HCl} + 2\text{H}_2\text{O}$)] due to loss of one HCl and two H_2O molecules (Fig. S7b, ESI[†]). The stability difference between **1** and **1'** can be understood from discrepancy in their fragmentation patterns.

A plausible route for the creation of **1'** (Scheme 1) involves the interaction of **1** with FeCl_3 leading to the formation of an

ionic species [**1**- H_2] $^{2+}\cdot 2\text{Cl}^-$ (a) by protonation on benzimidazolyl nitrogens with *in situ* generated HCl (from aqueous solution of FeCl_3). Species (a) involves intermolecular $\text{H}\cdots$ -bonding with the Cl^- atom and is also stabilized by forming a $\text{H}\cdots$ -bond with a water molecule. The background presence of Fe^{3+} in solution induces conformational switching of IQ arms *via* interaction with five nitrogen donor sites of (a) resulting in the formation of (b). It can be assumed by calculating bond lengths and bond angles of an artificially created centroid within the five nitrogen donor set of **1'** (Fig. S8, ESI[†]). The interaction of Fe^{3+} withdraws electron density from the nitrogens, thus liberating a proton from quaternary N-H to Cl^- generating HCl. Free HCl generated in this way reduces Fe^{3+} to Fe^{2+} (Fig. 2), like some HCl in the stomach may reduce Fe^{3+} to Fe^{2+} .^{11a,b} Direct reduction of Fe^{3+} to Fe^{2+} in water in acidic medium has also been observed.^{11c} The Fe^{2+} with a relatively large ionic radius may not be fitted within the five nitrogen donor set of (b) and is thus released into the solution to afford **1'**.

Furthermore, the proposed mechanism has also been supported by electrochemical studies. Rotor **1** is redox inactive,^{10b} though addition of Fe^{3+} (0.25 equiv.) to the solution of **1** ($100\text{ }\mu\text{M}$) leads to the appearance of an irreversible (-0.375 V) and a reversible (-0.499 V) reductive wave along with a reversible oxidative wave at ($+0.472\text{ V}$) (Fig. 2). Further addition of Fe^{3+} (0.5–2.0 equiv.) causes a concomitant decrease in the current intensity for the higher potential reductive wave and an increase for the one at lower potential. Interestingly, a reversible reductive wave vanished and a prominent irreversible wave appeared at -0.398 V . However, the oxidative wave feature remains the same. It is obvious that the reductive wave at higher potential corresponds to the reduction of free Fe^{3+} while the lower one is due to the reduction of Fe^{3+} interacting with **1**. This suggests that interaction of **1** facilitates the reduction of Fe^{3+} to Fe^{2+} . Notably, the appearance of an oxidative wave assignable to oxidation of the Fe^{2+} to Fe^{3+} indicates the presence of Fe^{2+} species in the solution.

X-ray single crystal analysis revealed a monoclinic system for **1** ($P2_1/n$) and **1'** ($C2/c$) (Fig. S9, Table S2, ESI[†]). Four molecules of **1** and six molecules of **1'** completed respective unit cells. From a symmetry point of view **1'** has a C_2 -axis which is lacking



Scheme 1 A plausible mechanism for the creation of **1'** from **1** in the presence of Fe^{3+} .

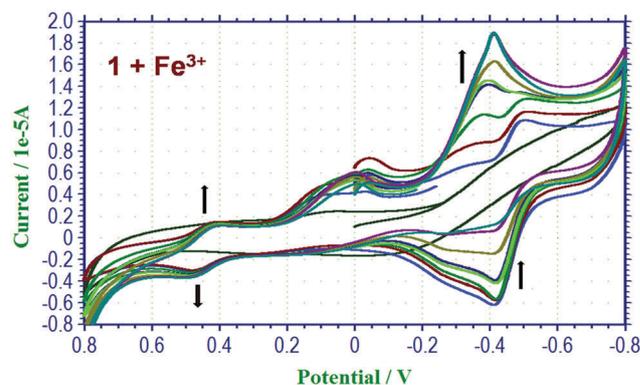


Fig. 2 Cyclic voltammogram of **1** in the presence of Fe^{3+} (0.0–2.0 equiv.), showing reduction of Fe^{3+} to Fe^{2+} and oxidation of Fe^{2+} to Fe^{3+} .

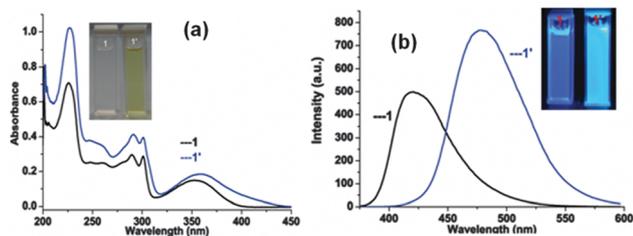


Fig. 3 (a) UV/VIS and (b) fluorescence spectra of **1** and **1'** (10 μ M); insets showing (a) chromogenic and (b) fluorogenic changes between **1** and **1'**.

in **1** (Fig. S10, ESI †). The IQ arms in **1** are almost perpendicular, whereas these are virtually parallel in **1'** (Fig. S10a, ESI †). In **1**, all the members of IQ rings are almost planar, while nearly half of these lie out of the plane in **1'**. Bite angles about sp^3 -carbon centers are very close to the ideal T_d geometry that keeps nitrogen atoms in a non-chelating fashion both in **1** and **1'**. The bond distances and angles are comparable to those in other analogous systems.¹⁰ Notably, **1'** is stabilized by H \cdots O bonding with HCl and H $_2$ O forming Cl \cdots O rectangles (Fig. S11a, ESI †). The presence of $\pi\cdots\pi$ interactions only in **1'** suggested its greater tendency to form excited state dimers through face-to-face interactions (see ESI † ; S18).

The UV/VIS spectrum of **1** (Fig. 3a) exhibited a low energy (LE) band at 350 nm and three high energy (HE) bands at 300, 290 and 225 nm.¹⁰ Considering naked eye results, various metal ions (5.0 equiv., see ESI †) were added to a solution of **1** wherein only Fe^{3+} showed a significant hyperchromic and a minute red shift (~ 3 –6 nm) in the LE and HE bands (Fig. S12, ESI †). Notably, these bands differ from the pure form of **1'** (isolated from the reaction mixture), which displays transitions at 359, 300, 290 and 225 nm (Fig. 3a). Higher optical density of the former may be due to the presence of free Fe^{3+} in solution. Titration of **1** with Fe^{3+} (0–2 equiv.) led to an incessant hyperchromic shift for both LE and HE bands along with a small red shift (~ 6 nm, Fig. S13, ESI †). The role of pH in conformational switching was studied by titrating **1** with 1.0 M HCl (> 3.0 equiv.), which induces a large red shift (30 nm) in LE and a hyperchromic shift for HE bands (Fig. S14, ESI †). Spectral features with HCl (unlike **1'**) indicated conformational retention of **1** and this species is anticipated as (a) (Scheme 1; S19, see ESI †).

Due to the presence of the IQ fluorophores **1** shows intense photo-luminescence (PL) at λ_{em} , 427 nm (λ_{ex} , 350 nm, Fig. 3b). The quantum yield (Φ) of **1** has been determined to be 100% in methanol^{12a} which is the highest among analogous systems.¹² To assess cation selective conformational tuning tested metal ions (5.0 equiv.) were added to a solution of **1**, whereas only Fe^{3+} causes PL 'turn-on' with red shifted PL maxima (λ_{em} , 480 nm; Fig. S16, ESI †). In addition, 5.0 equiv. of some of the metal(III) ions (Al^{3+} , Cr^{3+} , Co^{3+}) were added separately to the solution of **1** which induced only small PL quenching (Fig. S17, ESI †). The pure form of **1'** also displayed changes similar to that for **1** + Fe^{3+} . The difference in Stokes shifts between **1** and **1'** was found to be 53 nm suggesting a possibility of their discrete PL lifetime (*vide supra*). In titration experiments, addition of Fe^{3+} (0.1–0.6 equiv.) to a solution of **1** led to 89% fluorescence

quenching and a small red shift (20 nm, Fig. S18a, ESI †). Further addition of Fe^{3+} (0.7–2.0 equiv.) induced 40% PL 'turn-on' along with a substantial red shift (~ 53 nm), which may be associated with dimer formation due to face-to-face interaction of the IQ arms. It can also be understood from the difference in ground state dipole moments (μ) of **1** (4.90 D) and **1'** (25.19 D), calculated using DFT (Table S3, ESI †). Dipole-dipole interactions between a donor and an acceptor can operate at large distances (~ 100 Å) where excitonic energy is transferred through the space.¹³ The dipole moments of **1** and **1'** in the excited states (μ^*) were 13.10 D (**1**)/10.26 D (**1'**) and **1'** showed double exponential transient PL with decay constants yielding lifetimes of τ_1 , 3.0 ns and τ_2 , 15.1 ns (Fig. S19, Tables S3 and S4, ESI †). It may be attributed to the coexistence of dimeric and monomeric species. Conversely, **1** exhibited single exponential PL with the decay constant yielding a lifetime τ of 8.7 ns and indicating the lack of dipole-dipole/dimeric interactions. Job's plot analysis revealed 1:1 stoichiometry between **1** and Fe^{3+} (Fig. S20, ESI †). Further, titration of **1** with 1.0 M HCl (> 3.0 equiv.) led to a large PL quenching ($\sim 90\%$) with a small red shift (33 nm) which is unlike the PL for **1'** (Fig. S22, ESI †). It strongly suggested Fe^{3+} triggered conformational switching of **1** to **1'** (S19, ESI †).

The significant effect of the conformational changes on photophysics was revealed by lower values of Φ for **1** and **1'** (Fig. 4, Table S4, ESI †) estimated to be 21.9 and 26.2% (powder), and 24.0 and 25.0% (film). Lower Φ for **1** compared to **1'** may be ascribed to a more pronounced concentration-quenching effect in **1** which may originate from enhanced dipolar interactions between molecules in the excited state. It can be understood by higher calculated μ^* for **1** relative to **1'**. Moreover, differences in the concentration quenching may also be attributed to the collision induced intramolecular and bimolecular radiationless transitions, which can be suppressed by introducing rigidity in the film. Due to H \cdots O bonding, **1'** is more stabilized in the solid state resulting in a rather higher rigidity of the film compared to **1**. It is noteworthy to mention here that in contrary, the lower Φ for **1'** relative to **1** in the solution is attributed to the significant increase in the optical density of **1'** absorption spectrum relative

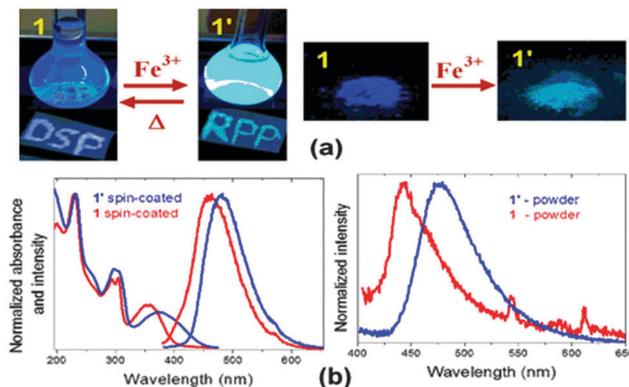


Fig. 4 (a) PL responses for **1** and **1'** in solution and solid state, DSP and RPP written by spatula on filter paper (λ_{irr} , 354 nm) showing solid state PL dye nature (b) absorption and PL spectra in spin coated (left), in powder (right).

to **1**. Compound **1** does not show any shift in the absorption band in solid and solution states, while a small PL red shift in its solid state relative to solution (34 nm, film; 16 nm, powder) may be due to dipolar effects (Fig. 4b). Notably, **1'** exhibited significant absorption and emission red shifts compared to **1**¹⁴ and transient decays both for **1** and **1'** (film) showed double exponential character (Table S4, ESI[†]). It can be explained by the combined effect of the molecular proximity and enhanced μ in the excited state than in the ground state for **1**, whereas parallel interaction of IQ arms in **1'** leads to the red shifted PL.¹⁵

Reversibility in a molecular rotor is as important as conformational switching; therefore, solution of **1'** was heated between 27 and 80 °C (Fig. S23, ESI[†]). Notably, changes were observed in a fairly opposite direction and **1** was generated at 80 °C. Further, PL quenching in the reverse plot is only 32%, because H-bonded HCl evaporates at higher temperature, raising the pH. This strongly suggested PL quenching for **1** at low pH.

Density Functional Theory (DFT) suggested a long single exponential decay of **1** (8.7 ns) relative to common emitters due to the de-excitation mechanism *via* internal charge transfer between the pyridine core and the other parts of the molecule or restricted molecular movement through hydrogen bonding (Fig. S24, ESI[†]).¹⁶ Thermal (TGA) analyses showed a significant stability difference in **1** and **1'** (Fig. S26, ESI[†]). Eventually, our hypothesis is strongly supported by developing a model compound **M** containing only one IQ-arm (Fig. S27, ESI[†]). Notably, Fe³⁺ induced only PL quenching in **M** (Fig. S28, ESI[†]),¹⁷ whereas low pH caused changes similar to that for **1**. Detailed depiction related to the results obtained from theoretical calculations, thermal studies and model compounds are given in the ESI[†] (S20 and S21).

Through this work we present a Fe³⁺ amenable, highly fluorescent molecular rotor **1** that serves as a naked eye and fluorimetric switch. The X-ray single crystal structure of both the conformers has been determined and the direct influence of the structural changes on optical behaviour has been established. The Fe³⁺-induced conformation **1'** lacks Fe³⁺ in its structure, and presents a unique example for any small molecule. The inevitability of Fe³⁺ for conversion of **1** to **1'** (not pH change) has been observed for the first time. Ultimately, model compound **M** strongly supported the results. We believe that the present report will facilitate the scientists to affirm the role of the metal ion or pH in various organic and bio-molecular reactions.

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