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Regioselective nitration of a biphenyl derivative to derive a fluorescent chloride sensor

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ABSTRACT

Methyl 2′-aminobiphenyl-4-carboxylate, an optical chloride sensor has been synthesized via Suzuki-Miyaura cross-coupling followed by regioselective nitration. In general biphenyl systems are prone to undergo poly nitration whenever they are subjected to nitration via different nitrating agents. But in this present work, a highly selective nitration in the 2′ position of methyl biphenyl-4-carboxylate was achieved using 70% HNO_3 and acetic anhydride to derive **3**. Upon reduction, **3** produces **4** which shows bright blue emission in different organic solvents. In presence of chloride ion the blue emission of the sensor changes to enhanced bright green emission. The chloride sensing has also been explored using other spectroscopic techniques such as ^{1}H NMR, UV–vis spectroscopy, and theoretical study.

Introduction

In recent times huge attention has been drawn towards the design of supramolecular sensors for anions [1–8]. These supramolecular sensors utilize different non-covalent interactions to interact with the anion and the interaction is exhibited in terms of color change, change in the fluorescence emission, electrochemical response, etc. Now among various anions, chloride is highly important from different point of views. It is a very crucial electrolyte in the blood for the living systems. It keeps the proper balance of fluid inside and outside the cells [9]. It also helps to maintain appropriate blood pressure and pH inside our human body. The chloride level in the urine of a healthy person lies in the range of 110–250 mmol L^{-1}. So monitoring the chloride level in urine can also provide important information regarding renal diseases [10,11]. Bizarre level of chloride in the sweat, serum, and cerebral spinal fluid (CSF) may indicate diseases like cystic fibrosis (CF), metabolic alkalosis, Addison's disease, and amyotrophic lateral sclerosis [12,13]. That is why from a medical diagnosis point of view chloride sensing is highly important. Apart from that detection of Cl^- is also important in various environmental monitoring purposes [14–17], food industries [18,19], and various industrial applications [20,21]. That is why scientists all over the world have developed various kinds of chloride sensors in the last decade which include protein [22], organic fluorescent sensors [13,23–25], amperometric sensor [26], colorimetric sensors [27,28], electrodes [29–31], hybrid nanomaterial [32], etc. Out of them both fluorescent and colorimetric sensors are highly useful because they provide visual detection under ambient light or UV light. So designing such a kind of chloride sensor will be highly useful from both academic as well as practical application point of view. In this present work, we have developed a biphenyl-derived chloride sensor via the Suzuki-Miyaura cross-coupling.

As far as designing a chemosensor is concerned, it is very much crucial to place particular functional groups at particular positions of a molecule. So regioselective synthesis is an important part of designing a chemosensor. Here in this current work, we have performed a regioselective nitration of methyl biphenyl-4-carboxylate. Our target was to introduce the nitro group at the 2′ position because of two reasons. First of all 4′ position is more prone towards nitration because of lack of steric hindrance and so getting 2′ nitro substituted product was a challenging task. The second point was to utilize the nitro product for designing an anion sensor via the reduction of that nitro group because amines are known to form hydrogen bonds with anions. As far as designing a fluorescent chemosensor is concerned, the concept of rigidity becomes very prominent. It has been observed that a rigid molecular system has a higher tendency towards showing photoluminescence than that of its flexible counterpart. For example, the fluorescence intensity of 8-hydroxyquinoline is much less than

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its Zn(II) complex because the latter is more rigid in nature [33]. Similarly fluorene's quantum yield is 5 times more than that of its flexible analog biphenyl [33]. So using the concept of restricted rotation, a chloride sensor has been designed using methyl 2′-aminobiphenyl-4-carboxylate.

Results and discussion

In this present work, biphenyl-4-carboxylic acid (**1**) was synthesized via the Suzuki-Miyaura cross-coupling reaction by reacting 4-bromobenzoic acid and phenylboronic acid in water with a water soluble palladium catalyst (Fig. 1) [34]. Then our target was to produce regioselective nitro derivative from compound **1**. We were interested to get the nitro group at 2′ position because that could act as a precursor for different useful compounds such as carbazole, amino acid, etc. But the task was not simple because biphenyl is an electron rich system. So normal nitration with biphenyl using mixed acid can lead to multi-nitro substituted products. Even if we lower the temperature, 4′ position is more likely to become nitrated than that of 2′ position because of lesser steric strain. The only possible way to synthesize 2′-nitrobiphenyl is to use costly 2-nitrophenylboronic acid. From that angle, the challenge was taken to synthesize this in a cost-efficient manner. At first, we tried to nitrate compound **1** directly. But there was a problem regarding the solubility. To increase the solubility, compound **1** was esterified. Compound **2** was prepared by esterification of compound **1** using thionyl chloride and methanol. Then compound **2** was subjected to nitration using 70% nitric acid and acetic anhydride at −15 °C and methyl 2′-nitrobiphenyl-4-carboxylate (**3**) was obtained with 80% yield. To confirm the position of the nitro group more accurately, we crystallized compound **3** in a methanol-acetone mixed solvent. Good quality yellow colored single crystals were obtained in a methanol-acetone mixture. Compound **3** was also characterized using single crystal XRD. The crystal was diffracted in Bruker saint (CCDC 2033350). The monoclinic crystal structure of compound **3** is given in Supplementary Fig. S1. Table S1 shows the detail of the crystal. Supplementary Fig. S2 shows the higher order packing diagram of compound **3**. The selectivity towards 2′ position is arising because the nitronium ion in association with acetic anhydride interacts with the ester oxygen of compound **4**. Via this interaction, the nitronium ion gets closer access towards 2′ position and as a result, selective nitration takes place at 2′ position (Supplementary Fig. S3). We tried to prepare an amine derivative from that nitro compound. In general amine compounds are good hydrogen bond donors and biphenyl compounds are non-rigid molecules. So an interaction of an anion with an amine compound can lead to either change of fluorescence or color. So it can act as a guest responsive material. Upon reduction of this nitro derivative using iron powder and acetic acid, methyl 2′-aminobiphenyl-4-carboxylate (**4**) is obtained (Fig. 1).

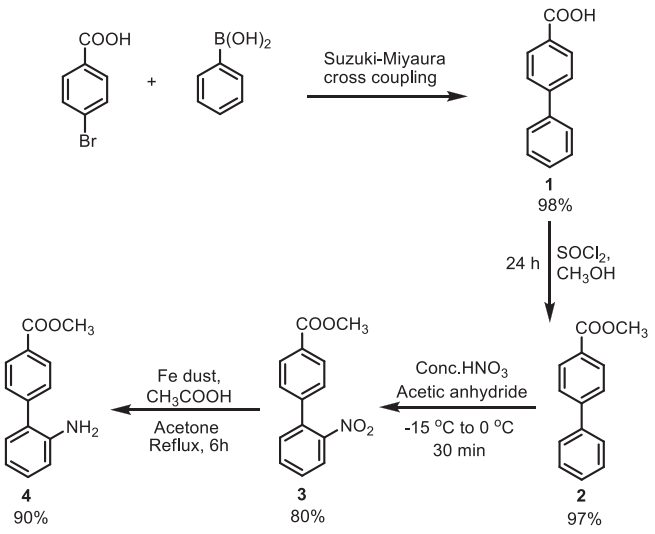

Fig. 1. Synthetic scheme of compound **4**.

All the compounds were characterized by NMR spectroscopy, IR spectroscopy, and mass spectrometry. Compound **4** is a biphenyl derivative and as a result, it shows bright blue fluorescence. In general, fluorescence is favored for rigid molecules. But biphenyl derivatives contain a pivotal bond via which two phenyl rings are attached to each other and free rotation of the phenyl rings along the pivotal bond always takes place unless the *ortho* substituents of the phenyl rings are not too bulky. Thus, if we compare biphenyl and the rigid analog of the biphenyl i.e. fluorene, then we will find that the quantum yield of biphenyl system is pretty much less as compared to fluorene. The marked difference in the fluorescence output of biphenyl and fluorenone arises due to the additional methylene group in fluorene which restricts the free rotation of the two phenyl rings. The reason for the lower quantum yield for non-rigid molecules is due to the enhancement in the rate of internal conversion which increases the chance of radiationless deactivation whereas in the case of rigid molecules, the rate of radiationless deactivation is much less and this results in higher quantum efficiency. In the case of compound **4**, there is one amine group at the 2′ position of the two phenyl rings with respect to the pivotal bond. If somehow this amine group is utilized to bind a guest molecule via hydrogen bonding then this will prevent the free rotation of the phenyl rings which will enhance the emission of the guest-bound biphenyl. Amine being a good hydrogen bond donor, anion binding experiment was thought with compound **4**. Different tetrabutylammonium anions were added to the THF solution of compound **4**. THF solution of compound **4** shows bright blue emission. But in presence of chloride ion, the emission changed to bright green instantaneously (Fig. 2). No significant changes were observed in the case of other anions.

To investigate the binding process, we performed UV–vis and fluorescence spectroscopy. Fig. 3 shows the change in the emission and absorption spectra of **4** in THF in the presence of different anions. Compound **4** shows emission maxima around 460 nm (Fig. 3a). But after the gradual addition of chloride ion, the emission intensity increased with a little red-shift. While in the case of absorption spectroscopy, compound **4** showed two absorption maxima at 251 and 332 nm (Fig. 3b). But after the gradual addition of chloride ion to the solution of compound **4**, the intensity of the band at 332 nm was found to decrease to an extent. We have checked the effect of other anions on compound **4** using fluorescence spectroscopy (Supplementary Fig. S4). But only in presence of chloride ion significant emission enhancement was observed (Supplementary Fig. S5). Using the fluorescence spectroscopy, the binding constant and binding stoichiometry were determined from the Benesi-Hildebrand double reciprocal plot (Fig. 4a). The binding constant value was 1.06 X 10^4 M^{-1} and binding stoichiometry was 1:1. We have also determined the 1:1 binding stoichiometry via Job's plot (Supplementary Fig. S6). From the fluorescence spectroscopy, the detection limit for chloride ion in THF was found to be 1.43 μM (Fig. 4b). We have also compared the detection limit of our sensor with earlier reported sensors (Supplementary Table S2). To investigate the chloride binding process more accurately, ^{1}H NMR spectroscopy was also performed (Fig. 5). ^{1}H NMR spectroscopy was performed in $CDCl_3$. Compound **4** was dissolved in $CDCl_3$ and to this solution, tetrabutylammonium chloride (TBACl) was added gradually. Compound **4** has eight aromatic protons and there are six signals in the range of 6.7–8.2 ppm. In the ^{1}H NMR spectroscopy, all the aromatic protons underwent an upfield

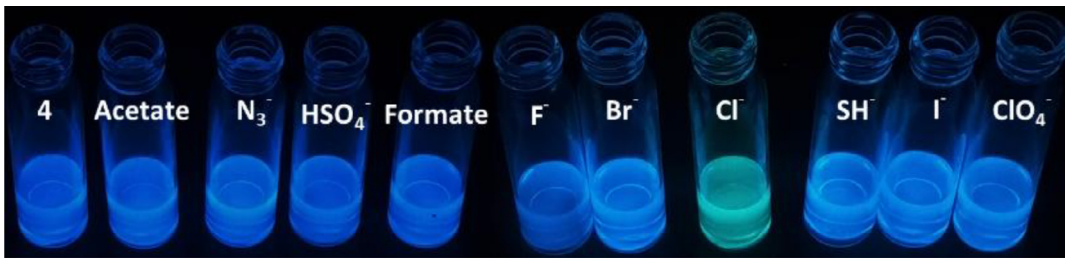

Fig. 2. Chloride sensing in THF by compound **4**. Color change of the solution of **4** in the presence of different tetrabutylammonium anions (10 equivalents) under 366 nm UV irradiation. The bright blue solution of **4** becomes bright green after interacting with chloride anion.

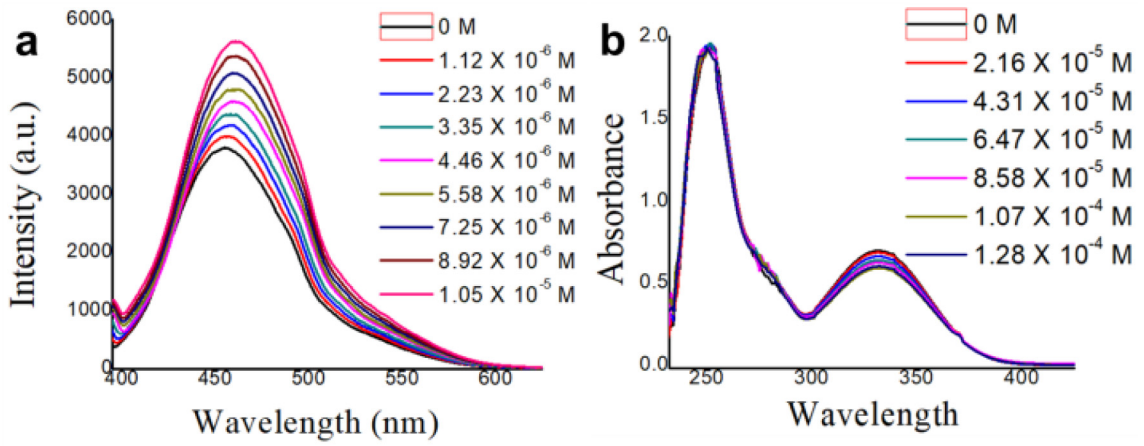

Fig. 3. (a) Change in the fluorescence spectra of compound **4** with gradual addition of tetrabutylammonium chloride in THF (excitation wavelength = 332 nm) and (b) Change in the UV–vis spectra of compound **4** with gradual addition of tetrabutylammonium chloride in THF.

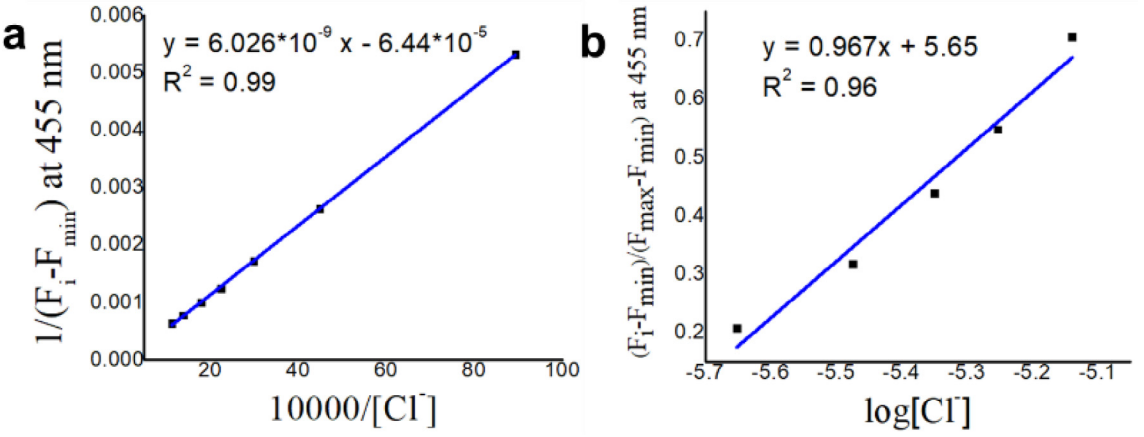

Fig. 4. (a) Benesi-Hildebrand double reciprocal plot for determining the binding stoichiometry; (b) Detection limit calculation for chloride ion.

shift after chloride binding. It indicates that both the phenyl rings of compound **4** become electron-rich. This is only possible if the overall chloride bound compound **4** becomes somewhat rigid and electron density is circulated from one ring to the other. For compound **4**, the signal of amine protons appears as a broad signal around 3.6 ppm. Upon addition of tetrabutylammonium chloride to the solution of **4**, the signal of amine proton was also expected to undergo a downfield shift. But after the addition of tetrabutylammonium chloride the signal was found to vanish (Supplementary Fig. S7). This might be due to the rapid proton exchange of amine protons with the water content associated with the highly hygroscopic material tetrabutylammonium chloride.

During this process the interaction between Cl^- and adjacent aromatic C—H is important. There are several reports of an interaction between Cl^- and aromatic C—H in the literature. [35] More importantly there is also a possibility of interaction between Cl- and adjacent aromatic C—H. So from the knowledge gained from both the fluorescence and ^1H NMR spectroscopy, we have proposed the chloride binding model in Supplementary Fig. S8.

To understand the binding process of chloride ion to compound **4**, we have performed the Density Functional Theory (DFT) [36] using Gaussian 09 [37] program package. Computation is performed with B3LYP [38] functional and correlation-consistent polarized valence double-zeta basis, abbreviated as cc-pVDZ [39].

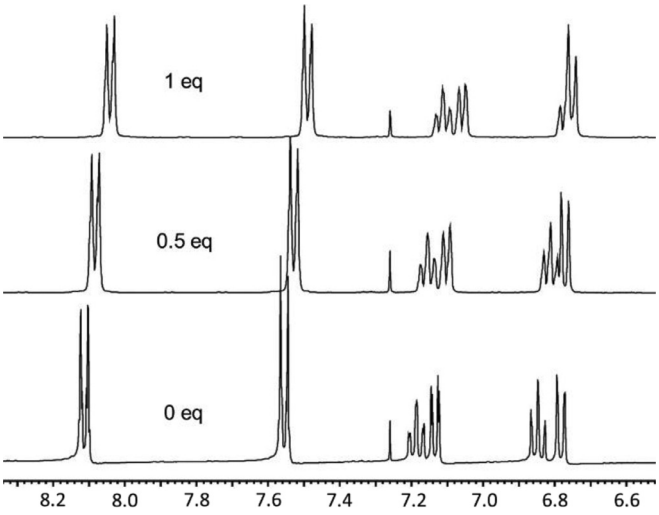

Fig. 5. A part of ^{1}H NMR spectra of compound **4** with gradual addition tetrabutylammonium chloride in $CDCl_3$.

This functional and basis are chosen because it is proven that for main group chemistry this combination of functional and basis produce very accurate geometry and spectral information [40–42]. To compute the absorption spectra of compound **4** with chloride ion, Time-dependent DFT (TD-DFT) [43,44] is used. The geometry optimizations and spectral studies are done within the polarized continuum model (PCM) of solvation [45] taking THF as the solvent. This solvent is chosen as experiments are performed with this solvent. To find out the binding of chloride ion, we have chosen different models of binding. But we found that only the formation of hydrogen bond by chloride ion with the amine NH_2 group is practically feasible. The optimized geometry is presented in Fig. 6.

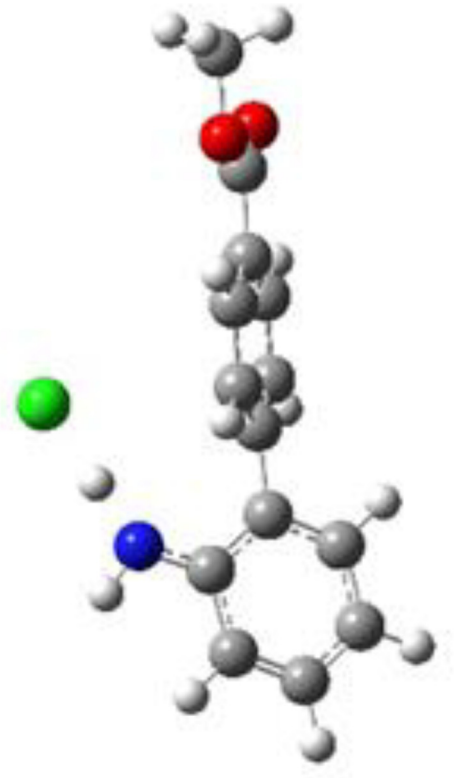

Fig. 6. Optimized geometry of compound **4** with chloride ion.

From the optimized geometry of the chloride bound compound **4** it is observed that the N—H bond is elongated from 1.0 Å to 1.26 Å due to the hydrogen bond formation. But importantly, N — H – Cl bond is linear and it is oriented in a perpendicular direction with respect to the other benzene ring. This result raises the question of stabilization for such kind of interaction. There is only one possibility i.e. the sharing of benzene π electron with the vacant *d* – orbital (d_{x2-y2}) of the chlorine atom. To test this possibility, we performed the electronic orbital analysis. We observed that one of the occupied orbitals (HOMO-1) which is very close to the HOMO supports our claim. This is presented in Fig. S9. The orbital analysis was found very helpful to investigate the emission. The energy gap between HOMO and LUMO is equivalent to 452 nm and this is very close to that of our emission maxima during chloride sensing. Since chloride is a borderline ligand with very high electronegativity, it easily forms the hydrogen bond and gets better stabilization by donor–acceptor interaction with distant benzene and facilitates ligand to ring electronic transition. Thus, we observed that only the chloride ion is able to make a color change.

Conclusion

So in conclusion we have developed a regioselective nitration of a biphenyl derivative to get the less likely product **3** in major quantity. Then compound **3** was reduced to produce compound **4** i.e. the amine analog of **3**. The amine product was designed for sensing anions. In this sensing, the key points were to utilize the hydrogen bonding tendency of the amine group and restricted free rotation of biphenyl. Compound **4** was fluorescent and this made the sensing much easier and effective. After binding with chloride ion, the free rotation of two phenyl rings of **4** stops and fluorescence emission is enhanced. The THF solution of only compound **4** shows blue emission under 366 nm UV light. But the mixture of **4** and tetrabutylammonium chloride shows enhanced bright green emission due to chloride binding. Thus compound **4** was utilized as a chloride sensor.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152750.

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