THEORETICAL STUDY ON PHYSICOCHEMICAL AND GEOMETRICAL PROPERTIES OF THE ADRIAMYCIN CONJUGATED GOLD NANOPARTICLES

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ABSTRACT

Adriamycin (or Doxorubicin) is well known anti-cancer agent. It is an anthracycline antibiotic due to its severe cardiotoxicity. The cytotoxicity of Adriamycin can be minimized by linking it to an affinity tag. In this report, the molecular structure, Binding Energy (BE), Dipole Moment (DM), log P and some physicochemical properties of Adriamycin and Adriamycin conjugated gold nanoparticles were investigated using Density functional Theory (DFT) calculations. Our results indicate that this complex mentioned above can be used to improve anti cancer activity and water-solubility of Adriamycin.

Keywords: Anti-cancer drug, DFT calculations, Adriamycin-gold nanoparticles, Adriamycin.

INTRODUCTION

One of the most ordinary used anticancer medicines is Adriamycin. It is an anthracycline antibiotic, which intercalates DNA. Adriamycin is used to medicate a vast range of cancers, including hematological malignancies, many types of carcinoma, and soft tissue sarcomas. Nevertheless, when Adriamycin is applied directly, it is without the tumor-targeting ability leading to poor bio-distribution and curative effects as well as critical unpleasant side effects. The scheme of Adriamycin is illustrated in Fig 1.

Effective freeing of these therapeutic elements at the target place is essential for efficient therapy. Payloads release can be activate by internal (e.g., glutathione (GSH) or pH) or external (e.g., light) stimuli1-4. Furthermore, drug delivery systems (DDSs) with a high drug loading level can act as ‘drug reservoirs’ for supplied and supported drug release, thereby protecting the drug application within the therapeutic window. There have been a number of interesting statements in recent years on the use of functionalized Au NPs for drug delivery usage. Gibson et al. announced the direct functionalization of Au NPs with paclitaxel using hexaethylene glycol as a connection for cancer therapy5. Tom et al. investigate the drug release manner of ciprofloxacin functionalized Au NPs and discovered that it was influenced by both the size of the functionalized Au NPs and the type of release medium6. Paciotti et al. functionalized Au NPs with a combination of tumor necrosis component (TNC), PEG and paclitaxel, which was worked as a multifunctional vector susceptible to target solid tumors7,8,9. Because Au NPs can begin local heating when they are illuminated with light, El-Sayed et al. investigate the possible usage of Au NPs in photothermal demolition of tumor tissues. In their research, citrate-stabilized Au NPs were covered with an anti-epidermal growth factor receptor (ERGER) to target human oral squamous cell carcinoma (HSC3 cancer cells)10-12. In another research, Paasonen et al. created an optically reactive delivery system by merging Au NPs into liposomes Upon UV exposure, fluorescent markers contained in the liposomes were release, which was expedited by the heating of the Au NPs13. In comparison with polymeric micelles and liposomes, which are extensively research for hydrophobic drug delivery usage, functionalized Au NPs usually have much smaller sizes that are preferable for (1) inactive targeting of tumor tissues via the increased permeation and retention (IPR) effect; and (2) decreased reticuloendothelial system (IES) clearance14-16.

Many studies indicated and confirmed that coating nanoparticles with PEG car decrease opsonization on their surface and extend the circulation time in the blood stream, thereby let the nanoparticles to reach the tumor tissue via the EPR17.

Adriamycin conjugated gold nanoparticles complex was synthesized by Shaoqin Gong and colleagues18. The conjugation scheme is in Fig. 2. Furthermore, the optimized structure of Adriamycin conjugated Au NPs has been showed in Fig. 3. The geometry of Adriamycin conjugated Au NPs were optimized at B3LYP/6-31G* level of theory using Gaussian 0319. In study unit number of PEG is 2.

In this study Quantum mechanical molecular simulation can be used to study drug delivery.
Fig. 2: Synthesis scheme for the preparation of Adriamycin conjugated Au NPs\textsuperscript{24}.

Fig. 3: Structure optimized of Adriamycin conjugated Au NPs n=2
In this study, we intend to show some the characteristics of Adriamycin, Adriamycin conjugated Au NPs which have been mentioned above and have been obtained by other researchers experimentally through predictable computational calculations including molecular energy, binding energy, dipole moment, log P, distance bound and angle bound.

RESULTS AND DISCUSSION

The geometry structure of Adriamycin and Adriamycin conjugated Au NPs were optimized at B3LYP/6-31g* level of theory. Table 1 presents the geometrical parameters of this complex mentioned above around linking position (hydrazon group), see also Fig 4.

Some physicochemical properties of Adriamycin conjugated Au NPs and Adriamycin such as Refrectivity, polarizability, Hydration energy, binding energies (BE), log P and Dipole moment (DM) are obtained from optimal structure which have been shown in Table 2. The binding energy per molecule was computed using the formula (1):

\[ \Delta E = E_{\text{complex}} - E_{\text{drug}} - E_{\text{carrier}} \]

Table 1: Geometrical parameter of complex around linking position

<table>
<thead>
<tr>
<th>Complex</th>
<th>( R(C=N) ) (Å)</th>
<th>( R(N=N) ) (Å)</th>
<th>( R(N-C) ) (Å)</th>
<th>( C-N=N ) (°)</th>
<th>( N-C-O ) (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamycin conjugated Au NPs</td>
<td>1.297</td>
<td>1.591</td>
<td>1.377</td>
<td>111.877</td>
<td>119.881</td>
</tr>
</tbody>
</table>

Table 2: Some calculated physicochemical properties of Adriamycin conjugated Au NPs and Adriamycin

<table>
<thead>
<tr>
<th>Physicochemical properties</th>
<th>Adriamycin-Au NPs</th>
<th>Adriamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refrectivity*</td>
<td>206.06</td>
<td>135.50</td>
</tr>
<tr>
<td>Polarizability</td>
<td>81.41</td>
<td>52.00</td>
</tr>
<tr>
<td>Hydration energy*</td>
<td>-31.27</td>
<td>-24.03</td>
</tr>
<tr>
<td>Surface area (Å²)</td>
<td>1138.88</td>
<td>729.45</td>
</tr>
<tr>
<td>Log P</td>
<td>-0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>Dipole moment (Debye)</td>
<td>7.025</td>
<td>6.848</td>
</tr>
<tr>
<td>BE (ev/mol)</td>
<td>-1069.919</td>
<td>-</td>
</tr>
</tbody>
</table>

*Data were calculated using HyperChem 8 software

CONCLUSION

Density functional Theory (DFT) calculations were applied to study some physicochemical properties of Adriamycin conjugated Au NPs and Adriamycin. Regarding the calculation results, hydrophilicity of Adriamycin conjugated Au NPs is higher than that of Adriamycin; this fact can be verified through the log P obtained for this complex using Hyperchem. therefore, Adriamycin conjugated Au NPs is more soluble than of Adriamycin. These calculations also show that Adriamycin release from Adriamycin conjugated Au NPs complex takes place in a long period of time. On the other hand it means that we have a gradual release which is predictable according to Binding Energy.

Our results indicate that this complex mentioned above can be used to improve anti cancer activity and water-solubility of Adriamycin.

REFERENCES


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