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An isoquinoline as cation assisted ON–OFF–ON fluorescence switch with methionine and fluoride ion

Tapas Kumar Achar [†], Ved Prakash [†], Himansu S. Biswal, Prasenjit Mal [*]

School of Chemical Sciences, National Institute of Science Education and Research (NISER), Institute of Physics Campus, PO Sainik School, Bhubaneswar, Orissa 751 005, India

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ABSTRACT

Basic Al_2O_3–$Cu(OTf)_2$ acts as an efficient heterogeneous catalyst for the one step synthesis of 1-amino-3-aryl isoquinoline (**IQ**) from tricyanomesitylene. This **IQ** shows fluorescence ON–OFF–ON molecular switch to fluoride ion, Brønsted–Lowry bases (amines) in the presence of H^+, and also selective to methionine with Hg^{2+} in an analogous manner.

Examples of isoquinoline based natural products[1] as well as their biological activities are considerably well known.[2] Several methodologies have been reported in the literature for the synthesis of isoquinoline derivatives, whereas, very few have been known for the synthesis of 1-amino-3-aryl-isoquinolines from the corresponding *o*-tolunitriles.[3] Generally, synthesis of isoquinoline[4] from *o*-tolunitriles has been documented in the literature by using a strong base for example, alkyl lithium or amide bases in relatively harsh condition.[5,6] These methodologies are reported only for the mono-cyano derivatives and no report has been found for the synthesis of isoquinolines from the *o*-alkyl aromatic cyano derivatives having either multiple cyano group or any sensitive functional group like aldehydes. However, we have developed a methodology that is, basic Al_2O_3–$Cu(OTf)_2$ mediated synthesis of isoquinoline derivatives (**IQ**, Fig. 1) under heterogeneous condition[7,8] as a single step reaction from tricyanomesitylene (**1**)[9] in 45% yield.

Scheme 1 represents the proposed mechanism for the formation of **IQ** from **1**. The mechanism can be rationalized as the initial step is tautomerization of **1** into **2** in the presence of $Cu(OTf)_2$[10] (Lewis acid, Scheme 1a).

In Scheme 1(b), it is shown that the reaction of tautomer **2** and Lewis acid adduct of **1** led to the formation of intermediate **3** which further rearranges to the **IQ** via **4** and **5**. To the best of our knowledge, like photo-induced tautomerization of *o*-alkyl aromatic carbonyl compounds,[11] tautomerization of *o*-alkyl aromatic nitriles for example, **1** using Lewis acid is hitherto unknown. This heterogeneous catalyst was efficient for the synthesis of isoquinolines with multiple functional groups. However, our attempt to synthesize the **IQ** using the literature reported procedures like using LDA or butyl lithium was unsuccessful and an inseparable mixture of polymeric products were obtained (Supplementary data or SI, Fig. S4). To understand the role of basic alumina, reactions were carried out in the presence of neutral as well as acidic alumina–$Cu(OTf)_2$ combinations and interestingly reactions were found to be sluggish. Probably, basic alumina helps to initiate the formation of tautomer **2** in the presence of Lewis acid (Fig. 1b). Furthermore, $Cu(OTf)_2$ in the absence of alumina support in appropriate solvents, $Cu(OTf)_2$–silica gel combination, or other Lewis acids[12] like $La(OTf)_3$, $Yb(OTf)_3$, $FeCl_3$ etc. also failed to give the desired product[13] in reasonable yields (ca. <10%).

The **IQ** was isolated as a fluorescent compound (Table 1) and that prompted us to investigate its competency as sensory material.[14,15] The fluorescence detection at the emission maxima of the cation loaded probe was utilized to explore either the ratio or the change in intensities of these two species considering that coordination of certain cations at the nitrogen donating centers of the isoquinoline moiety may alter the fluorescence response.[16] Strategically, one should be able to detect one's cation in the presence of other competitors, selectively for example, certain metal ions like zinc(II) and mercury(II) exhibit contrasting fluorescence response to a particular system.[17] Thus, the input regulated emission behavior of **IQ** could lead to the construction of electronic function at the molecular level for example, ON–OFF switch.[18] And addition of anion to the cation loaded system could again

* Corresponding author.
E-mail address: pmal@niser.ac.in (P. Mal).
† These authors contributed equally to this work.

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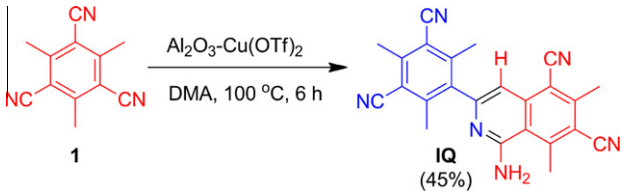
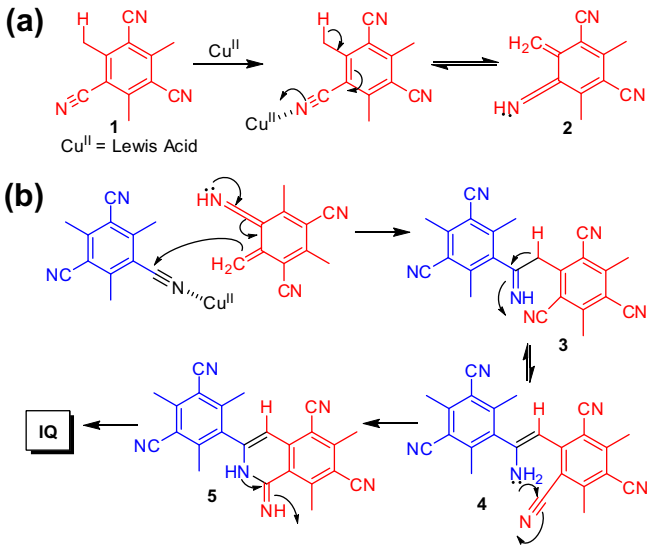


Figure 1. Synthesis of **IQ** from tricyanomesitylene **1**.



Scheme 1. (a) Lewis acid catalyzed tautomerization of **1**–**2**; (b) mechanism of formation of **IQ** from the reaction of **1** and **2**.

Table 1
Fluorescence quantum yield (Φ_{Fl}), absorption and emission wavelengths of **IQ**

Entry	Solvent	λ_{max} (abs)	$\varepsilon \times 10^3$ (mol^{-1} cm^{-1})	λ_{max} (em)	Φ_{fl}
1	Chloroform	354	13.4	455	0.88
2	DCM	354	14.8	458	0.78
3	Isopropanol	357	8.0	484	0.67
4	Ethanol	358	12.1	484	0.66
5	Methanol	356	12.7	486	0.57
6	Acetonitrile	357	12.5	478	0.67
7	DMSO	362	10.2	491	0.65

build up a new or extended molecular electronic function which ultimately may lead to input controllable ON–OFF–ON molecular switches[19–21] from a simpler ON–OFF system via dual functionality.[22]

The fluorescence quantum yield Φ_{Fl} of **IQ** was found to be 0.88 in chloroform (Table 1) and fluorescence lifetime τ_{Fl} was 10.9 ns. The **IQ** displays notable selectivity in terms of fluorescence output (quenching) for H^+ and Hg^{2+} compared to the other cations such as Li^+, Na^+, K^+, Ca^{2+}, Mg^{2+}, Ba^{2+}, Ni^{2+}, Co^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} etc. This selective cation binding ability of **IQ** was further exploited toward anion binding by the cation loaded ligand as a dual functional system. The dual functionality technique is becoming a popular technique due to its convenience of handling and cost effectiveness. As shown in Figure 2, when **IQ** was coupled with H^+, it shows discrimination for fluoride ion (e.g., fluorescence enhancement) compared to other anions like chloride, bromide, iodide, perchlorate etc. In the literature, contrasting to halogen bonding,[23] fluoride ion detection[24] has been reported by exploiting different interactions like hydrogen bonding,[24] boron-fluoride,[25] silicon-fluoride,[26] anion-π[27] etc. in either non-aqueous or aqueous media.[28,29,13] Moreover, detection of fluoride ion by a proton coupled system (Fig. 2) is relatively little known.[28] The detection limit of **IQ** is found to be quite high that is, $\approx 10^{-5}$ M for H^+ and $\approx 10^{-6}$ M for F^- in DCM.

The successful execution of the detection of fluoride ion by the proton coupled **IQ**, also motivated us to explore the potential of binding of sulfur containing amino acids (cysteine or methionine) by **IQ** + Hg^{2+} complex system. Due to poor solubility of cysteine in organic solvents, our focus was mainly on methionine during the present studies. Even though, in the literature, the detection of cysteine by Hg^{2+} coupled ligands is well executed, report on methionine sensor is either scanty or unexplored in an analogous manner. Contrastingly, methionine attached to pyrene or naphthalene based ligands were used to detect Hg^{2+}. Interestingly, **IQ** + Hg^{2+} combination was found to be a successful attempt for methionine sensor (Fig. 3). The fluorescence response of **IQ** in the presence of different ions also led to a development of fluorescence ON–OFF–ON switch. To the best of our knowledge, this is an unprecedented example of methionine sensor using dual functionality technique.

In order to get further insight into the binding sequence as well as the mechanism of binding of **IQ** with cation and followed by cation assisted anion,[30] we were interested to determine the binding constants of **IQ** in the presence of (H^+) as well as ($H^+ + F^-$) using UV/vis absorption and fluorescence titration. Firstly, we have established 1:1 binding of **IQ** and H^+ using Job's plot (SI). The good agreement of the binding constants obtained by both methods

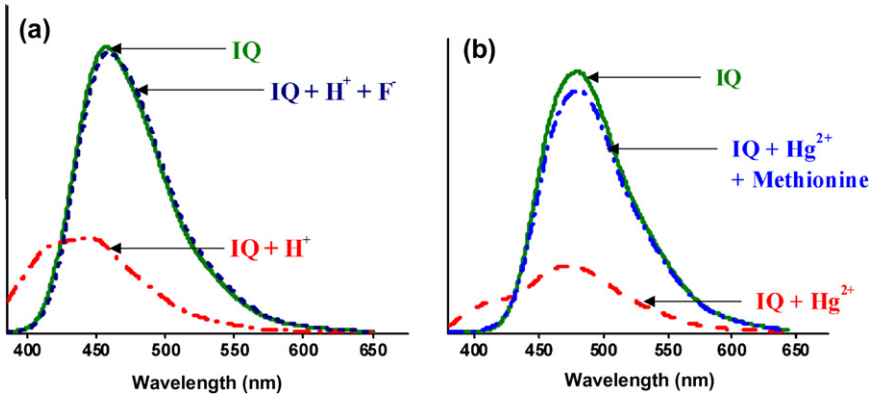


Figure 2. (a) Emission spectra of **IQ** at 1.0×10^{-5} M (excitation wavelength 350 nm) and in the presence of 2.0 equiv of H^+ ion and followed by 2.0 equiv of F^- ion (dichloromethane was used as solvent). (b) Emission spectra of **IQ** at 1.0×10^{-4} M and in the presence of 4 equiv of Hg^{2+} ion and followed by 14 equiv of methionine (right, acetonitrile was used as solvent).

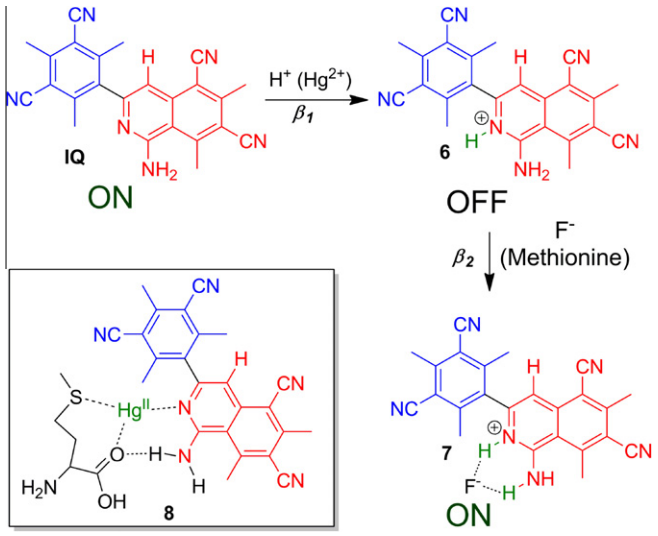


Figure 3. Proposed mechanism for cation (H^+) assisted molecular ON–OFF–ON switch with anion (F^-) and the model structure of **IQ** + Hg^{2+} + Methionine complex **8** (inset).

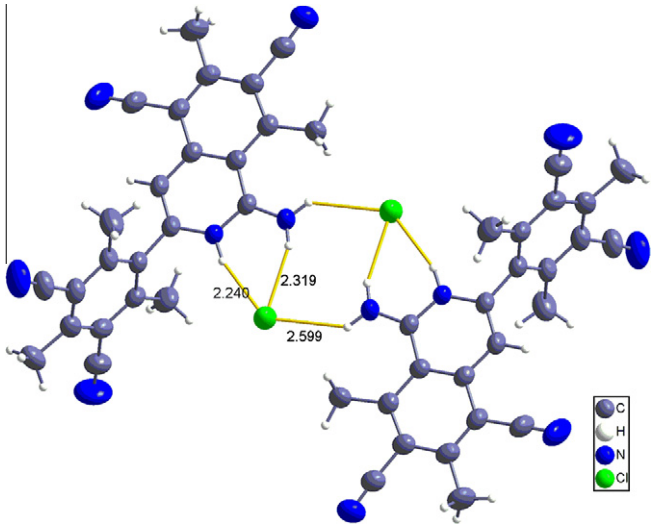


Figure 4. X-ray crystal structure of **IQ**+H^++Cl^- complex, N–H…Cl bonds is shown in yellow color; the numbers across the bond indicate bond distance in Å.

Table 2
Vertical excitation energy and oscillator strength of **IQ**, **IQ** + H^+, and **IQ** + H^+ + F^- as obtained from the TD-B3LYP/6-31G* level of theory

Entry	System	Vertical excitation energy λ_{max} in (nm)	Oscillator strength (f)	Transition
1	**IQ**	360.24	0.1452	π–π*
2	**IQ** + H^+	373.47	0.0055	π–π*
3	**IQ** + H^+ + F^-	359.77	0.1556	π–π*

(UV/vis and fluorescence) for [**IQ** + H^+] as well as [(**IQ** + H^+)+F^-] in DCM (UV/vis: $\log\beta_1 = 4.62 \pm 0.01$ and $\log\beta_2 = 5.99 \pm 0.02$; fluorescence: $\log\beta_1 = 4.78 \pm 0.01$ and $\log\beta_2 = 6.17 \pm 0.01$) allowed a reasonably accurate determination of the speciation curves in solution (Figs. S14, 15, in SI). Similarly, the binding constant data for [**IQ** + Hg^{2+}] as well as [(**IQ** + Hg^{2+}) + methionine] in acetonitrile were: using UV/vis: $\log\beta_1 = 3.25 \pm 0.01$ and $\log\beta_2 = 2.17 \pm 0.08$. From the analysis of the speciation curves we were able to extract the information of exact amount of [**IQ** + H^+] at different concentrations of acid in combination with the individual contributions from **IQ**.

To support and rationalize our experimental findings, we have taken the help of quantum chemical calculation. The ground state geometry optimization followed by frequency calculation of **IQ**, **IQ** + H^+, **IQ** + H^+ + F^-, **IQ** + Hg^{2+}, and **IQ** + Hg^{2+} + methionine were performed using the density functional theory (DFT; B3LYP/6-31G*). The details of the theoretical calculation have been provided in supporting information. The DFT calculations suggest that the ground state dipole moment of **IQ** is 6.52 Debye and its direction is toward the isoquinoline moiety of **IQ** (Fig. S24, in SI). In addition, the time dependent density function theory (TDDFT) studies show that the orbitals involved are π and π* and the isoquinoline and phenyl moieties are very weakly coupled as they are almost perpendicular to each other. This observation is also further supported by X-ray crystal structure analysis (*vide infra*).

Solvent polarity dependent λ_{max} shift (red shifted absorption in more polar solvent, Fig. S9, in SI) and the value of molar extinction coefficient (absorption studies, Table 1) clearly prove that **IQ** is fluorescent due to the π electron delocalization across the isoquinoline moiety. As a result, during the addition of cation, firstly the donor part of **IQ** has interacted with added cation (H^+/Hg^{2+}) and led to quenching of fluorescence that is, OFF state. Consequently, after addition of anion (F^-) or amino acid (methionine) the enhancement of fluorescence was observed that is, ON state. Thus, **IQ** could build ON–OFF–ON molecular switches with fluoride ion as well as with methionine in the presence of H^+ and Hg^{2+}, respectively. The proposed models of **IQ** + H^+, **IQ** + H^+ + F^-, and **IQ** + Hg^{2+} + methionine as shown in Figure 3, obtained from DFT calculation.

The experimentally observed ON–OFF–ON mechanism is also strongly supported by the DFT and TD-DFT (time dependent density functional theory) calculation (see Table 2 and Figs. S24, S25 in SI).

The mechanism of cation assisted fluorescence response of either F^- or methionine by **IQ** was further confirmed by X-ray crystal structure analysis. We were successful in co-crystallizing **IQ** and HCl instead of HF by slow evaporation of **IQ** solution in dichloromethane–methanol (1:1) and HCl at room temperature (Fig. 4). We assumed that both fluoride and chloride ion should behave analogously because after addition of the anion to **IQ** + H^+ there was 36% enhancement of fluorescence intensity with chloride ion compared to 95% with fluoride ion (Fig. S19, in SI). It is shown in Figure 4, H^+ gets associated to isoquinoline nitrogen atom (rather than $–NH_2$ group) which acts as chloride ion acceptor via two N–H…Cl hydrogen bonds. Bond distances of aromatic N–H…Cl and amine N–H…Cl are found to be 2.24 Å and 2.32 Å, respectively. The torsion angle between the isoquinoline ring and the aromatic group is 105°.

In addition to X-ray analyses (*vide supra*), NMR and IR titration experiments were also helpful to shed some light upon the association behavior of H^+ or Hg^{2+} with **IQ** (Fig. 3). After protonation at isoquinoline nitrogen atom, the methyl groups at −6 and −8 positions are expected to experience the deshielding effect due to resonance (Fig. S5, in SI). As can be seen from ^{1}H NMR spectra (Fig. S6), methyl protons of −6 and −8 protons have a downfield shift of 0.08 and 0.11 ppm, respectively. Analogous behavior was also observed for the methyl groups of 3-aryl group of **IQ**. Similarly, when F^- was added to **IQ** + H^+, significant up field shift of amine proton (9.27–5.89 ppm, Fig. S7, in SI) indicates the participation of fluoride ion with the amine proton of **IQ**. This apparently demonstrates the structure of the complexes **IQ** + H^+ and **IQ** + H^+ + F^- as proposed in Figure 3. In parallel, we have also established the structure of **IQ** + Hg^{2+} using IR spectra analyses, when ^{1}H NMR study led to

inconclusive results. It is shown in Figure S8 (SI) that $-NH_2$ peak $\sim$3550 cm^{-1} remains unchanged during the addition of Hg^{2+}, followed by methionine. Therefore, it is convincing that the nature of **IQ** and Hg^{2+} association is same as it is proposed in Figure 3. Furthermore, we have also demonstrated the possible structure of **IQ** + Hg^{2+} + methionine. Addition of non-sulfur containing amino acids like alanine, isoleucine, tryptophan etc. did not change the emission behavior of **IQ** + Hg^{2+}. Significantly, the addition of ethane thiol (50 equiv) or dimethyl sulfide (70 equiv) to the solution of **IQ** + Hg^{2+} led to an enhancement of emission intensity of **IQ** up to $\sim$65% and $\sim$63%, respectively (Figs. S21, S22, in SI). However, 14 equiv of methionine was needed for >90% of recovery of emission intensity (Fig. 2) and also ethyl 2-mercaptoacetate (70 equiv) did not alter the emission nature of **IQ** + Hg^{2+} (Fig. S23, in SI). These facts clearly point not only toward the proposed structure of **IQ** + Hg^{2+} + methionine complex is **8** (Fig. 3) but also the selectiveness of methionine for **IQ** + Hg^{2+} system.

We have also performed proton migration[31–33] studies with **IQ** + H^+ and Brønsted–Lowry bases (amines). Addition of either triethyl amine or diisopropyl amine to **IQ** + H^+ led to full recovery of emission intensities (Fig. S20, in SI) and that proves the migration of proton takes place from **IQ** to amine bases. This indicates that the isoquinoline–proton complex is also sensitive to Brønsted–Lowry bases, not necessarily to fluoride ion until and unless selectivity is considered among the anions (*vide supra*).

Therefore, from the analysis of spectroscopic data it can be rationalized as, sequential addition of cations followed by anions should open a way to turn on a molecular electronic function, thus become helpful to be a promising strategy for the realization of input controllable molecular switches. We could further demonstrate that a single molecule was utilized to detect four different ions or molecule in a rational way. Thus, on **IQ**, a prototype of 'lab-on-a-molecule'[34,35] was evidently established.

In conclusion, we have presented a novel methodology for the direct synthesis of 1-amino-3-aryl isoquinoline from *o*-tolunitrile derivative in a mild condition. It is also established that the **IQ** has a potential to act as fluoride ion sensor among the anions in the presence of H^+ and methionine sensor in the presence of Hg^{2+} via ON–OFF–ON molecular switch and clearly establishes a 'lab-on-a-molecule' model.

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Supplementary data

Supplementary data (the file contains the details of synthesis procedure, photo-physical studies, theoretical calculations and X-ray crystal structure analysis. The crystallographic data for IQ+H^++Cl^- complex have also been deposited with the Cambridge Crystallographic Data Centre as entry CCDC 888629. These data can be obtained free of charge from. The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/ciffile) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.025.

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