

Đánh giá về việc sử dụng các tính toán hóa học lượng tử trong phát triển các cảm biến huỳnh quang

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TÓM TẮT

Trong bài đánh giá này, các ứng dụng tính toán hóa học lượng tử được công bố gần đây trong việc phát triển cảm biến huỳnh quang đã được giới thiệu, bao gồm các tính toán trong quá trình phát triển cảm biến huỳnh quang mới dựa trên sự chuyển electron do cảm ứng ánh sáng (PET); nghiên cứu cấu trúc, tính chất và bản chất của các tương tác trong các hợp chất, đặc điểm hấp thụ và huỳnh quang của các hợp chất dựa trên các tính toán của trạng thái cơ bản và trạng thái kích thích, và phân tích orbital liên kết thích hợp (NBO). Các ứng dụng này có thể không toàn diện, nhưng chúng nhằm mục đích làm nổi bật, hướng dẫn và thúc đẩy việc sử dụng các tính toán hóa học

**Tác giả liên hệ chính.*

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On the use of quantum chemical calculations in the development of fluorescent sensors

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ABSTRACT

In this review, recently published quantum chemical computing applications in the development of fluorescent sensors were introduced, including the calculations in the development of the photoinduced electron transfer (PET) - based new fluorescent sensors; the study of structure, property, and nature of interactions, absorption, and fluorescence characteristics of compounds based on calculations of the ground state and excited state, and the natural bond orbital (NBO) analysis. These applications may not be comprehensive, but they aim to highlight, guide and promote the use of quantum chemical computation in the development of fluorescent sensors.

Keywords: *Quantum chemical calculations, fluorescent sensors, PET, ground state, excited state.*

1. INTRODUCTION

Today, along with the development of computer science, from hardware to software, simulation methods and theoretical computation are strongly developed and becoming effective tools in many fields, especially in chemistry,¹ physics,² biology,^{3,4} medicine,^{5,6} and environmental issues.⁷

The Nobel Prize in Chemistry 2013 was awarded to the work "the development of multiscale models for complex chemical systems" by Martin Karplus (Université de Strasbourg, France and Harvard University, Cambridge, MA, USA), Michael Levitt (Stanford University School of Medicine, Stanford, CA, USA), and Arieh

Warshel (University of Southern California, Los Angeles, CA, USA), implemented since 1970. Before those studies, the Nobel Prize in Chemistry 1995 was awarded to three computational chemists, Paul J. Crutzen, Mario J. Molina, and F. Sherwood Rowland for their work in atmospheric chemistry, particularly concerning the formation and decomposition of ozone. The Nobel Prize in Chemistry 1998 was divided equally between Walter Kohn for his development of the density-functional theory and John A. Pople for his development of computational methods in quantum chemistry. These are considered as a vivid evidence, honoring the effective contributions of computational chemistry.

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Up to now, computational chemistry has been successfully applied in various fields. In particular, computational chemistry is widely used in studying the structural characteristics, the nature of bonds and the properties of compounds;^{8,9} the ability to participate in reactions, pathways, mechanisms and products of chemical reactions.^{10,11} On that basis, computational chemistry has been flexibly applied in many different fields.

In materials research, computational chemistry is used to study the structure,¹² material properties such as ionization energy, binding energy, HOMO and LUMO energy gap,¹² UV-Vis spectra, the catalytic role of metal clusters,¹³ the relationship between structure with inhibition of metal corrosion, and metal corrosion remedies.^{14,15}

In drug research, computer-aided drug design (CADD) is a computational chemical method that effectively assists in screening

and evaluating the biological activity of active ingredients such as inhibitory activity on cancer cells,¹⁶ inhibitory activity on virus and enzymes,¹⁷⁻¹⁹ antioxidant properties, free radicals scavenging activities.²⁰ This method helps to screen, evaluate and quickly detect active ingredients with desired activity in tens of thousands of research compounds.²¹ This helps to reduce significantly the volume of experimental research, shorten the research time, as well as clarify the nature and mechanism of the processes.²² Therefore, there are many publications on Covid-19 treatment drugs using this method.^{23,24}

The main content of this review focuses on introducing recently published quantum chemical computing applications in the development of new fluorescent sensors. These applications may not be comprehensive, but they aim to highlight, guide and promote the use of quantum chemical computation to the development of fluorescent sensors.

2. RESULTS AND DISCUSSION

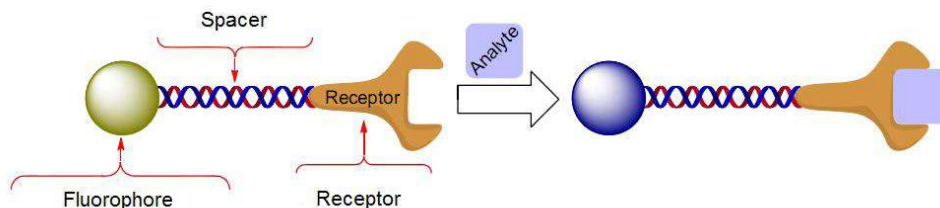


Figure 1. Basic compositions of a fluorescent sensor.²⁵

The fluorescent sensors are molecular sensors based on the change of fluorescence signal resulting from the interaction of the analytes with sensors. The fluorescent sensor is typically

composed of three main parts: “fluorophore–spacer–receptor” (Figure 1).²⁵ Figure 2 shows an illustration of a fluorescent sensor with three main parts for detection of HClO in cancer cells.²⁶

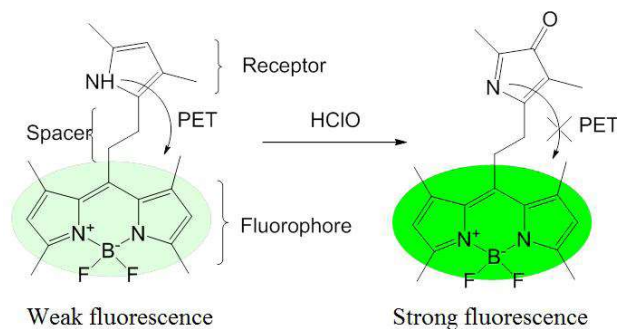


Figure 2. An illustration of fluorescent sensor with three main parts "fluorophore-spacer-receptor".²⁶

The first fluorescent sensor is a chemodosimeter based on spirolactam ring-opening process of rhodamine B derivative for the detection of Cu(II) ions, published in 1992 by A. W. Czarnik.²⁶ Nowadays, the number of published new fluorescent sensors has been rapidly increased. New fluorescent sensors have been reported almost every week in the world.²⁷ This is because the fluorescent sensors are often sensitive to the analytes, easy to carry out, and less expensive.²⁸ In particular, fluorescent sensors can be used for detection of some items in living cells like Fe(III) in Hepatic cells,²⁹ Cu(II) in HepG2 cells,³⁰ Hg(II) in PC3 cells³¹...

Following the successes of computational chemistry, new computer-aided-developed fluorescent sensors have been published more and more regularly. This is because these processes have made the development of new fluorescent sensors more efficient. In which, quantum chemistry calculations have been orienting experimental research, helping to reduce the volume of experimental studies, increase the probability of success, as well as clarify the nature and mechanism of processes, create a scientific basis for further research.

a) Quantum chemistry calculations in the development of PET (Photoinduced Electron Transfer) - based fluorescent sensors

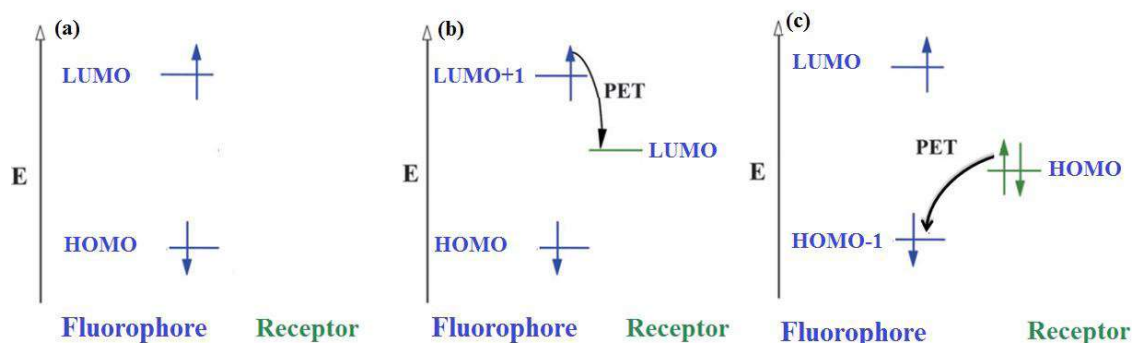


Figure 3. Electron transition process in excited state of fluorescent sensor without PET process (a), with PET process (b), (c).^{32,33}

Computational chemistry has been used to study fluorescent sensors which operate based on PET mechanism, mainly the calculations for selection of the appropriate fluorophores and receptors, or for explanation of fluorescent signal changes.^{32,33} For fluorescent sensor without PET process, the transition of electron from ground state to excited state takes place in two consecutive MOs (of the fluorophore), LUMO and HOMO (Figure 3a).^{32,33} In this case, the de-excitation process is the transition of electron from LUMO to HOMO, and is accompanied by fluorescence emission. Meanwhile, for fluorescent sensor with PET process, the transition of electron from ground to excited state takes place in two

non-consecutive MOs (of the fluorophore). There is an empty orbital (Figure 3b) or a filled orbital (Figure 3c) (of receptor) whose energy level lies between the two orbitals of the transition of electron from ground state to excited state. In this case, the de-excitation process occurs the PET process, which is the transition of electron from LUMO+1 to LUMO (Figure 3b), or from HOMO to HOMO-1 (Figure 3c). This leads to the de-excitation process without fluorescence emission. The reaction between PET sensors and the analytes induces either the presence or the absence of orbital whose energy level lies between the two orbitals in the main transition of the fluorophore, resulting in fluorescence quenching or enhancement, respectively.^{32,33}

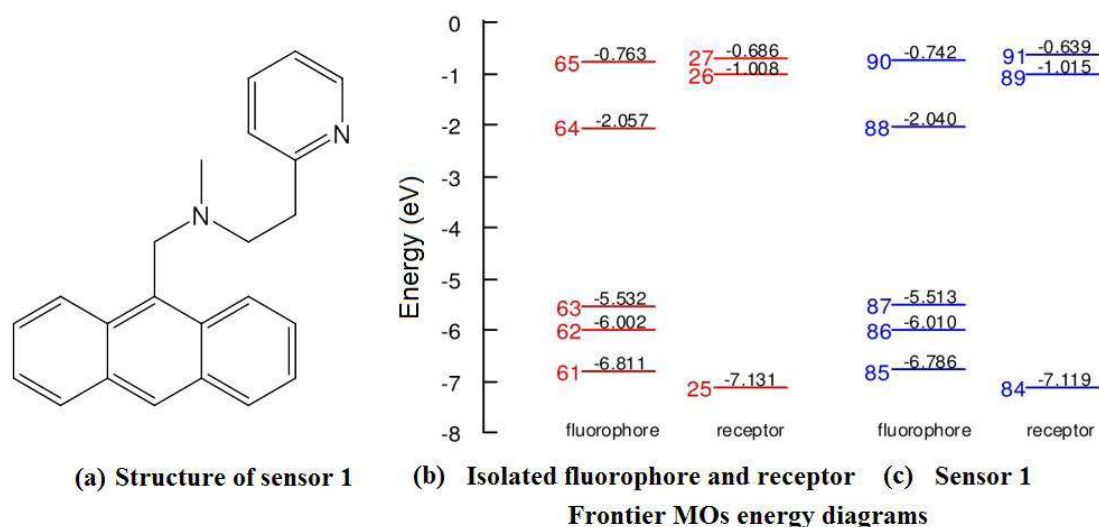


Figure 4. Structure of sensor (a), Frontier MOs energy diagrams of isolated fluorophore and receptor (b), and of sensor **1** (c).³⁴

When designing sensor **1** for detection of Zn(II) ion based on anthracene derivative as a fluorophore and pyridine derivative as a receptor, George A. Hudson and co-authors used the density functional theory (DFT)/B3LYP and time-dependent (TD)-DFT/B3LYP methods, with the basis set 6-31G(d,p), 6-31+G(d,p), 6-311G(d,p), and 6-311+G(d,p) to calculate the relative energy levels of the frontier MOs of compounds. The calculation results showed that the relative energy levels of the frontier MOs of compounds were not nearly unchanged when using the above six basis sets. This indicated

that any of the above six basis sets can be used in calculating the relative energy levels of the frontier MOs.

The calculation results also showed that the relative energy levels of the frontier MOs of the independent fluorophore and receptor were not nearly altered when they were linked together in sensors (Figure 4). Therefore, it was possible to select fluorophores and receptors for the design of sensors based on the calculation results of the frontier MOs energy levels in the isolated parts. These are promising outcomes for the computational design of sensors.³⁴

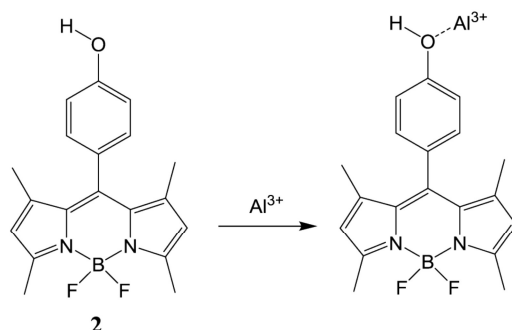


Figure 5. Fluorescent sensor **2** for detection of Al(III) based on BODIPY derivative.³⁵

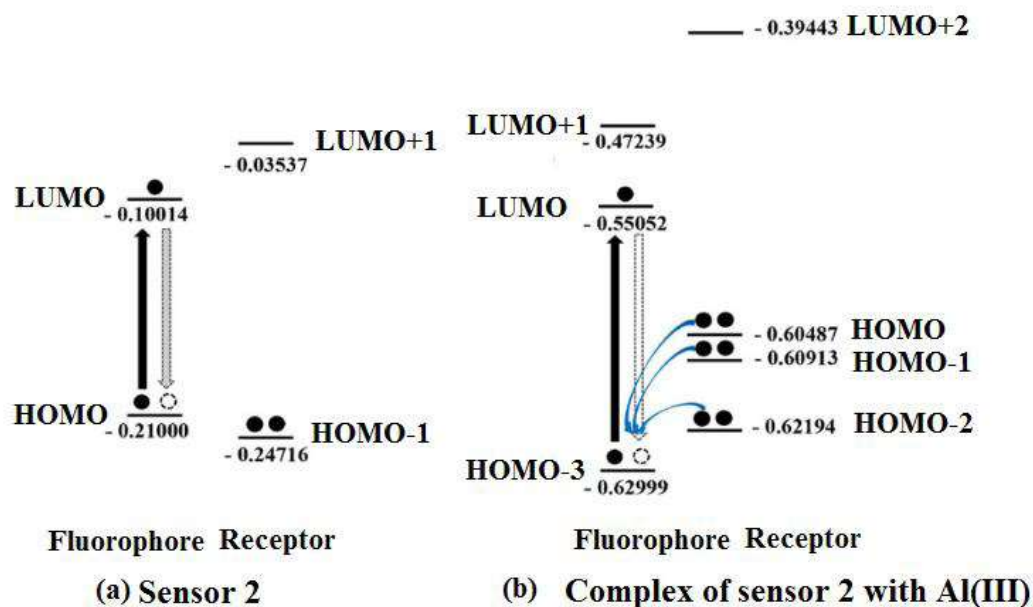


Figure 6. Frontier MOs energy diagrams of sensor 2 (a), complex of sensor 2 with Al(III) (b).³⁵

Fluorescent sensor **2** for detection of Al(III) based on BODIPY (boron-dipyrromethene) derivative was published by Tasawan Keawwangchai and co-authors (Figure 5). In this work, the authors used TD-DFT method to explain the experimental results of the change in fluorescent signal before and after the sensor **2** reacted and formed complex with Al(III). In the free state of sensor **2**, the singlet electron transition from the ground state to the excited state was mainly contributed by the HOMO→LUMO transition. Therefore, the PET process does not occur in sensor **2** and it is a fluorescent compound (Figure 6a). Meanwhile, in the complex of sensor **2** with Al(III), the singlet electron transition from the ground state to the excited state was mainly contributed by the HOMO-3→LUMO transition (Figure 6b). This leads to the occurrence of PET process and the complex does not emit fluorescence.³⁵

In general, on the basis of the operating mechanism of the PET fluorescent sensor, the theoretical calculations have been successfully used in determining the relative energy levels of the frontier MOs of the fluorophore and receptor to design sensors, investigating on the electron

transition in excited state to predict or explain the fluorescence properties of compounds.³⁴⁻³⁹ The calculated results predicting the fluorescence properties of the compounds were in good agreement with the experimental results.^{36-38,39-40} However, this approach may face some limitations. It is only possible to confirm that a compound does not fluoresce when the PET process is determined.³⁹ In contrast, although the PET process was not found in a compound, it could not be confirmed that it was a fluorescent compound. It is due to many other reasons, for example, the HOMO and LUMO energy gap is too small,⁴¹ the lack of overlapping between HOMO and LUMO.^{41,43} In these cases, further study to excited states is essential.

b) Study of the structure, absorption and fluorescence characteristics of compounds based on the calculations of the ground state (GS) and excited states (ESs)

As another application, computational chemistry has been used to study the structure, absorption and fluorescence characteristics of fluorescent sensors and compounds, by using calculations of the GS and ESs.⁴⁴⁻⁵⁷

Shigehiro Sumiya and co-authors introduced fluorescent sensor **3** for detection of Hg(II) (Figure 7). In this work, the absorption and fluorescence properties of compounds were studied by using DFT and TD-DFT method to calculate the excitation processes based on their optimized geometries at the (GS). The calculation results in Table 1 show that in sensor **3**,

the $S_0 \rightarrow S_2$ transition is the most dominant of the singlet electronic transitions from GS to ESs, with an oscillator strength (f) of 0.290, much stronger than that of the other transitions. The $S_0 \rightarrow S_2$ transition is mainly contributed by HOMO $\rightarrow$ LUMO transition, with a largest contribution of 72.27%. The corresponding excitation energy is 2.91 eV (427 nm).⁴⁴

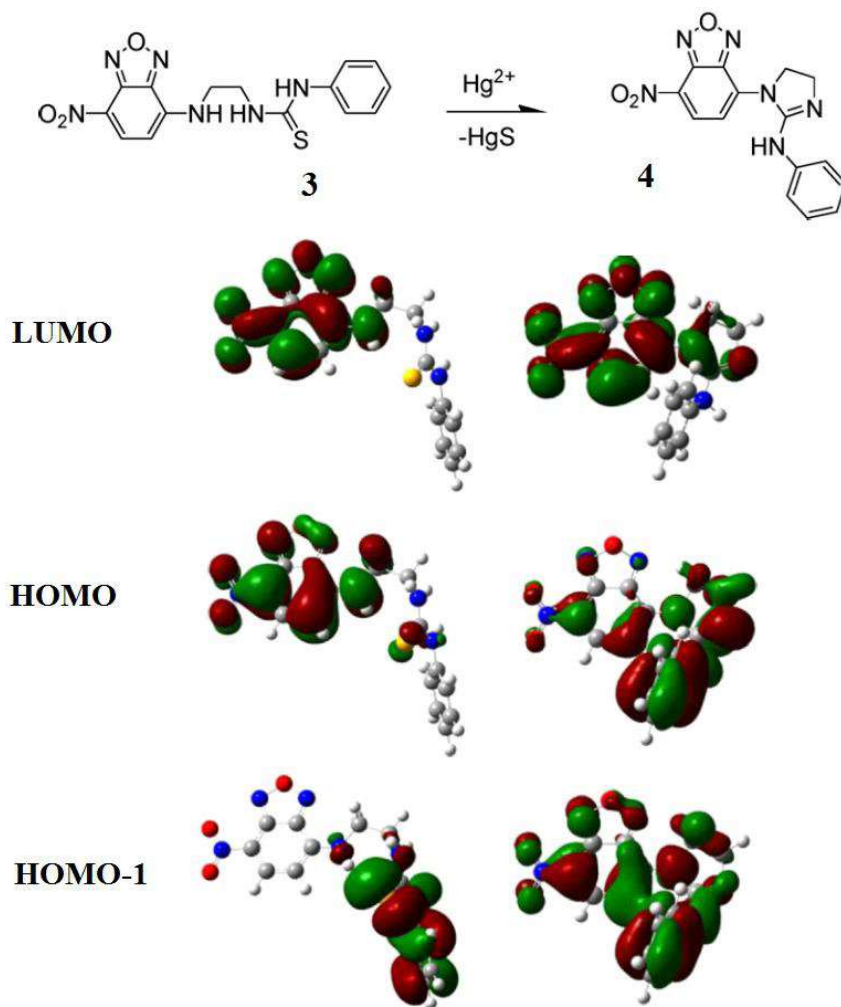


Figure 7. Sensor **3** and frontier MOs of sensor **3** and compound **4**.⁴⁴

For compound **4**, the $S_0 \rightarrow S_2$ transition is also the most dominant of the singlet electronic transitions from GS to ESs, with a greatest oscillator strength (f) of 0.333. This transition is mainly contributed by HOMO-1 $\rightarrow$ LUMO transition, with a largest contribution of 75.04%. The corresponding excitation energy is 2.80 eV (443 nm).⁴⁴ This calculation results are found to be in

good agreement with the experimental maximum absorption wavelengths of **3** and **4**, 468 nm and 462 nm, respectively.⁴⁴ In sensor **3**, the singlet electron transition from GS to ES takes place in two consecutive MOs (HOMO $\rightarrow$ LUMO), resulting in no PET process. Meanwhile, in compound **4**, the singlet electron transition from GS to ES takes place in two non-consecutive

MOs (HOMO-1 $\rightarrow$ LUMO), resulting in PET process.⁴⁴ The calculation results of frontier MOs of compounds (Figure 7) also show that, in sensor **3**, the electron density in HOMO and LUMO is predominantly distributed on the NBD moiety. Meanwhile, the electron density in HOMO-1 is predominantly distributed on aniline moiety. Therefore, the PET process from aniline to NBD subunits in the excited state does not

occur and sensor **3** is a fluorescent compound. In compound **4**, the electron density in HOMO-1 and LUMO is predominantly distributed on the NBD moiety, the electron density in HOMO is predominantly distributed on aniline moiety. Therefore, the PET process from aniline to NBD subunits in the excited state occurs, and **4** is not a fluorescent compound.⁴⁴

Table 1. Calculated excitation energy (*E*), wavelength (λ), and oscillator strength (*f*) for low-lying singlet state of sensor **3** and compound **4**.⁴⁴

Compound		Main transitions	<i>E</i> (eV)	λ (nm)	<i>f</i>	Percentage contribution (%)
3	$S_0 \rightarrow S_1$	HOMO-2 $\rightarrow$ LUMO	2.86	433.2	0.0059	8.64
		HOMO-1 $\rightarrow$ LUMO				88.31
	$S_0 \rightarrow S_2$	HOMO-1 $\rightarrow$ LUMO	2.91	426.7	0.2906	3.19
		HOMO $\rightarrow$ LUMO				72.27
		HOMO $\rightarrow$ LUMO+1				5.09
4	$S_0 \rightarrow S_1$	HOMO-1 $\rightarrow$ LUMO	2.34	530.4	0.0397	10.13
		HOMO $\rightarrow$ LUMO				86.37
	$S_0 \rightarrow S_2$	HOMO-1 $\rightarrow$ LUMO	2.80	442.8	0.3337	75.04
		HOMO $\rightarrow$ LUMO				5.35

The research results showed that there was a good agreement between the experimental and calculated absorption spectra.^{39-44,58} However, it is necessary to select methods, functions and basis sets for the research objects to obtain good results.

For example, there were different methods used to calculate excited states such as TD-DFT, BSE@GW, CIS, CIS(D), ADC(2), CC2, ADC(3), EOM-CCSD, CC3, EOM-CCSDT, SCI, FCI, EOMCCSDTQ, and CASPT2/NEVPT2 methods. Denis Jacquemin and co-authors performed a comparative evaluation of these methods.⁵⁹ Each method had its own advantages and limitations. Currently, the TD-DFT method is most commonly used because it is simple, suitable for large molecules,⁶⁰ contains many functions, so it can be improved by editing, or adding or subtracting functions.⁶¹

Duong Tuan Quang and co-authors used the PBE, BP86, PBE0, B3LYP, M06, M06-2X, CAM-B3LYP, LC-wPBE, APDF, wB97XD and PW6B9D3 functions to calculate the maximum absorption wavelength of 21 coumarin derivatives. The results showed that M06-2X functional gave the best predictive performance, with the smallest value of the mean absolute error (MAE_{fix} = 7 nm).⁶²

In summary, each method, function or basis set has its own advantages and limitations. They are usually only suitable for specific research purposes and objects. Therefore, it is necessary to evaluate when using, or verifying based on experimental data.

Theoretical investigations on the excitation processes based on optimized ground state geometry (GS) are mainly used to investigate singlet electron transitions from GS to excited

states (ESs), thereby predicting or explaining the absorption and fluorescence properties based on excitation process. This method does not directly study the singlet electron transitions from ES to GS. Therefore, the nature of the fluorescence emission process is not clarified, the fluorescence emission wavelength cannot be determined exactly. This is only solved when calculations on optimized geometries of excited states (ESs) are used to directly study the singlet electron transitions from ESs to GS.⁴⁸

Figure 8 shows the Jablonski diagram for calculation of excitation energy and fluorescence emission energy in a simple case. Accordingly, the vertical absorption energy ($E^{\text{vert-abso}}$) from GS to ES is the difference between the energy of ES and GS at the ground state optimized geometry (R^{GS}). The vertical fluorescence energy ($E^{\text{vert-flu}}$) from ES to GS is the difference between the energy of ES and GS at the excited state optimized geometry (R^{ES}).^{49,50}

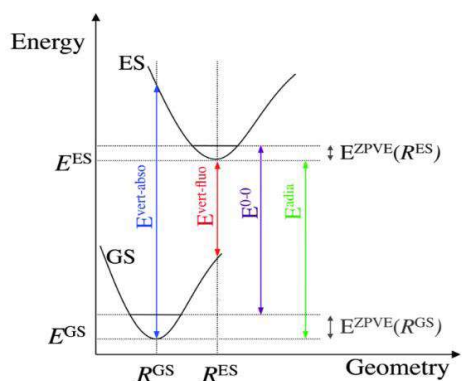


Figure 8. Jablonski diagram for calculation of excitation energy and fluorescence emission energy.^{49,50}

Nguyen Khoa Hien and co-authors introduced fluorescent sensor **5** for detection of biothiols (Figure 9). The results of the theoretical investigations on the electron excited states by TD-DFT method show that the fluorescence of the product of the addition reaction between sensor **5** and biothiols is not in accordance with Kasha's rule. This is an exception from the Kasha's rule. Fluorescence emission occurs from the higher lying singlet electron excited

state (S_2) instead of the lowest lying singlet electron excited state (S_1). This is because the electron transition from S_1 to S_0 is forbidden since the lack of overlapping between MOs in transition, and the small energy gap between S_2 and S_1 excited states. The fluorescence from the higher-lying singlet electron excited states leads to markable fluorescence enhancement at long wavelength in the products of addition reaction between biothiols and sensor **5**.⁴³

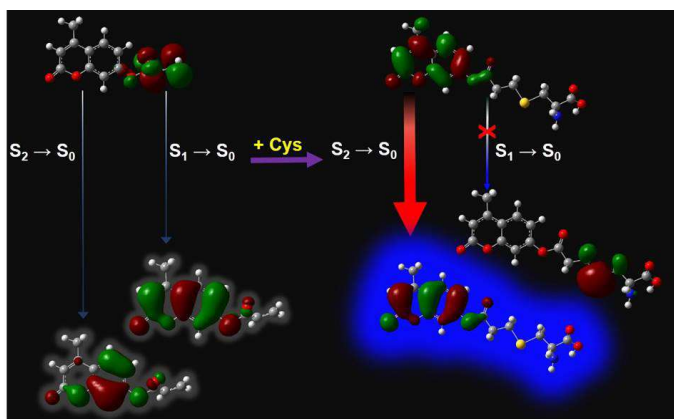


Figure 9. Sensor **5** for detection of bithiols based on coumarin derivative.⁴³

Caterina Bernini and co-authors investigated the excited state geometries and emission energies of 11 organic D- π -A dyes, with using the CAM-B3LYP, MPW1K, ω B97X-D, LC-BLYP, LC- ω PBE, and M06-HF functionals, in combination with the cc-pVDZ, 6-31+G(d,p), and 6-311+G(2d,p) basis sets. Polarizable Continuum Model was also performed in both LR and SS formalisms. The LR-PCM/TD-DFT results showed that accurate emission energies were obtained only when solvent effects and a range separated hybrid functional was used. The maximum mean absolute error of the vertical emission energy was 0.2 eV. The accuracy was further improved using the SS-PCM formalism.⁵⁶ According to this approach, some publications have successfully applied to investigate on the absorption and fluorescence spectra of compounds, as evidenced by a quite good agreement between theoretical calculations and experimental results.⁵¹⁻⁵⁵ However, calculation on optimized geometry of excited states is not simple. This requires an extremely strong configuration of computer system rather

than calculations on optimized geometry of ground state, especially for large compounds, complexes and in the environment of solvents. Therefore, up to now, the calculations on excited state optimized geometry are still very rarely published, and mainly used for small and simple compounds.⁵¹⁻⁵⁵

In addition, theoretical investigations on excitation processes are also applied to study the mechanisms of some other processes, such as the excited state intramolecular proton transfer (ESIPT),⁵⁶ twisted intramolecular charge transfer (TICT)⁵⁷...

Yang Li and Tian-Shu Chu used DFT and TD-DFT methods to study the excitation processes of fluorescent compound **6** (Figure 10). The calculated results on the optimized geometry and energy of the ground state and excited states show that there is an ESIPT process. Accordingly, compound **6** exists as an enol in its ground state. In the excited state, it converts to compound **7** in the keto form through an ESIPT process, resulting in a shift in fluorescence emission to the long wavelength region.⁵⁶

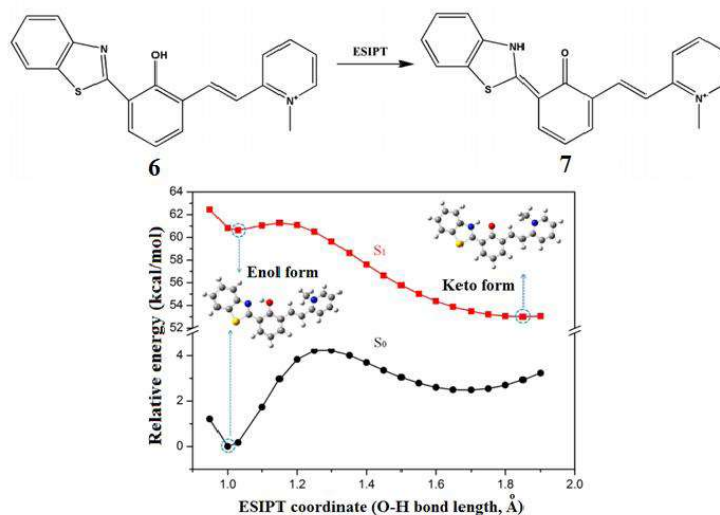


Figure 10. Theoretical investigation of an ESIPT case in fluorescent compound **6**.⁵⁶

When utilizing DFT and TD-DFT methods to study the fluorescence properties of 4-N, N-dimethylamino cinnamaldehyde (**8**), Surajit Ghosh and co-authors reported that, after being excited, compound **8** undergone the

twisted intermolecular transformation to reach a minimum on the potential energy surface (PES), accompanied by twisted intramolecular charge transfer (TICT), resulting in a transition from locally excited (LE) state to TICT excited state

(Figure 11). Due to the intramolecular charge transfer, the polarization of the TICT state was higher than that of the LE state. As a result, the TICT state was more stable than the LE state

in solvents of greater polarity. This led to a red shift in fluorescence emission and absorption, from weaker polar solvents to stronger polar solvents.⁵⁷

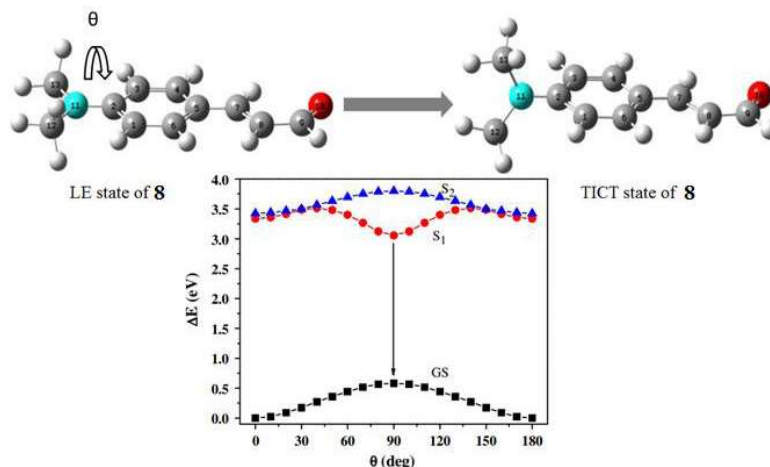


Figure 11. Theoretical investigation of an TICT case in fluorescent compound **8**.⁵⁷

Mai Van Bay and co-authors introduced fluorescent sensor **9** for detection of Hg(II) ions (Figure 12).⁴³ The DFT calculation results show that **9** molecule is composed of three moieties, in which ethylenediamine as a spacer is the bridge between rhodamine and dimethylamino-cinnamaldehyde (DACA). Rhodamine moiety in **9** exists in the spirolactam ring form and is not a fluorescent compound. Although the configuration of the DACA moiety in **9** is unchanged from the free state of DACA fluorophore, **9** is a non-fluorescent compound. This has been clarified when studying excitation states. TD-DFT calculation results show that

after being excited, the molecule **9** undergoes intramolecular twisting, accompanied by the process of the twisted intermediate charge transfer (TICT). As a result, there is a transition from the locally excited (LE) state to the TICT excited state. Consequently, the $S_1 \rightarrow S_0$ de-excitation occurs at TICT state. Unfortunately, the strong charge transfer in the TICT state leads to a complete difference in the localization of electron density, resulting in the lack of overlapping between HOMO and LUMO. The $S_1 \rightarrow S_0$ transition at TICT state is strongly forbidden. These may be the reasons why RLED does not fluoresce.⁴³

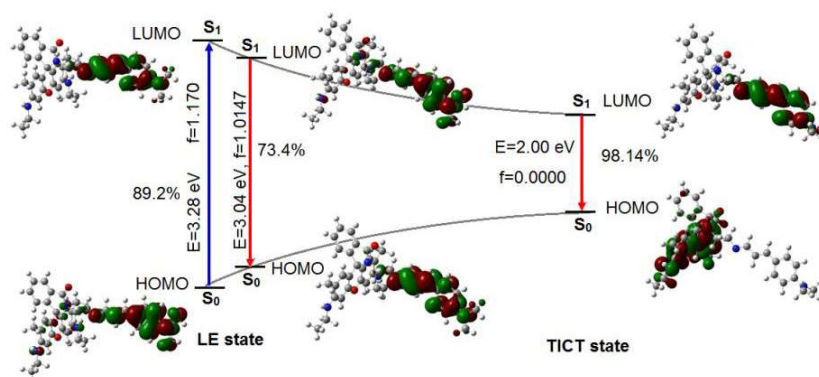


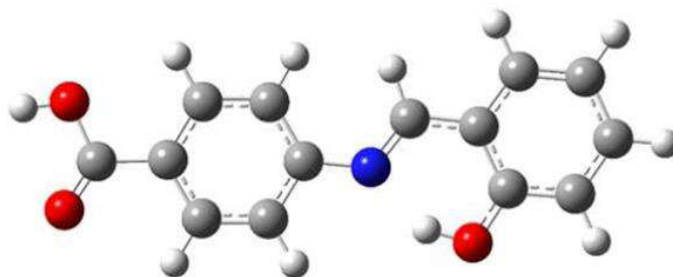
Figure 12. TD-DFT calculations used to explain the fluorescence properties of **9**.⁴³

c) Study of the structure, property and nature of interactions in compounds, absorption and fluorescence characteristics of compounds based on the natural bond orbital (NBO) analysis

When studying fluorescent sensors, a fairly common application of computational chemistry is the use of NBO analysis to investigate the structure, property and nature of interactions in compounds. The calculation results obtained from NBO analysis are mainly second-order interaction energy and charges of atoms in molecules. The second-order interaction in NBO analysis is the interaction between the NBO donor and NBO acceptor. The greater second-order interaction energy leads to the stronger interaction, the more stable bond, and the greater

degree of conjugation in the system. Therefore, NBO analysis is often used to investigate the degree of conjugation of the π electron system, thereby explaining the fluorescence properties, as well as comparing the durability of compounds based on the value of the second-order interaction energy.⁶³⁻⁶⁵

When studying a fluorescent sensor for detection of Fe(III) based on 4-(2-hydroxybenzylideneamino) benzoic acid (**10**), Gurpreet Singh and co-authors computed NBO analysis to study the fluorescence properties of compounds. The calculation results showed that there existed a π electron conjugation system in the molecule of sensor **10**. That caused sensor **10** to be fluorescent (Figure 13).⁶³



10

Figure 13. Fluorescent sensor **10** for detection of Fe(III).⁶³

When studying fluorescent sensor **11** used for detection of Cu(II) and Hg(II) (Figure 14), Yong Xia and co-authors conducted NBO analysis to investigate on the interactions in complexes between sensor **11** with metal ions including Cu(II), Hg(II), Zn(II), Cd(II), and Pb(II). The calculation results showed that the complexes were stabilized mainly by donor-acceptor interactions from lone pair (LP) of the O and N atoms to the empty LP* or RY* (Rydberg) orbitals of the central metal ions. In this case, the interactions from the LP of the N atoms to the LP* or the RY* of the metal ions were much stronger than the interactions from the LP of the O atoms. The calculation results also

showed that these interactions in Hg(II) complex were stronger than those in Cu(II) complex, and even stronger than in other complexes. As a result, the most stability was Hg(II) complex, followed by the Cu(II) complex, and then the other complexes. These results were completely consistent with the calculation results in which the Gibbs free energy of complexation reaction of **11** with Hg(II), Cu(II), Zn(II), Cd(II), and Pb(II) was -433.3, 386.9, 333.6, 276.7, and 236.6 kcal.mol⁻¹, respectively. These results led to the prediction that Hg(II) may react to displace Cu(II) from the complex between Cu(II) and sensor **11**. Therefore, sensor **11** could also be used to detect Hg(II).⁶⁴

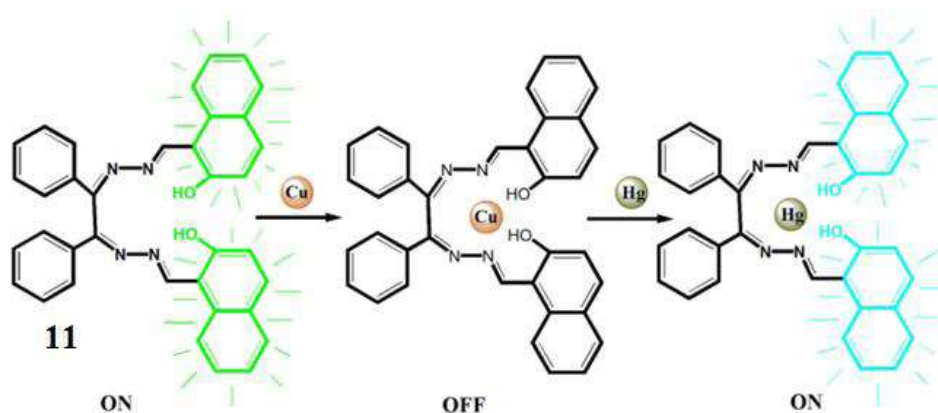


Figure 14. Fluorescent sensor **11** for detection of Cu(II) and Hg(II).⁶⁴

A fluorescent sensor (**12**) based on benzothiazolium hemicyanine derivative for Hg(II) detection was synthesized and studied by Doan Thanh Nhan and co-authors (Figure 15).⁴¹ Free sensor **12** exhibited a red emission at 585 nm. Hg(II) coordinated to ligand **12** with a stoichiometry of 1:1 and led to the fluorescence quenching. The detection limits of the colorimetric and fluorescent method are 15.3 and 11.8 ppb, respectively. The optimized molecular structures, absorption and fluorescence characteristics of the sensor **12** and its complex with mercury ions were carried out using the

calculations at the B3LYP/LanL2DZ level of theory, combined with Atoms In Molecules and Natural Bond Orbitals analyses. The NBO analysis results showed that the complex was stabilized mainly by donor-acceptor interactions from lone pair (LP) of the O and S atoms to the empty LP* orbitals of the central mercury atom. The formation of these interactions led to a significant transfer of electron density from ligands to the metal ions, and broke the π -electron conjugated system in the **12** ligands. This was an important factor leading to fluorescence quenching and color change in the complex.

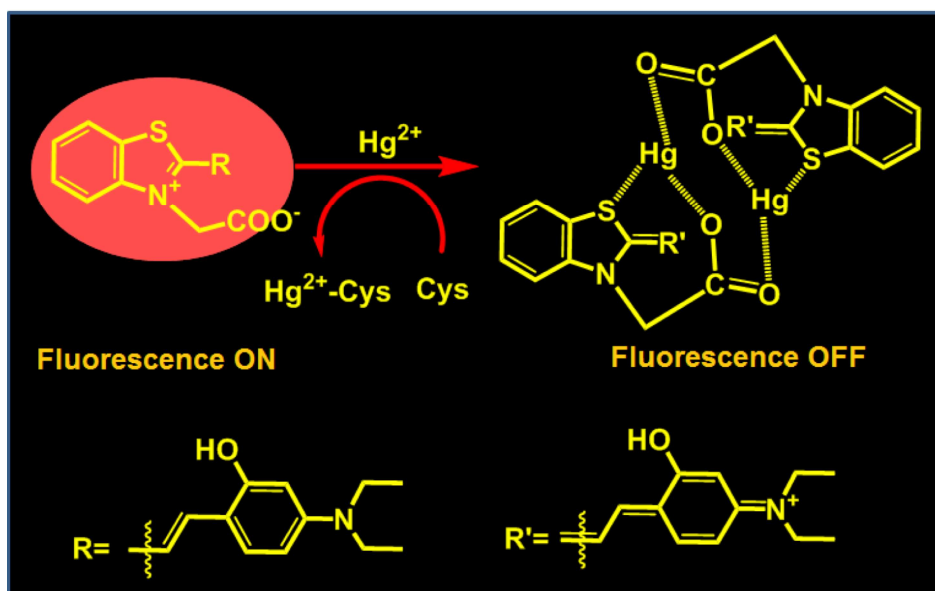


Figure 15. Fluorescent sensor **12** for detection of Hg(II) based on benzothiazolium hemicyanine derivative.⁴¹

d) Determine values of energy and constants for reactions based on the optimized geometries and the single point energies of the compounds

Sairam S Mallajosyula and co-authors used computational chemistry to study the mechanism of action of a 1,3-dithiole-2-thione-based fluorescent sensor (**13**) (Figure 16). The optimized geometric structures of sensor **13** and its complexes with metals and water were carried out using the DFT method and the B3LYP/LanL2DZ level of theory.

From these structures, the authors calculated the formation energy of complexes and determined the pathway of complex exchange reaction between $\text{As}(\text{H}_2\text{O})_3$ and ligand P (sensor **13**). The calculation results also showed that the formation of AsP_3 complex was more thermodynamically favorable than that of HgP_4 complex, with more negative formation energy of $-174.19 \text{ kcal.mol}^{-1}$. Since then, sensor **13** was predicted to be more selective detection of As(III), compared with Hg(II).⁶⁵

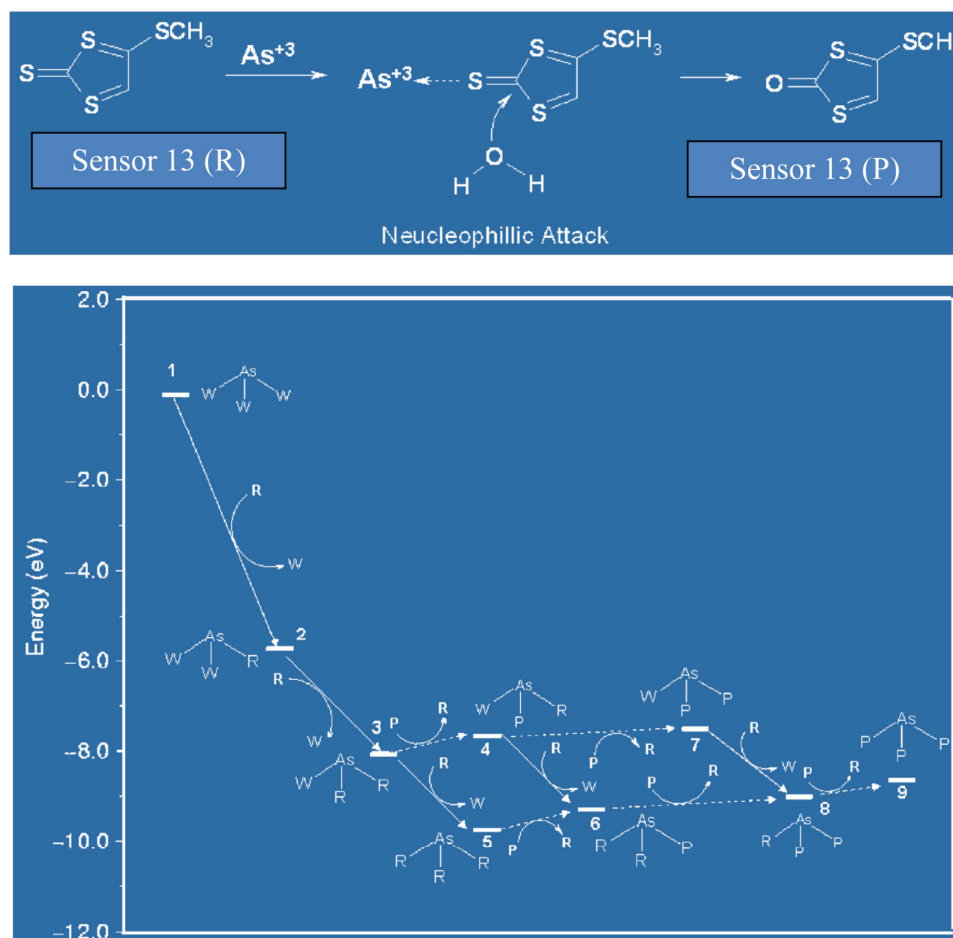


Figure 16. Theoretical investigation on mechanism of action of fluorescent sensor **13** (W: H_2O , R: reactant, P: product).⁶⁵

To investigate the possibility of using the complex between **14** and Cu(II) as a fluorescent chemosensor for detection of biothiols (Figure 17a), Nguyen Khoa Hien and co-authors used the theoretical calculations of the stability constant of complex.⁵⁸ Accordingly, the theoretical stability

constant of the complex was theoretically calculated based on the solvation model and the Gibbs free energy of ligand-exchange reactions, obtained from the thermodynamic cycle (Figure 17a). As a result, the calculated complexation equilibrium constant of 14-Cu(II) was $10^{7.16}$.

This value of complexation equilibrium constant of Cu(II) ions with **14**, was much smaller than of Cu(II) ions with biothiols. These results led to an expectation that the complex of **14** with Cu(II) ions could be used as a fluorescent sensor for detection of biothiols based on the complex

exchange reactions. The obtained results were in good agreement with the experimental data. The **14**-Cu(II) complex could be used as a fluorescent sensor for detecting biothiols in the presence of non-thiols containing amino acids, with a detection limit for cysteine of 0.3 μM .⁵⁸

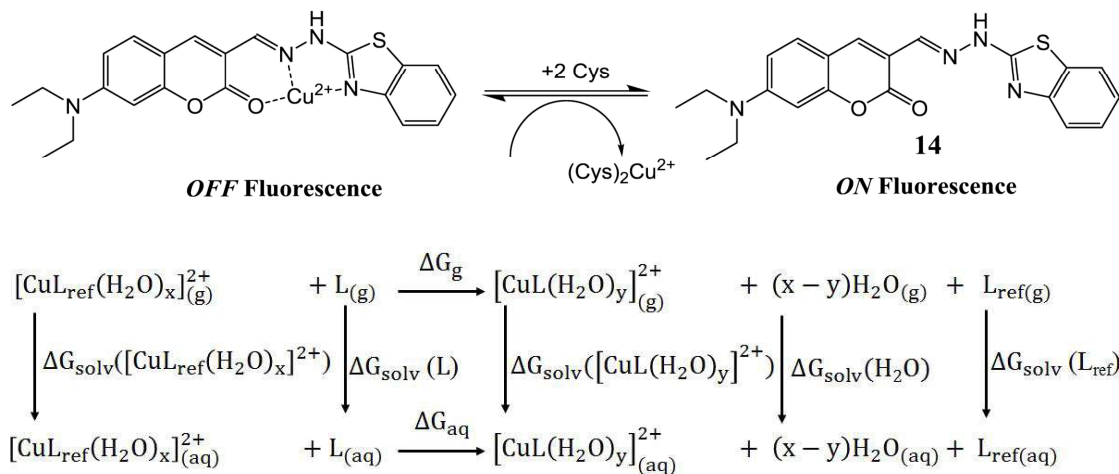


Figure 17. (a) Illustrative diagram of the reaction between the **14**-Cu(II) complex and Cys; (b) Thermodynamic cycle for the calculation of Gibbs free energy of ligand-exchange reaction in aqueous solution, ΔG_{aq} .⁵⁸

3. CONCLUSIONS

This review introduced the recently published quantum chemical computing applications in the development of PET-based fluorescent sensors. It was involved in the study of the structure, absorption, and fluorescence characteristics of compounds based on the calculations of the ground and excited states; the study of the structure, property, and nature of interactions in compounds, absorption and fluorescence characteristics of compounds based on the NBO analysis; and determination of energies and constants for reactions based on the optimized geometries and the single point energies of the compounds.

The results showed that quantum chemical calculations have been successfully used in the design and development of new fluorescence sensors, predicting as well as explaining the absorption and fluorescence properties of compounds. The calculated results are more significant when combined with experimental studies. This combination is to increase the

likelihood of success, reduce the volume of experimental study, and create the scientific basis to adjust and recommend appropriate calculation methods for next studies.

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