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ARTICLE

Facile detection of organophosphorus nerve agent mimic (DCP) through a new quinoline-based ratiometric switch

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In this paper, a quinoline-based **(BIMQ)** probe has been developed which displays a ratiometric detection of organophosphorus (OP) chemical vapor threat, DCP. Upon addition of the nerve agent mimic diethyl chlorophosphate (DCP), a fluoroscence color change from blue to cyan was observed. The chemodosimeter **(BIMQ)** undergoes nucleophilic substitution reaction with DCP followed by a ring closure to yield the final product and shows a explicit fluorescence response towards DCP. The probe (**BIMQ**) selctively detects DCP over other toxic analytes. Now the detection limit of **BIMQ** for DCP was established to be in the order of 10^{-8} M in solution phase which suggests that **BIMQ** is efficient in detecting DCP in very minute level. This ratiometric switch has a potential application as a portable kit for detecting DCP vapour with high sensitivity. TDDFT calculations have been carried out in order to unveil the electronic properties theoretically.

Introduction

Chemical warfare agents (CWAs) are comprised of nerve agents, blood agents, vesicant agents, incapacitating agents, cytotoxic proteins etc.[1] Among these CWAs, nerve agents are one of the most exceptional dangerous brand which has extreme harmful effects on health of every living beings if inhaled or through any kind of contamination to foods or drinks.[2,3] These odorless and colorless chemicals along with the advantage of their cheap and easy fabrication process possess a high risk of being used as a most dangerous tool of mass annihilation in the battle field through terrorists attacks.[4,5] These nerve agents are a class of chemically active and highly toxic volatile liquids or gases derived from organophosphates which are considered to be one of the most poisonous chemicals to human beings as well as to any other human beings.[6] Nerve agents, such as sarin (GB), soman (GD), and tabun (GA), are extremely lethal organophosphates which consists of very good leaving groups owing to which they are called essential phosphorylating and phosphonylating agents.[7-11] So they act as a potent inhibitors of acetylcholinesterase (AChE) in the central nervous system by irreversibly binding with the hydroxyl group of this enzyme which is mainly responsible for the hydrolysis of acetylcholine neurotransmitters.[12-15] The interaction of the nerve agent with AChE actually blocks the decomposition of acetylcholine. This accumulation of acetylcholine results in the neurological imbalance in the cholinergic synapse, the neuromuscular paralysis, hindrance of muscle relaxation, organ failure, eventually leading to rapid death.[16-20] So due to these massive threats offered by the nerve agents in our environment, there is an utmost need of developing a reliable, facile and rapid method of detecting them distinctly. An associated compound, diethyl chlorophosphate (DCP), which has comparable reactivity and structure as compared to the real nerve agents is usually used as a nerve gas-mimic agent for scientific research purpose owing to the fact that the actual nerve agents are hard to avail and also possess too much toxic nature.[21]

In recent years, a variety of noteworthy methodologies for detecting the nerve agent mimics have been introduced which includes mass spectrometry,[22-24] electrical sensors[25-27], enzyme-based biosensors,[28-31] use of enzymatic assays,[32] photoaccoustics,[33] PET based probes,[34] cyclisation reactions,[35] ion mobility spectroscopy,[36] nucleophilic substitution reactions,[37] complex formation based probes,[38] lanthanide luminescence,[39] photonic crystals,[40] optical-fibre arrays,[41] nanomaterials (nanotubes or nanowires)[42,43] etc. But these methods have some disadvantages such as low specificity, inadequate selectivity, reduced sensitivity and difficulties in real-time monitoring. So the designing of small molecule based fluorescent probes is considered to be an unrivalled methods to discriminate these harmful toxic nerve agents owing to their high sensitivity and stability, low-cost, real-time monitoring, easy portability and operational simplicity.[44,45] The sensing mechanism of these probes mainly includes the addition of phosphoryl group of these organophosphorous nerve agents to an aromatic or aliphatic hydroxyl group,[46] a pyridine group,[47] an oxime group,[48] an amine group,[49] a spirobenzopyran group[50] or a carbonyl group.[51] Although there

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are some reports on the sole detection of DCP via a fluorescent probe,[52] it still remains a potent field of research. Herein, we have designed and introduced the ratiometric fluorescent switch, BIMQ which consists of a quinoline and benzimidazole groups. The nitrogen atom of the benzimidazole moiety involves a nucleophilic attack on the phosphonyl group of DCP including a ring closure which actually increases the effectiveness of ICT mechanism that is responsible for the ratiometric emission profile of BIMQ. This fluorescent probe (BIMQ) can detect DCP in both gaseous and solution state and acts as an efficient portable tool kit for the detection of DCP.

Experimental

Materials and methods

All the organic reagents used in the synthetic procedure of BIMQ, including o-phenylenediamine were purchased from Sigma-Aldrich and the solvents were available from commercial sources and used without further purification. $CDCl_3$ was used as solvent in order to achieve NMR spectra and chemical shifts were recorded in δ units in ppm using tetramethylsilane (TMS) as an internal standard. ^1H and ^{13}C Elemental analysis was carried out in a 2400 Series-II CHN analyzer, Perkin Elmer, USA. NMR spectra were recorded on Brucker 300 MHz instrument. HRMS mass spectra were recorded on Waters (Xevo G2 Q-TOF) mass spectrometer. UV-Vis spectra were taken on a PerkinElmer Lambda 750 spectrophotometer. The luminiscence properties were studied using Shimadzu RF-6000 fluorescence spectrophotometer at room temperature (298 K). Thin layer chromatography (TLC) was done using Merck 60 F_{254} plates having thickness of 0.25 mm. The lifetimes were measured using a time-resolved spectrofluorometer from IBH, UK.

UV-Vis method

For UV-vis titration, the host solution was prepared in $CHCl_3$ solution in the order of 10 µM. The solutions of all the guest analytes in the order of 1×10^{-5} M, were prepared in chloroform. Solutions of a variety of concentrations of the probe and all other analytes were prepared separately. The spectra of these solutions were recorded with the help of UV-vis method.

Fluorescence method

For fluorescence titrations, the stock solution of the probe (10 µM) used was the same as that used for UV-vis titration. The solutions of all the analytes were prepared in chloroform in the order of 10^{-5} M. The host solution and the solution of all the analytes were prepared separately in different concentrations. The spectra of these solutions were recorded by means of fluorescence method.

Synthesis of *2-(1H-benzo[d]imidazol-2-yl)-8-methoxyquinoline (BIMQ)*

8-methoxyquinoline-2-carbaldehyde (0.16 g, 0.90 mmol) and o-phenylenediamine (0.12 g, 0.90 mmol) were taken in a round-bottomed flask and dissolved in DMF (5 mL) solution with the subsequent addition of a catalytic amount of p-TSA (~15 mg). The reflux was then started for 4 hours under inert atmosphere. After completion of the reaction, the reaction mixture was cooled at room temperature and then the whole of it was poured into ice-cooled water. The formation of a light-yellow colored precipitate was observed as soon as the reaction mixture came in contact with the ice-cold water. The precipitate was filtered using suction to yield our desirable solid yellow compound. The yield was 0.21 g, 81%.

Anal. Calc. for $C_{17}H_{13}N_3O$ (BIMQ): Calc. (%) C 74.17, H 4.76, N 15.26. Found (%), C 74.10, H 4.74, N 15.21. **^1H NMR (500 MHz, $CDCl_3$):** δ 4.11 (s, 3H), 7.11 (d, J = 7.5 Hz, 1H), 7.30 (m, 2H), 7.44 (m, 2H), 7.50 (t, J = 8 Hz, 2H), 8.28 (d, J = 9 Hz, 1H), 8.59 (d, J = 8.5 Hz, 1H), 11.72 (s, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 55.7, 108.9, 119.6, 122.7, 123.7, 127.6, 127.9, 129.1, 137.0, 139.0, 147.3, 150.8, 155.1, 156.2.

HRMS: calculated for $C_{17}H_{14}N_3O$ $[M + H]^+$ (m/z) = 276.1137; found = 276.1650.

Synthesis of BIMQ-DCP

2-(1H-benzo[d]imidazol-2-yl)-8-methoxyquinoline (BIMQ) (41 mg, 0.15 mmol) and DCP (26 mg, 0.15 mmol) were mixed in a round-bottomed flask and $CHCl_3$ was added into the mixture and was stirred for 2 hours at room temperature. After completion of the reaction, a yellowish brown precipitate was formed which was then filtered and collected.

Anal. Calc. for $C_{19}H_{17}ClN_3O_3P$ (BIMQ-DCP): Calc. (%) C 64.86, H 4.26, N 10.46. Found (%), C 65.63, H 4.06, N 11.20. **^1H NMR (300 MHz, DMSO-d_6):** δ 1.21 (t, J = 6.5 Hz, 3H), 4.09 (s, 3H), 7.17 (d, J = 7.5 Hz, 2H), 7.39 (d, J = 7.5 Hz, 1H), 7.56 (m, 2H), 7.72 (m, 1H), 7.90 (s, 1H), 8.66 (m, 1H), 8.70 (d, J = Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 16.0, 30.7, 55.9, 61.9, 109.9, 114.9, 119.6, 120.2, 125.5, 129.3, 129.7, 134.0, 137.9, 139.1, 142.5, 148.2, 155.2, 206.6.

HRMS: calculated for $C_{19}H_{17}N_3O_3P$ $[M+2Na^++Cl^-]^+$ (m/z) = 447.0491; found = 447.2069.

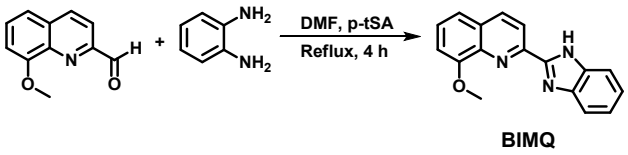
Theoretical study

All calculations were performed with Gaussian 09 program package[53]. Full geometry optimizations were carried out using the density functional theory (DFT) method at the B3LYP[54] level for the compounds. The vibrational frequency calculations were performed to certain that the optimized geometries represent the local minima having only positive eigen values. All elements were assigned 6-31+G(d) basis set. Vertical electronic excitations based on B3LYP optimized geometries were computed using the time-dependent density functional theory (TDDFT) formalism[55] in chloroform using conductor-like polarizable continuum model (CPCM).[56]

Results and discussion

Synthesis of the probe (BIMQ)

The synthetic design of **BIMQ** is shown in Scheme 1. 8-methoxyquinoline-2-carbaldehyde was prepared in accordance with the reported literature procedure.[57] Then 8-methoxyquinoline-2-carbaldehyde was reacted with o-phenylenediamine which yields the desired probe (BIMQ). The structure of BIMQ was confirmed by ^{1}H NMR, ^{13}C NMR and HRMS spectroscopy (Fig. S4–S8, ESI).



Scheme 1: Synthesis of the probe (**BIMQ**).

Sensing studies of the probe (BIMQ)

The sensing properties of BIMQ was studied in $CHCl_3$ solution in presence of other analytes such as diethylchlorophosphate (DCP), diethylcyanophosphonate (DCNP), acetic acid (CH_3COOH), hydrochloric acid (HCl), triethyl phosphate (TEP), tributyl phosphate (TBP), dimethyl methylphosphonate (DMMP) and pinacolyl methylphosphonate (PAMP) in $CHCl_3$ solution.

Fascinatingly, this chemosdosimeter (BIMQ) displayed highly distinct ratiometric fluorescence response solely for DCP among all the other guest analytes including the toxic nerve agents used in this experiment. The result of this irreversible chemodosimetric approach was prominent in both liquid and vapour states.

UV-Vis study

The absorption spectral studies of BIMQ were carried out in chlorofom solution with the incremental addition of different analytes. The solution of only BIMQ shows two peaks at 289 nm and 345 nm while upon gradual addition of DCP into the probe solution, a new peak appears at 257 nm whereas the peak at 289 nm decreased very slightly although the peak at 345 nm remains with formation of a shoulder peak at 333 nm and a brand new band at 384 nm was distinguished. Now accordingly three distinct isosbestic points are observed at 330 nm, 350 nm and 372 nm respectively (Fig. 1a). To establish the selectivity of BIMQ solely to DCP, UV-Vis studies were executed in presence of other relevant and available analytes. But only DCP was noticed to be detected alone by BIMQ. No other analytes present showed any noteworthy outcome on the absorption spectral pattern of BIMQ (Fig. 1b). The appearance of the new peak at 384 nm may be the result of internal charge transfer (ICT) process occurring to the probe (BIMQ) after coming contact with DCP.

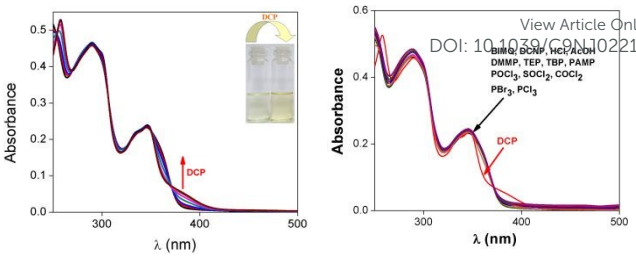


Fig. 1: (a) Absorption spectra of **BIMQ** (10 μM) upon gradual addition of DCP (0-20 μM) in $CHCl_3$ solution and (b) upon addition of different guest analytes (20 μM) in $CHCl_3$ solution.

Fluorescence study

The emission spectra of BIMQ (10 μM) exhibits a moderately strong emission band at 405 nm (λ_{ex} = 346 nm) in $CHCl_3$ solution. But after incremental addition of DCP to the solution of BIMQ, a sharp red-shift of about 66 nm is noticed and the peak at 405 nm gradually decreases while a new peak at 471 nm appears clearly accounting for the ratiometric emission enhancement of BIMQ with a distinctive isoemissive point at 423 nm (Fig. 2a). Subsequently, this emission changes results in the evident emission colour change from blue to cyan under UV light (Fig. 2a, Inset). Importantly, this emission changes have come to abrupt stop when the concentration of the DCP added in the probe solution has reached ~10 μM. From the mole ratio plot of BIMQ, it is concluded that after addition of almost 11 μM of DCP, no major changes in emission intensity at 471 nm is exhibited thereby demonstrating the fact that the saturation has taken place (Fig. S1). The sensing aptitude of the probe, BIMQ was also studied in presence of the other similar toxic guest analytes like CH_3COOH, HCl, DCNP, TEP, TBP, DMMP, PAMP, $POCl_3$, $SOCl_2$, $COCl_2$, PBr_3 and PCl_3 only to reveal that they do not have any significant sensing response towards BIMQ except $POCl_3$, $COCl_2$ and HCl (Fig. 2b). Thus BIMQ can be established as a potential ratiometric sensor for the exclusive detection of DCP in $CHCl_3$ solution. This significant ratiometric emission enhancement of BIMQ was noticed owing to the intermolecular charge transfer (ICT) mechanism.

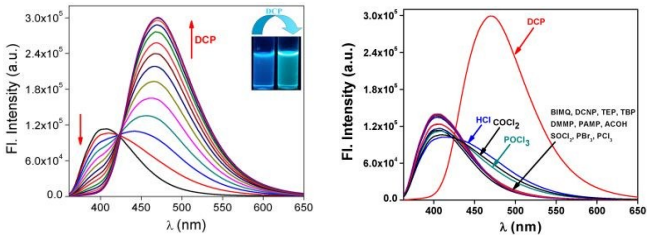


Fig. 2: (a) Emission spectra of **BIMQ** (10 μM) upon the incremental addition of DCP (0 to 11 μM) in $CHCl_3$ solution. Inset: visible emission color change of **BIMQ** in the absence and presence of 10 μM of DCP under UV light. (b) Change of emission spectra of BIMQ (10 μM) after addition of different toxic guest analytes (10 μM) in $CHCl_3$ solution. λ_{ex} = 346 nm.

The emission intensity of the probe (BIMQ) at 471 nm increases linearly within the range of 0 to 9.5 μM with the incremental addition of DCP and maintained the linear

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relationship with a good R^2 value of 0.992. (Fig. S1, ESI). From the fluorescence spectral change obtained from the emission titration experiment using the equation DL = K × Sb_1/S, where K = 3, Sb_1 is the standard deviation of the blank solution and S is the slope of the calibration curve,[58] the detection limit of the sensor was also determined and it was found to be 9.38 × 10^{-8} M (Fig. S2, ESI).

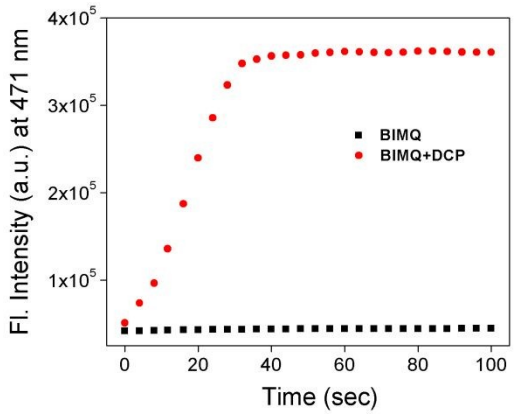


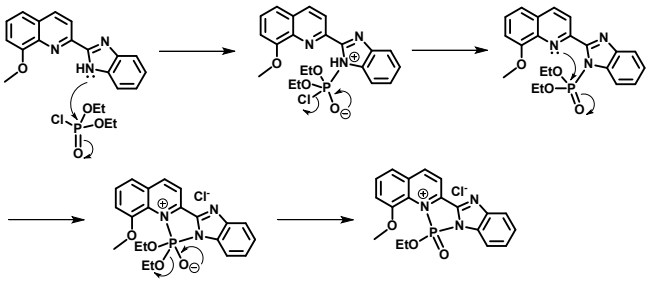
Fig. 3: Time dependent emission spectra of BIMQ (10 μM) after addition of DCP (20 μM), noted within 0-2 min time interval in $CHCl_3$ solution.

Moreover, the reaction time has been found to be a very significant factor in order to explain the fast fluorescence response of every chemodosimetric probe. So herein, the time-dependant emission response of the probe, BIMQ towards DCP is shown. The fluorescence response profile of BIMQ (10 μM) was investigated over a 0-2 min time period with addition of 2 equivalents of DCP into it (Fig. 3). From the recorded emission spectra, it was noticed that the fluorescence intensity enhancement of BIMQ occurred at 471 nm reached its saturation after almost 30 seconds which basically suggests the closure of the reaction. Thus it can be stated that this new probe, BIMQ is highly competent in detecting DCP within a very short time-span (almost 30 seconds) thereby making itself a very proficient switch for the identification of DCP.

The fluorescence lifetime measurements were also carried out for the probe (BIMQ), before and after addition of DCP in order to grasp the excited state stability. The lifetime decay profile of the probe (BIMQ) solely, shows mono-exponential decay and the lifetime is found to be 1.88 ns while BIMQ-DCP moiety too fit well with mono-exponential decay curve and display a very high lifetime of 10.39 ns (Fig. S3).

Reaction mechanism

The sensing mechanism of this new chemodosimeter (BIMQ) with DCP is discussed and shown in scheme 2. The substituted product, BIMQ-DCP is actually responsible for all the spectral changes of BIMQ on addition of DCP. The nucleophilic attack from N-atom of the benzimidazole group towards the electrophilic phosphonyl group of DCP followed by further ring closure from quinoline nitrogen results into the formation of BIMQ-DCP. The internal charge transfer (ICT) process which may be the reason of ratiometric emission change as well as visible color change of BIMQ through naked eye upon addition of DCP, is enhanced by the formation of the adduct product, BIMQ-DCP. Further the enhancement of the emission intensity of the probe (BIMQ) at 471 nm may be attributed to the rigidity of the compound (BIMQ-DCP) formed after addition of DCP to BIMQ.



Scheme 2: Probable sensing mechanism of **BIMQ** with DCP

The BIMQ-DCP product was isolated and characterized through ^1H, ^{13}C and ^{31}P NMR spectroscopy in order to support the proposed sensing mechanism (Fig. S7-S10, ESI). In the ^{31}P NMR, DCP itself showed a singlet at 4.94 ppm[59], whereas a new upfield signal at -1.540 ppm was appeared for BIMQ-DCP thereby proving the formation of the aforementioned product. To further support the formation of BIMQ-DCP product, HRMS was also executed. The HRMS of the probe (BIMQ) itself showed a peak at m/z 276.1650 while for BIMQ-DCP, a new peak at m/z 447.2079 was observed which may be due to the formation of $[BIMQ\text{-}DCP+2Na^+\text{+}Cl^-]^+$. Thus from the spectroscopic studies of BIMQ-DCP product, it is evidently clear that the proposed product is formed after the reaction of BIMQ and DCP (scheme 2). A comparison view of the probe (BIMQ) with few previously reported DCP-detecting probes is shown in table S4 (ESI).

Dip-stick experiment for vapour phase detection of DCP by BIMQ

The probe, BIMQ has shown an instant response in presence of DCP thereby proving its potential in order to use it as an efficient portable kit for detecting the nerve agent mimic. The detection of DCP in solid and liquid state has its own notable effects but its identification in vapour phase is a significantly demanding application which could be achieved via

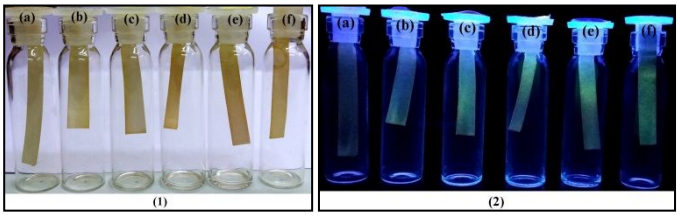


Fig. 4: Pictures of Whatman filter papers dipped in BIMQ solution and after exposed to various concentration of DCP vapour for 60 sec. taken in ambient light (1) and under UV-light (2). (a) only BIMQ, (b) BIMQ + DCP (0.5 ppm), (c) BIMQ + DCP (1.0 ppm), (d) BIMQ + DCP (2.0 ppm), (e) BIMQ + DCP (3.0 ppm) and (f) BIMQ + DCP (6.0 ppm)

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introducing an important experiment known as "dip-stick method". It is a very trouble-free procedure because it gives instantaneous qualitative information by visual outcome without even the aid of any instrument.

So to facilitate the execution of this experiment, whatman filter papers were used which were immersed into the solution of BIMQ (2×10^{-4} M) in $CHCl_3$ and then were dried by evaporating the solvent in air. After drying the filter papers, they were placed in a sealed vial in order to come into contact with the vapour of nerve agent mimic, DCP as displayed in figure 4. Consequently, a color change was observed (Fig. 4). The filter papers dipped into BIMQ solution were colorless at first but showed a light brown color change when came in contact with different concentrations of 0.5 1.0, 2.0, 3.0 and 6.0 ppm of DCP vapour in ambient light while a green fluorescence color change was observed under UV-light. So by performing this method, we have concluded that the probe (BIMQ) can detect DCP vapour with a concentration of as low as 1.0 ppm thereby proving this to be an exceptionally dependable and facile contender to identify nerve agent mimic (DCP).

We have studied this same testing pattern with other possible interfering toxic analytes via absorbing BIMQ solution by filter paper followed by exposure to different analytes (vapour) and the photograph is shown in fig. 5. From fig. 5, it is evident that no discrete change of BIMQ is detected in presence of other toxic guest analytes except a mild change in case of HCl, $COCl_2$ and $POCl_3$ vapour. Hence BIMQ can be used as a capable fluorescence switch for the detection of DCP in vapour state.

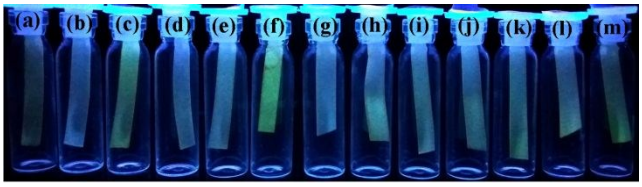

Fig. 5: Fluorescence response of BIMQ (experimented with whatman filter papers) after 60 s exposure to other toxic analytes (a. BIMQ; b. TEP; c. HCl; d. TBP; e. PAMP; f. DCP; g. DMMP; h. DCNP; i. AcOH; j. TEP; k. $POCl_3$; l. $SOCl_2$; m. $COCl_2$). Photos are taken in UV-chamber (λ_{ex} = 346 nm).

Computational Study

To better understand the structural changes of BIMQ during reaction with DCP, density functional theory (DFT) calculations were carried out by B3LYP/6-31+G(d) method using Gaussian 09 program. The optimized structures of BIMQ and BIMQ-DCP are shown in figure 6. The selected higher energy occupied molecular orbitals (HOMOs) and lower energy unoccupied molecular orbital (LUMOs) of BIMQ and BIMQ-DCP are shown in figure S11 and figure S12 respectively (ESI). The HOMO-LUMO energy gap of BIMQ is found to be 3.93 eV which is significantly reduced in BIMQ-DCP complex (2.95 eV). This significant change in HOMO-LUMO energy gap is well corroborated with the bathochromic shift in low energy band in absorption spectrum of BIMQ-DCP. In time dependent density functional theory (TDDFT) calculation, solvent correction is incorporated by CPCM model and $CHCl_3$ is chosen as solvent. The calculated vertical excitations of BIMQ exhibits strong transitions at 358 nm (f=0.3933) and 329 nm (f=0.3283), which are due to HOMO→LUMO and HOMO-1→LUMO transitions respectively. However for BIMQ-DCP, HOMO→LUMO and HOMO-1→LUMO transitions are shifted to 497 nm (f=0.0257) and 443 nm (f=0.3032) respectively (Table S1). Moreover, the calculated absorption peaks of BIMQ and BIMQ-DCP have agreed well with the experimentally observed peaks.

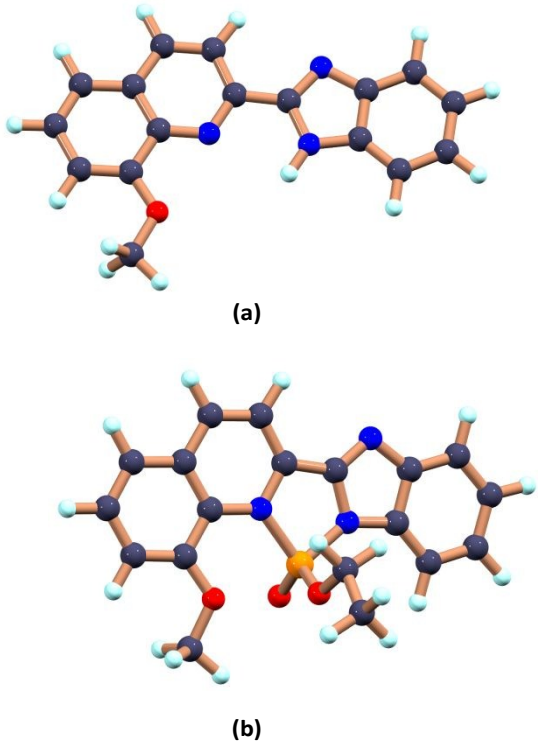

Fig. 6: Optimized structure of (a) BIMQ and (b) BIMQ-DCP calculated by DFT/B3LYP/6-31+G(d) method

Conclusions

So a new fluorescent ratiometric probe (BIMQ) was designed and synthesized for the efficient detection of DCP, a lethal nerve-agent mimic. The probe here displayed a striking ratiometric fluorescence change with a bathochromic shift upon incremental dose of DCP with a low LOD value. BIMQ showed this ratiometric change towards DCP solely in presence of other toxic guest analytes. These observations show that this quinoline-based probe can be used as a capable chemodosimeter with an instantaneous detection route upon exposure to the nerve agent mimics.

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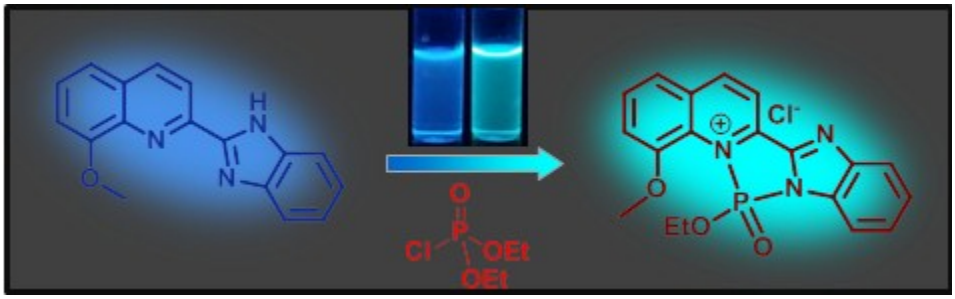

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