Theoretical model study of adsorbed antimalarial-graphene dimers: doping effects, photophysical parameters, intermolecular interactions, edge adsorption, and SERS

Zakir Ullah\textsuperscript{a,b,#}, Prasad M. Sonawane\textsuperscript{b,k}, Y. Sheena Mary\textsuperscript{c}, Y. Shyma Mary\textsuperscript{c}, Pratap Mane\textsuperscript{d} and David G. Churchill\textsuperscript{a,f}

\textsuperscript{a}Department of Chemistry, Molecular Logic Gate Laboratory, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Republic of Korea; \textsuperscript{b}Graduate School of Energy, Environment, Water and Sustainability (EEWS), Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Republic of Korea; \textsuperscript{c}Thushara, Kollam, Kerala, India; \textsuperscript{d}Seismology Division, Bhabha Atomic Research Centre, Trombay, Mumbai, India; \textsuperscript{e}High Pressure and Synchrotron Radiation Physics Division, Bhabha Atomic Research Centre, Trombay, Mumbai, India; \textsuperscript{f}Therapeutic Bioengineering Section, KAIST Institute for Health Science and Technology (KIHST), Daejeon, Republic of Korea

Communicated by Ramaswamy H. Sarma

ABSTRACT

Future diagnostics and therapy applications are in part riding on the discovery and implementation of new optical techniques and strategies (which often derive from dyads) for example, prediction of features in surface-enhanced Raman spectroscopy requires the study of chromophore-chromophore interactions involving intermolecular forces, drug delivery, and photo mechanisms which are of great interest. New matches between chromophore systems (i.e. FRET), and π-delocalized surfaces are important to study. We explore low-molecular weight drug molecules and their interaction with the reporter material/surface of graphene. Bonding, charge transfer and orbital interactions for \textit{2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole (megazol or AMIT)} on graphene were carried out. The graphene model substrate was monotonically/monatomically substituted (doped) with one neutral heteroatom (N/O/S/B) in place of one carbon center; chemical adsorption of AMIT is due to charge transfer from doped graphene to AMIT (DFT). Our AMIT-nanocluster studies show that the nanoclusters will act as a sensor component for the detection of drugs due to SERS. Our findings identified that the greater the energy of the charge transfer, the stronger the calculated chemical adsorption. Additionally, charge transfer is higher for the N-doped systems and least for pristine graphene, resulting in a stronger adsorption energy for \textit{N-doped graphene}. Mulliken charge analysis of structures confirms enhancement found in \textit{QD-AMIT} systems.

1. Introduction

During the period of 2020–2021 there has been a nearly unprecedented need to think about new biotechnological ways forward. Throughout human history, viral and other infections have resulted in millions of casualties.

Separately, apart from the acute needs in the COVID-19 era, cancer is the world’s fastest growing illness by the number of sufferers worldwide; many people are both diagnosed and treated for their cancers across the globe every year using molecular diagnostics and relevant drugs, respectively.

Furthermore, of importance, neglected tropical diseases are a group of roughly twenty diseases that, in tropical and subtropical countries, affect the poorest populations. Therefore, the quest for the discovery of novel antiviral agents, which are both highly active and less harmful, as resistance to available antiviral drugs and their technical implementation continues to define this as a global health challenge.

There is an inherent need that drives us and other researches to find new molecular scaffolds that are useful in molecular diagnostics, drug discovery and drug delivery and to assess how they interact with both biomolecules (receptors) and artificial/synthetic systems (Abdillah et al., 2021; Lee et al., 2020; Starzak et al., 2019; Yudhistira et al., 2020). Diagnostics often involves optical readouts such as fluorescence, phosphorescence or SERS; many new molecular systems have been prepared such as those which exhibit SERS. Chemotherapy-administered medications have a narrow therapeutic index, (T. I. = ‘a quantitative measurement of the relative safety of a drug’) that induces drug resistance so that there is a high occurrence of unintended side effects (Çevik et al., 2020).
In heterocyclic chemistry, the thiadiazole ring is a crucial group that sets up a pharmacological context in medicine. Many medications contain thiadiazole as an active ingredient (Tang et al., 2016). The biologically influential compounds of 1,3,4-thiadiazole derivatives also possess a number of biological activities (Bekhit et al., 2019). Whereas antibiotic cefozopran is the only commercial 1,3,4-thiadiazole medication, a number of thiadiazoles with extensive biological activities are available (Demirbas et al., 2009). Megazol is such a thiadiazole-based drug; also, it is a nitroimidazol which in the initial stage, as in the chronic one, turns out to be generally successful in combating American Trypanosomiasis or Chagas Disease and the African disease, better known as sleeping disease. These two illnesses are both of considerable concern on the American and African continents. Due to their important therapeutic potential, thiadiazole derivatives have attracted considerable attention as a privileged scaffold (Chhiakara et al., 2019). Closely related derivatives have also been studied with relevance to drug discovery. Pund et al. (2020) recently discussed the synthesis of thiadiazole derivatives and their biological activity (Liu & Zhu, 2011). Certain chemical feature and functionalities often take precedence in drug discovery designs. Thiadiazole aromacity has a profound effect to help impart a lower toxicity to the heterocycle and also to impart in vivo stability (Serban et al., 2018). Of the bonds found in living systems, the amide bond is one of the most prevalent chemical bonds and plays an important role in the intricate construction and cycling of biological systems; it is usually found in major medicines, organics and biomolecules (Brown & Bostrom, 2016).

Several biologically active 1,3,4-thiadiazole analogues have been reported to-date (Bekhit et al., 2008; Yavari et al., 2020). Nitroimidazoles are major nitrogen heterocyclic compounds reported that exhibit various biological activities (Cao et al., 2021; Li et al., 2019; Liu & Zhu, 2011). Azomycin (2-nitroimidazole) has been used as an intermediate platform to produce several nitroimidazole-based drugs as primary synthetic precursors. Metronidazole, secnidazole, tinidazole, ornidazole, satranidazole, benzimidazole, pretomanid, delamanid, megazol and fexinidazole are all azomycin-derived nitroimidazoles. Infections caused by drug-resistant bacteria, tuberculosis, protozoal infections, etc., are treated with these agents (Eseola et al., 2011; Nepali et al., 2019). The chemical composition of antibiotics such as megazol, metronidazole, and benzimidazole, ascomiconazole, and ketocconazole as antimicrobials, antiprotozoans and antifungal agents all include imidazole rings (Kamal et al., 2020).

In preclinical studies, megazol, an imidazole-thiadiazole derivative, has remarkable efficacy and it is of interest. Naturally occurring and synthetically-obtained substances, have various effects as therapeutics, antibiotics and as alkaloids (Gür et al., 2020). Since their various effects emerged, nitrogen containing systems made considerable progress in different chemical and medicinal fields (Singh et al., 2020).

In the experimental treatment of various animal models, AMIT also showed great efficacy (Santiago et al., 2020). Matwijczuk et al. reported the stationary fluorescence spectroscopy and time-resolved spectroscopy studies of thiadiazole analogs in aqueous media containing different concentrations of hydrogen ions (Matwijczuk et al., 2017). Non-typical fluorescence effects and biological activity in thiadiazole derivatives are reported by means of spectroscopic, TD-DFT methods and antioxidative data obtained by calculations (Budziak et al., 2019).

In terms of photochemistry, the consideration of how chromophores can stably interact, and how photomechanisms play a large part in determining the viability of light-based therapies as well as which optimal detection mechanisms paves ways for a new angle of chemical and biological/medical research.

With the great research thrust into the use of graphene, there are certain main molecules recently being used in conjunction with graphene in particular in a new mode of monolayer surface chemistry.

It is good to help match the optical potential of graphene with molecules that are smaller and drug related. In terms of the base surface substrate, in recent years, nanoscience has offered a variety of constructs with which to work and use as substrates. Along with nanomaterials such as nanoparticles, nanotubes, nanowires and nanosheets, biomolecules provide specific characteristics that have synergistic effects for the tasks at hand (Emanet et al., 2015). Graphene nanosheets have attracted growing attention among various types of nanomaterials due to their characteristics (Kemp et al., 2013). In addition, variations of graphene are allowed to pass through biological membranes and has a wide surface area that attracts further interest. As a result of their ability to adsorb higher concentration of drugs, graphene is used as a drug delivery system (Ali-Boucetta et al., 2013). Kamel et al. have theoretically reported amino acid interactions with graphene (Kamal et al., 2020). With the interest in calculating graphene, there are also many ways to model the graphene such as using a smaller version of it in calculations.

Recently, a number of studies on adsorption on graphene sheets have been reported by us (Almuqrin et al., 2021a; Al-Otaibi et al., 2020; Leenaerts et al., 2008; Mary et al., 2020). DFT studies have recently focused on the effect of impurities on the structural, electronic, optoelectronic, and nonlinear optical properties of the carboxyl group functionalized graphene nanosheets (Mary et al., 2020). Due to its novel mechanical properties, graphene is among the most promising of nanomaterials for structural applications (Al-Otaibi et al., 2020). Graphene and its modified forms seem to extend conceptually to different applications in energy and biomedical fields (Tran et al., 2020). Nanomaterials based on graphene and related groups are efficient adsorbents for removal of various types of industrial effluent and sewage pollutants (Ghahghaey et al., 2021). N-doped reduced graphene oxide filters have been developed and applied by Liu et al. to help remove various selected organic pollutants through catalytic oxidation and physical adsorption (Liu et al., 2016). For example, Shanmugam et al. studied adsorption of ions on doped and defective graphene (Shanmugam et al., 2020). In these materials, the band gap was found to be able to be altered by different heteroatoms such as boron, nitrogen,
sulfur, and phosphorus; the Fermi levels can be adjusted by controlling dopant atom concentration (Ma et al., 2016). The doping of B and N atoms are naturally used due to their atomic sizes which are found to be quite close to that of C atom. The N and B atoms act as a hole-donor and an electron-acceptor, respectively (Duan et al., 2015). In carbon materials research, sulfur atom doping is still quite rare and represents an emerging field as the electrondetracting nature of sulfur results in a larger band gap and helps enrich the inherent properties of graphene (Zhang et al., 2016). Al-Otaibi recently reported adsorption of benzodiazepine systems with graphene (Al-Otaibi, 2020). Due to their pharmacological profile, physicochemical and pharmacokinetic properties, 1,3,4-thiadiazole derivatives have been extensively studied as adsorbant molecules (Calborean et al., 2017; Cuevas et al., 2017; Serban, 2020; Shi et al., 2012; Zhang & Wang, 2019). The intermolecular interactions of various molecules with various versions of graphene (doped and undoped) have also been determined as well (Rodríguez et al., 2020).

Ultimately, the important interactions relate to a certain set of intermolecular interactions; they are found to be important for the surface and adsorbed molecule to achieve a thermodynamically stable pair and an effective and useful optical readout. Interactions of molecules involve engaging of molecular forces such as hydrogen bonding in which hydrocarbon groups may also participate in C-H-X interactions, as well as \( \pi-\pi \) stacking, in which two flat molecules are coming into contact face to face.

In the present work, interaction and adsorption studies of megazol (AMIT) with both substituted and unsubstituted (doped and undoped) model graphene sheets are studied theoretically. This study is a proof of principle theoretical report and relates to what might be possible spectroscopically in future reports. In the flat AMIT molecule, there is a central rotatable bond and also a secondary rotatable bond of C-N bonds. Interactions of interest are thought to occur more at the edge of both molecules with parallel \( \pi-\pi \) stacking interactions being of lesser importance for the time being.

2. Computational methodology

Theoretical computations which are growing routine in the chemical sciences were used and have allowed us to explore a range of molecular conformations with our molecules of interest, namely, between the two rigid \( \pi \)-delocalized molecules: the QD graphene ‘surface’ molecule, and the AMIT adsorbent molecule. In modeling AMIT on QDs, all the structures are optimized independently (Figures S1–S3); then, the true minima were confirmed by carrying out frequency calculations which revealed no negative frequencies. To find AMIT-QD interactions, initially, AMIT is placed carefully in a parallel position with the surface of a well-defined flat QD, the wB97x-D/6-31G* level of theory was used with Gaussian 09 (Frisch et al., 2013) and Gaussview (Dennington et al., 2009). The adsorption energy (\( E_{ads} \)) of AMIT-QD derivatives is using that calculated geometry as in the method Almugrin et al. (2021b). Using the PBE-GGA code in VASP (Kresse & Hafner, 1993, 1994), further simulations where then carried out. In order to describe the weak Van der Waals forces, the Grimme DFT-D2 dispersion was incorporated (Grimme, 2006).

3. Binding and geometrical details

3.1. Binding interactions within the nanocluster-drug assembly

Computations allowed us to explore a number of single atom substitutions in the graphene ring. The selection of an internal C atom in the graphene model was made; it needed to be replaced by a neutral \( X \) atom (\( X = B/N/O/S \)). This substitution was made for novelty, to avoid graphene planar distortion and to help retain QD functionalized edges; hence, the atom in position 8 which is central in the coronorone-like molecular model fragment was chosen for replacement. Chemical substituents can be placed sensibly at the edges so to have hydrogen bonding edge-edge interactions. Assessing the geometries between the two rigid \( \pi \)-delocalized molecules, therefore, involves (i) the QD graphene, and (ii) one AMIT molecule which are able to become in contact in different ways. Figure S2 displays the optimized graphene and carboxylate group (COOH)-functionalized graphene (QD) geometries, as the doped and undoped versions. The widths of QD derivatives are found to extend from 1.35 to 1.37 nm, enough of a ‘landing strip’ to allow for realistic AMIT adsorption modelling; if we want to consider a face to face interaction, a single AMIT (0.96 nm separation) was placed parallel to each QD derivative.

C-C bond lengths in the QD were found to be on the order of \( \sim 1.43 \) Å (Feng et al., 2017); when \( X (X = B/N/O/S) \) is present as a dopant in the QD, a surface distortion is observed with a shift in C-X bond length. In the current case, the bond lengths (C-X) (Å) were found to be 1.42, 1.33, 1.43 Å for AMIT-QD-G, 1.43, 1.43, 1.42 Å for AMIT-QD-COOH, 1.53, 1.51, 1.50 Å for AMIT-QD-B, 1.43, 1.42, 1.42 Å for AMIT-QD-N, 1.49, 1.50, 1.56 Å for AMIT-QD-O, and 1.85, 1.88, 1.85 Å for AMIT-Q-D derivatives, accordingly, and different from those of QDs (Rad, 2015).

The C-X-C bond angles about the included heteroatom (X) in the assemblies are (°), 120.3, 120.0, 119.7° for AMIT-QD; the values were found to be 120.2, 120.5, 119.3° for AMIT-QDCOOH; the values are 120.1, 120.2, 119.7° for AMIT-QDB; the values were found to be 121.5, 120.0, 118.5° for AMIT-QDN; the values are 120.3, 118.6, 121.0° for AMIT-QDO; the values were determined to be 100.2, 99.3, 99.1° for AMIT-QD-S, different from those of other previously reported QDs (Wuest & Rochefort, 2010). For QD-S, the C-S bond length is larger due to the geometric distortion similar to other QDs in which S atoms can be found above the nanocluster plane (Figure S2).

3.2. End-on interactions of molecule on doped graphene

Next, we introduced AMIT molecules in the calculations with the doped graphene sheet and allowed it to relax geometrically. As we have considered 2D graphene with a periodic
boundary condition, we have introduced the molecule structurally above the dopant, at a distance of ~2.5 Å, oriented perpendicular to the graphene sheet. With the AMIT parallel to the QD surface, there will most likely be a greater degree of interactions between the two molecules. Figure S5(b) displays the relaxed structure of QD-N-AMIT. AMIT is absorbed on QD-N; the stabilization is due in part to charge transfer. Figure S7(a) shows the PDOS for the 2p orbital of the isolated N and graphene + N+AMIT systems. Similarly, Figure S7(b) displays PDOS for 2p orbital of the Q (QD-G carbon 2p orbital, QD-N-AMIT; in AMIT for isolated AMIT and AMIT adsorbed onto QD-N). We observe that there is enhancement in the electronic states for the O 2p orbital of AMIT compared to that of the isolated AMIT molecule. This indicates as expected that there is charge gained by the AMIT due to interactions with the N doped graphene. From the Bader charge portioning, an 0.18 e charge is transferred from N doped graphene to the AMIT molecule. The charge transfer to the molecule for the QD-G and the QD-COOH in a nearly parallel way; the AMIT NO2 group position found to be proximal to the QD hydrogen. Whereas for all other QDs, namely the NH2 group of the AMIT molecule is proximal to the -COOH group of the QDs. In all cases, AMIT is near to the QDs in a horizontal side-by-side fashion as depicted in Figure 2.

Adsorption energies were also able to be determined. This was done by subtracting the sum of individual calculated energies for AMIT and QDs from the total energy of the combined nanocluster system: the QD adsorbed AMIT cluster. The energies of the AMIT adsorption over QDs is provided (Table S1). The AMIT adsorption energy was found to be highest for QD-N (~–14.61 eV) and lowest for QD-G (~–10.62 eV). For other QD sets, it was found within the range of ~–13.0 and ~–14.0 eV (Kumar et al., 2014).

Our geometry and energy calculations also allow for an analysis of the intermolecular distances and angles that exist within these clusters. The distance from one atom of one molecule to the nearest atom of the second molecule is one simple metric to help us identify the type and degree of intermolecular forces at play. In AMIT-QD-G adsorption, the O(NO2)H(graphene) distances are 2.57 and 2.54 Å, whereas with QD-COOH adsorption, these O(NO2)H(graphene) distances are 2.54 and 2.57 Å, favorable for intermolecular interactions between AMIT and QDs. The AMIT-QD derivate (B/N/O/S) systems were also analyzed: the H(NH2)O(C–O) and N(thiazole)H(OH) distances are 1.76 and 1.62 Å for QD-B; the distances are found to be 1.72 and 1.67 Å for QD-N; the distances are found to be 1.75 and 1.59 Å for QD-S systems with the hydrogen deprotoxonated from the OH group due to the favorable interaction that was created between AMIT and QD-S (Figure 2). But for QD-O systems, no such detachment is seen and H(NH2)O(C–O) was determined to be 1.84 Å.

3.4. Structural details for QD-AMIT nanocluster systems

As already mentioned and described, our surface science study uses a small coronene molecule serving to model the infinite graphene plane but that which is edge functionalized. The molecular plane is shown to be discretely chemically doped (substituted) by one neutral non C heteroatom; we have constructed a model of doped graphene bearing a neutral N, S, O, or B atom. The discrete non-infinite quality of the graphene model required there to be boundary functional groups at its periphery for good measure; this boundary helps fashion the graphene model into a QD, and that which has solubilizing groups too that can interact with the drug molecules at the edge on one side and with water as the solvent molecules on the other (in practice). As part of the 2D graphene sheet with its outer boundary, we included discrete carboxyl (COOH) groups on the edges, again signifying the boundary of the quantum dot which is thus different and conjugates in this in study possess inhibitory effects against these selected receptors.

After geometry optimizations were performed, AMIT was found to undergo intermolecular interaction with the different fragments. These different structures were geometry optimized. The AMIT becomes adsorbed at the edges of the QD-G and the QD-COOH in a nearly parallel way; the AMIT NO2 group position found to be proximal to the QD hydrogen. Whereas for all other QDs, namely the NH2 group of the AMIT molecule is proximal to the -COOH group of the QDs. In all cases, AMIT is near to the QDs in a horizontal side-by-side fashion as depicted in Figure 2.

Drug delivery mechanisms were created to improve the therapeutic characteristics of pharmaceuticals and to make them more successful in releasing drugs in a controlled manner at specific locations. As a result, they have an impact on drug distribution (Liu et al., 2012; Vashist et al., 2011) and a range of other parameters. Drug carriers with nanostructure and atomic contact energy values of 39.22 and 39.13 27.32 kcal mol–1 for 5IPO with 5JYH PDBs. Such findings help identify that the drugs and conjugates in this in study possess inhibitory effects against these selected receptors.
and is in practice helping with solubility; the otherwise fully H-substituted coronene parent molecule would be expected to be extremely insoluble. Each structure was calculated and allowed to relax geometrically according to the in silico instructions. The resulting structure of N-doped (substituted) graphene is displayed in Figure S5(a).

There is a change in C–C bond length of pristine graphene when doped. The bond length is longer for the sulfur doping; C–S bond lengths in this case equal 1.62 Å, marking the structure as undergoing bond elongation relative to C–C bond lengths. This will impart a geometric distortion rendering the $p$-delocalization at the graphene surface uneven. There is not much change e.g. in the C–N bond lengths; N, after all, has an atomic number and atomic radius closer to that of the neighboring C which is the native atom.

4. Electronics and optical studies

4.1. Electronic property prediction for QD-AMIT nanocluster systems

To help obtain insights about the electronic properties of doped graphene based on our model systems and results obtained, we also completed the computed PDOS values. Figure 5(a) displays the PDOS for the S 3p orbital of the isolated S (Figure 5a, upper panel) of the S doped graphene and the AMIT molecule held to the S doped graphene model (Figure 5a, lower panel). When S is doped on graphene, there is a reduction of electronic states near the Fermi level for the S 3p orbital, compared to that of an isolated S center. This depletion of electronic states (decrease in band gap) signifies the possibility of a charge transfer mechanism from the S 3p orbital to the C 2p orbital. Figure 5(b) shows the PDOS for C 2p orbital in QD-G, QD-S and QD-S-AMIT. For pristine graphene, we obtained a V-shaped density of states (DOS) graph with zero states found to be at the Fermi level, signifying the graphene derivative exhibits a semi-metallic quality/nature, as expected. When S is the graphene dopant, there is enhancement of electronic states near the Fermi level indicating charge gain by C 2p orbital from the S 3p orbital. The presence of electronic states at the Fermi level for the S-doped graphene indicates metallic character which matches reported DOS profiles from the literature such as that found in article(s) by Lu et al. (Lu et al., 2017).

To confirm the qualitative charge transfer displayed by the PDOS plot, we have performed quantitative Bader charge analysis (Figure 4) (Arnaldsen et al., 2011). As per the Bader charge partitioning, a 0.44e charge is able to be transferred from S to the (doped) graphene model sheet. For O and N doping, the charge transfer is originating from the graphene to the 2p orbital of either the respective O or N atom. This is because O has 4 p electrons and N has 5 p electrons in the outer shell. O and N tend to gain charge in order to fill the outer shell. According to Bader charge partitioning, 2.72e of charge is gained by N; the 1.26e charge gets transferred to the O center. The charge transfer for B and COOH doping is displayed in Table S6. For the doping of the O on graphene,
enveloping AMIT except for its CH₃ group, whereas the LUMO level is present with extensive coverage for the QD-N system. In the QD-O-AMIT cluster, the HOMO and LUMO levels are covering the QD-N system except for the COOH group which is distal from the AMIT molecule in the LUMO level and in the QD-S-AMIT system. In the QD-N-AMIT system, the HOMO and LUMO levels are found to be over the QD-N, except for the COOH group found proximal to the AMIT molecule which is covered by the HOMO level distribution.

The HOMO-LUMO gaps (Table S2) of AMIT over QDs are found to be decreased relative to the pristine value (3.5 eV) with the smallest value being for QD-B (0.3) and the largest value being for QD-G (1.7). This change, effected by one heteroatom, could at first be thought of as a simple bathochromic shift. There are large changes in the band gap of the AMIT region and seen for all QD calculations, which reveals evidence for charge transfer. The chemical potential of AMIT (−4.8 eV) doped with QDs becomes more negative, seen as a maximum for QD-B (−7.6 eV) and a minimum for QD-N (−6.5 eV); electrophilicity values are also very high, ranging from 25.6 (QD-G) to 199.6 (QD-B) (6.7 for AMIT) which support the bioactivity of the clusters to serve as a nano-drug carrier (Mary et al., 2018).

4.3. Mapping electrophilic and nucleophilic regions

In the molecular electrostatic potential map (MEP) (Figure S4), the electrophilic and nucleophilic regions become evident and can be distinguished graphically by color-coding as red and blue regions, respectively (Kumar et al., 2020). Red indicates the existence of a negative potential to which positive charges will be attracted. In all the chemical systems, the oxygen atom centers are electrophilic and N and H atoms are nucleophilic. Taking the charges of the doped atoms in QD-AMIT derivatives (B/N/O/S) into account now, B becomes more positive; the remaining other centers (N/O/S) become more negative with respect to charge distributions present in the QD. For AMIT adsorbed onto QDs, the N4 and N9 atom positions

| Compound      | UV absorption (nm) | Oscillator strength | LHE | ΔG_{inject} |
|---------------|-------------------|---------------------|-----|-------------|
| AMIT          | 324               | 0.6229              | 0.7617 | −3.39       |
| QD-G-AMIT     | 429               | 0.9186              | 0.9793 | −2.30       |
| QD-COOH-AMIT  | 435               | 0.7167              | 0.8080 | −11.75      |
| QD-B-AMIT     | 1257              | 0.0059              | 0.0135 | −50.12      |
| QD-N-AMIT     | 841               | 0.0013              | 0.0030 | −52.71      |
| QD-O-AMIT     | 573               | 0.0028              | 0.0065 | −36.80      |
| QD-S-AMIT     | 1026              | 0.0047              | 0.0108 | −47.31      |
| QD-D-AMIT     | 623               | 0.1132              | 0.2295 | −16.13      |
| QD-COOH-AMIT  | 512               | 0.0444              | 0.0971 | −6.18       |
| QD-S-AMIT     | 546               | 0.1615              | 0.3105 | −12.20      |

Table 1. Calculated DSSC properties for the compounds and clusters under present study (Kaur et al., 2012; Mary et al., 2015).

Figure S6 depicts the PDOS for O 2p orbital for the isolated O (upper panel), O doped graphene and AMIT on the O doped graphene (lower panel). Figure S6(b) shows the C 2p orbital for QD-G, the O doped graphene and AMIT on the O doped graphene. Since one O atom is being used as the dopant within a small version of a graphene sheet, there is not much of an increase in the band gap. The opening of the band gap would therefore increase with increasing number of O atoms incorporated into the graphene layer (Mary et al., 2011; Nasehnia & Seifi, 2011).

4.2. Frontier molecular orbitals and observed chemical properties

We next explored a frontier molecular orbital analysis (FMO) (Figure 5) of AMIT over QDs to help clarify the binding affinity between AMIT and QD derivatives. In the QD-AMIT systems, HOMO and LUMO level distributions are delocalized differently for all derivative systems resulting in a charge transfer and different enhancements due to adsorption. For the AMIT molecule, the HOMO and LUMO levels are particularly distributed all over the entire molecule except on the [S] and [CH₃] groups in the HOMO plot. For QD-G-AMIT and QD-COOH-AMIT systems, the HOMO level is enshrouding the AMIT molecule, whereas the LUMO level is covering QD-G. For QD-B-AMIT, both the HOMO and LUMO levels are blanketing the whole molecule except for the CH₃ group, a situation that involves polarity changes; In QD-N-AMIT, the HOMO is
receive more charge, whereas all other charges are observed to decrease (Table S3). QD oxygen atoms in the COOH group proximal to AMIT also show significant charge variations; the oxygen atoms of COOH, directed away from AMIT, show slight variations only. The oxygen atom charge in the carboxylic group remains almost the same as in the nanoclusters, whether there is a drug molecule adsorbed or not. The Mullikan charge values confirm the enhancement.

4.4. Blue shifting quantified and light harvesting efficiencies

The UV-vis spectroscopic absorption (Table 1) of AMIT (324 nm) is found to be blue-shifted in all QDs-AMIT nanoclusters with high values obtained for all B/N doped clusters (1257, 841 nm for QD-B-AMIT, and 1026 nm for QD-N-AMIT) (Figure 4). For QD-B/O-AMIT, absorptions have three and

![Figure 3. Calculated UV spectra of AMIT, QD-GAMIT, QD-COOH-AMIT, QD-B-AMIT, QD-N-AMIT, QD-O-AMIT, and QD-S-AMIT.](image-url)
two values, respectively. Light harvesting efficiency (Table 1) was found to be maximum for QD-G-AMIT and QD-COOH-AMIT systems which is more than that for AMIT itself, whereas for other QD-AMIT systems, however the value of this property is low. Also, the free energy of electron injection used for the design of DSSC photosensitizers (Table 1) showed that, for the AMIT systems, the values are high for GQ-B/N systems (Kumar et al., 2020).
4.5. Hyperpolarizability values and NLO values

First-order hyperpolarizability of AMIT-QD derivatives is found to be greater than that of AMIT (29.7 \times 10^{-30} \text{ esu}) except in the case of QD-N (17.1 \times 10^{-30}). A large enhancement of second hyperpolarizability of all AMIT-QDs show high values pertaining to NLO properties (Table 2). The polarizability also shows enhancement (Arnaldsen et al., 2011; Mary et al., 2011; Nasehnia & Seifi, 2011). The polarizability changes HELP enhance the hyperpolarizability values which are clearly seen in the vibrational mode readout. The theoretical IR spectra were calculated and also provided in the supporting material. As seen from the IR and Raman spectra, different modes at 1547, 1478, 1203, 1180 and 1089 cm^{-1} observed in Raman spectra have their counterparts in the IR spectra; their intensities are comparable which is due to the polarizability changes in the molecular systems (Arnaldsen et al., 2011; Mary et al., 2011; Nasehnia & Seifi, 2011).

4.6. The SERS mechanism of QD-AMIT nanoclusters

Finally, for the identification and investigation of a low amount of species (specificity and drug deliver), signal enhancement in spectroscopy is critical and it was attempted to be assessed. The surface enhanced Raman scattering (SERS) approach is commonly employed in Raman spectroscopy, allowing for an incredible scaling down to enable even single molecule identification (Canamares et al., 2008). It was observed that graphene with a covalently bonding dopant atom scan provides significant enhancement of the Raman signal; the existence of graphene-enhanced Raman scattering (GERS) was therefore established (Ling et al., 2012, 2013). SERS and GERS can contribute together to produce a molecular Raman signal (Sutrova et al., 2018; Vales et al., 2020) the use of doped graphene for improving and detecting molecules using the Raman signal has been demonstrated (Ketano et al., 2021). Sulfur, nitrogen, oxygen and boron atoms doped into a graphene model system can have a significant impact on graphene features, as well as function and adsorption properties. Figures S9–S15 feature Raman and SERS spectra of AMIT and AMIT with QDs. For all QDs, there is an increase in intensity for different modes of AMIT (Table S7). For QD-N-AMIT, the maximum enhancement is observed, supported by the highest adsorption energy. For QD-G/COOH-AMIT systems, NO\textsubscript{2} vibrational modes, 1478 and 1209 cm\textsuperscript{-1}, observed for AMIT are present in the enhanced spectrum at 1458, 1203/1463, 1203 cm\textsuperscript{-1} with high enhancement and a red shift in wavenumber (cm\textsuperscript{-1}). For all other systems i.e. (with B/N/O/S), NH\textsubscript{2} modes are enhanced with shifts in wavenumbers and enhancements in intensities. This shows that QDs nanoclusters will act as a sensor for detection of drugs through a reporting that includes SERS signaling.

5. Conclusion

The dyads under study have shone light in a theoretical way on what is possible with graphene quantum dots and an important drug class represented by 2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole (megazol or AMIT). Chemical adsorption of (megazol or AMIT) on closely related versions of graphene models were carried out, which are formally and centrally doped (single atom replacement) wherein one heteroatom has been exchanged for one C. These systems have been investigated through a range of DFT simulations and related calculations. AMIT is strongly adsorbed onto N doped graphene due to charge transfer to AMIT from N-doped graphene. Enhancement is found to be in the Raman spectra for all QDs-AMIT nanoclusters. QDs-AMIT UV spectra show a shift towards higher wavelength. At the adsorption of AMIT, the band gap in the QD-AMIT derivatives is reduced significantly. Docking and other results suggest that QDs are suitable for drug detection. From SERS results, it can be concluded that QD-based nanoclusters will act as sensors for detection of drugs such as AMIT and possibly as a delivery vehicle platform for drug molecules as well.

Acknowledgements

D.G.C. acknowledges financial support and resources from KAIST and the International Joint Usage Project with ICR, Kyoto University (2019-115 and 2020-124) to make this work possible. The Molecular Logic Laboratory is grateful for recent funding through the National Research Foundation of Korea (NRF) (2021R1F1A1046576). In addition, we are excited and grateful for the recent and perennial KC30 grant provided by KAIST (2021-). P.M.S. acknowledges the KGSP of Korea. B.C. would like to thank the BARC computer division for the supercomputing facility. This work was also supported by the Priority Research Centers Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2020R1A6A1A03041954).

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The author(s) reported there is no funding associated with the work featured in this article.
Kemp, K. C., Seema, H., Saleh, M., Le, N. H., Mahesh, K., Chandra, V., & Kim, K. S. (2013). Environmental applications using graphene composites: Water remediation and gas adsorption. Nanoscale, 5(8), 3149–3171. https://doi.org/10.1039/c3nr33708a

Ketano, N., Boer, T., Karakaya, M., Zhu, J., Podila, R., Rao, A. M., Kumaev, E. Z., & Moewes, A. (2021). Tuning the electronic structure of graphene through nitrogen doping: Experiment and theory. RSC Advances, 6, 56721–56727.

Kresse, G., & Hafner, J. (1993). Ab initio molecular dynamics for liquid metals. Physical Review B, Condensed Matter, 47(1), 558–R561. https://doi.org/10.1103/physrevb.47.558

Kresse, G., & Hafner, J. (1994). Ab initio molecular-dynamics simulation of the liquid-metal-amorphous-semiconductor transition in germanium. Physical Review B, Condensed Matter, 49(20), 14251–14269. https://doi.org/10.1103/physrevb.49.14251

Kumar, C., Panicker, C. Y., Fun, H. K., Mary, Y. S., Harikumar, B., Chandraju, Kumar, M. N. R. (2000). Nano and microparticles as controlled drug delivery systems. Expert Opinion on Drug Delivery, 3(33), 2511–2518. https://doi.org/10.1517/17425247.3.33.2511

Lee, W., Mulay, S. V., Shimodaira, S., Abdillah, A., Palma, J., Kim, Y., Lu, Z., Li, S., Liu, C., He, C., Yang, X., Ma, D., Xu, G., & Yang, Z. (2017). Vibrational spectroscopic studies and computational study of 4-fluoro-N-(2-hydroxy-4-nitrophenyl)phenylacetamide. Spectrochimica Acta Part A, Molecular and Biomolecular Spectroscopy, 150, 543–556.

Ma, R., Ma, Y., Dong, Y., & Lee, J. M. (2016). Recent advances in heterojunction graphene–metal interfaces: Water remediation and gas adsorption. Nano Advances, 1, 50–61. https://doi.org/10.1039/C5NA00905K

Mary, Y. S., Kumar, V. S., Mary, Y. S., K. S., & Thomas, R. (2020). Detailed quantum mechanical studies on three bioactive benzimidazole derivatives and their Raman enhancement on adsorption over graphene sheets. Polycyclic Aromatic Compounds, 1–10. https://doi.org/10.1007/s11104-020-18522-6

Mary, Y. S., Mary, Y. S., Resmi, K. S., Kumar, V. S., Thomas, R., & Sureshkumar, B. (2019). Detailed quantum mechanical, molecular docking, QSAR prediction, photovoltaic light harvesting efficiency analysis of benzo and its halogenated analogues. Helvyon, 5(11), e2825. https://doi.org/10.1002/hely.2019.e00285

Mary, Y. S., Minijar, P. B., Mary, Y. S., Resmi, Z. S., Panicker, C. Y., Armakovsk, S., Armakovsk, J. S., Thomas, R., & Sureshkumar, B. (2018). Synthesis and spectroscopic study of three new oxadiazole derivatives with detailed computational evaluation of their reactivity and pharmaceutical potential. Journal of Molecular Structure, 1173, 469–480. https://doi.org/10.1016/j.molstruc.2018.07.026

Mary, Y. S., Panicker, C. Y., Varghese, H. T., Raju, K., Boleti, T. E., Yildiz, I., Granadeiro, C. M., & Nogueira, H. I. S. (2011). Vibrational spectroscopic studies and computational study of 4-fluoro-N-(2-hydroxy-4-nitroph enyl)phenylacetamide. Journal of Molecular Structure, 994, 223–231. https://doi.org/10.1016/j.molstruc.2011.03.022

Mary, Y. S., Varghese, H. T., Panicker, C. Y., Girisha, M., Sagar, B. K., Yathirajan, H. S., Al-Saadi, A. A., & Van Alselen, C. (2015). Vibrational spectra, HOMO, LUMO, NBO, MEP analysis and molecular docking studies of 2-(4-chlorophenyl)-2-oxoethyl 3-nitrobenzoate. Spectrochimica Acta, 126, 208–219.

Kumar, M. N. R. (2000). Nano and microparticles as controlled drug delivery devices. Journal of Pharmacy and Pharmaceutical Sciences, 3, 234–258.

Kumar, V. S., Mary, Y. S., Pradhan, K., Brahman, D., Mary, Y. S., Thomas, R., Roxy, M. S., & Aisenov, C. Y. (2020). Synthesis, spectral properties, chemical descriptors and light harvesting studies of a new bioactiveaza imidazole compound. Journal of Molecular Structure, 1199, 127035. https://doi.org/10.1016/j.molstruc.2019.127035

Lee, W., Mulay, S. V., Shimodaira, S., Abdillah, A., Palma, J., Kim, Y., Yudhistira, T., & Churchill, D. G. (2020). Didactic approach recounting advances and limitations in novel glutathione and cysteine detection (reduced GSH probe) with mixed coumarin, aldehyde, and phenyl-selenium chemistry. Methods in Enzymology, 640, 267–289.

Leenaerts, O., Partoens, B., & Peeters, F. M. (2008). Graphene: A perfect substrate for reactive water purification membranes. JOURNAL OF BIOMOLECULAR STRUCTURE AND DYNAMICS, 179, 723–735. https://doi.org/10.1016/j.jbms.2009.06.093

Ling, X., Moura, L. G., Pimenta, M. A., & Zhang, J. (2012). Charge transfer mechanism in graphene-enhanced Raman scattering. The Journal of Physical Chemistry C, 116(47), 25112–25118. https://doi.org/10.1021/jp3088447

Ling, X., Wu, J., Xie, L., & Zhang, J. (2013). Graphene-thickness-dependent graphene-enhanced Raman scattering. The Journal of Physical Chemistry C, 117(5), 2369–2376. https://doi.org/10.1021/jp301564d

Liu, K., & Zhu, H. (2011). Nitroimidazoles as anti-tumor agents. Cancer Agents in Medicinal Chemistry, 11(7), 687–691. https://doi.org/10.2174/187152011796817664

Liu, Y., Yu, L., Ong, C. N., & Xie, J. (2016). Nitrogen doped graphene nanosheets as reactive water purification membranes. Nano Research, 9(7), 1983–1993. https://doi.org/10.1007/s12274-016-1089-7

Liu, Z., Wang, Y., & Zhang, N. (2012). Micelle-like nanoassemblies based on polymer-drug conjugates as an emerging platform for drug delivery. Expert Opinion on Drug Discovery, 9, 805–822.

Lu, Z., Li, S., Liu, C., He, C., Yang, X., Ma, D., Xu, G., & Yang, Z. (2017). Sulfur doped graphene as a promising metal-free electrocatalyst for oxygen reduction reaction: A DFT-D study. RSC Advances, 7(33), 20398–20405. https://doi.org/10.1039/C7RA00632B

Ma, R., Ma, Y., Dong, Y., & Lee, J. M. (2016). Recent advances in heterojunction graphene–metal interfaces: Water remediation and gas adsorption. Nano Advances, 1, 50–61. https://doi.org/10.1039/C5NA01712J

Shanmugam, S., Nachimuthu, S., & Subramaniam, S. (2020). DFT study of adsorption of ions on doped and defective graphene. Materials Today Communications, 22, 100714. https://doi.org/10.1016/j.mtcomm.2019.100714

Shi, G., Ding, Y., & Fang, F. (2012). Unexpectedly strong anion–π interactions on the graphene flakes. Journal of Computational Chemistry, 33, 14.

Singh, P., Choudhary, S., Kashyap, A., Verma, H., Kapil, S., Kumar, M., Arora, M., & Slakari, O. (2020). An exhaustive compilation on...
chemistry of triazolopyrimidine: A journey through decades. Medicinal Chemistry (Sharjah (United Arab Emirates)), 4, 487.

Starzak, K., Matwijczuk, A., Creaven, B., Matwijczuk, A., Wybraniec, S., & Karcz, D. (2019). Fluorescence quenching-based mechanism for determination of hypochlorite by coumarin-derived sensors. International Journal of Molecular Sciences, 20, 281.

Sutrova, V., Sloufova, I., Mojzes, P., Melnikova, Z., Kalbac, M., & Vickova, B. (2018). Excitation wavelength dependence of combined surface- and graphene enhanced Raman scattering experienced by free-base phthalocyanine localized on single layer graphene covered Ag nanoparticle arrays. Journal of Physical Chemistry C, 122, 20850–20860.

Tang, J., Liu, J., & Wu, F. (2016). Molecular docking studies and biological evaluation of 1,3,4-thiadiazole derivatives bearing Schiff base moieties as tyrosinase inhibitors. Bioorganic Chemistry, 69, 29–36. https://doi.org/10.1016/j.bioorg.2016.09.007

Tran, T. V., Nguyen, D., Le, H., Vo, D., Nanda, S., & Nguyen, T. D. (2020). Optimization, equilibrium, adsorption behavior and role of surface functional groups on graphene oxide-based nanocomposite towards diclofenac drug. Journal of Environmental Sciences (China), 93, 137–150. https://doi.org/10.1016/j.jes.2020.02.007

Vales, V., Drogovska-Horna, K., Guerra, V. L. P., & Kalbac, M. (2020). Graphene enhanced Raman scattering on single layer and bilayers of pristine and hydrogenated graphene. Scientific Reports, 10, 4516.

Vashist, S. K., Zheng, D., Pastorin, G., Al-Rubeaan, K., Luong, J., & Sheu, F. S. (2011). Delivery of drugs and biomolecules using carbon nanotubes. Carbon, 49, 4077–4097.

Wuest, J. D., & Rochefort, A. (2010). Strong adsorption of aminotriazines on graphene. Chemical Communications (Cambridge, England), 46(17), 2923–2925. https://doi.org/10.1039/b926286e

Yavari, I., Taheri, Z., Sheikhi, S., Bahemmat, S., & Halvagar, M. R. (2020). A synthesis of N-(1H-pyrazol-5-yl)-1,3,4-thiadiazol-2(3H)-imines from nitrile imines and Erlenmeyer thioazlactones. Molecular Diversity, 24(3), 727–735. https://doi.org/10.1007/s11030-019-09981-0

Yudhistira, T., Lee, W. H., & Churchill, D. G. (2020). Biosensor and chemosensor fluorophores that contain chalcogenide centers. Makara Journal of Science, 24(2), 119–134.

Zhang, J., Yang, Z., Wang, X., Ren, T., & Qiao, O. (2016). Homogeneous sulphur-doped composites: Porous carbon materials with unique hierarchical porous nanostructure for super-capacitor application. RSC Advances, 6(88), 84847–84853. https://doi.org/10.1039/C6RA17231H

Zhang, Y., & Wang, W. T. (2019). Tetrel bonding on graphene. Chemistry, 1147, 8–12.