The mechanism of nitric oxide release through gold nanoparticles-mediated catalytic decomposition of S-nitrosothiols by density functional theory

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Abstract. First principles calculations were performed to study the mechanism of nitric oxide release through the catalytic decomposition of S-nitrosothiols mediated by gold nanoparticles within the density functional theory. The gold nanoparticles and S-nitrosothiols were modeled by Au38 cluster and SPEN compound, respectively. The results reveals a two-step reaction process. The primary step is SPEN adsorbs on Au38 cluster surface by S atom to form the intermediate. In the next step, NO dissociates from SPEN under the catalysis of Au38 cluster and thereafter a specie of Au-thiolate complex was produced as the product. Furthermore, we found that the overall catalytic reaction is exothermic with a small energy barrier, which confirms the reaction process is kinetically feasible.

1. Introduction

Nitric oxide (NO) is an important messenger molecule and reactive free radical that can be generated regularly in living cells. Numerous experiments have demonstrated that NO involves in many diverse biological processes in the body, such as neurotransmission, immune regulation, vasodilatation and muscle relaxation [1,2]. Studies associated with NO detection, delivery, and targeting systems have been becoming one of the most active research areas for their increasingly growing biochemical and biomedical applications.

For NO release and delivery, S-nitrosothiols (RSNOs) is established as a promising NO donor among various classes of NO donor systems [3]. To achieve targeted drug release and delivery in biological systems, functionalized self-assembled monolayers of bioactive compounds on gold surface[4] and modified monolayer-protected gold clusters [5,6] loaded with NO donor moieties have been designed and synthesized, where gold nanoparticles (AuNPs) are employed as drug delivery vehicles and contrast agents due to their small size, high stability, excellent catalytic activity, and strong affinity for thiol groups to AuNPs surface. It has been demonstrated that thiol gold (S-Au) bond has higher dissociation energy relative to that of the S-NO bond (∼ 20 kcal/mol) [7], the presence of gold surfaces or nanoparticles could easily cleave the S-N bond in RSNOs and simultaneously yielding of NO. Therefore, AuNPs-mediated decomposition of RSNOs for NO release has been developed. For instance, Jia et al. [8] reported the phenomena and cause for the producing of NO by using AuNPs as catalysts from endogenous RSNOs in blood serum. Furthermore, the existence of Au-thiolate on the surface of AuNPs during reaction course has been identified by X-ray photoelectron spectroscopy (XPS) analysis. Priya et al. [9] described the catalytic effect of AuNPs in enhancing the release rate of NO up to 3.5 times from triphenylmethane nitrosothiol. Taladriz-Blanco et al. [10]...
realized controllable NO release from RSNOs in the presence of citrate-stabilized AuNPs via employing an amperometric technique to detect the maximum amount of NO released and then fit the experimental data with a proposed kinetic model. Also, evidence of Au-S stretching has been verified by surface-enhanced Raman scattering (SERS) analysis.

Since gold atoms could adopt several oxidation states when they bound to different ligands [11], various possible conjugations between AuNPs and thiolates can thus be produced, making it more complicated to study the mechanism of AuNPs-triggered NO release through RSNOs decomposition. Herein, theoretical investigations on AuNPs-mediated catalytic decomposition of RSNOs (e.g., SPEN compound) are presented to explain the reaction mechanism of NO release and the intrinsic catalytic activity of neutral AuNPs during reaction course. We hope the present study would provide evidence for further insight into details of the AuNPs-catalyzed reactions, and the role of AuNPs in facilitating NO release.

2. Computational methods
Our first principles calculations were carried out within the framework of density functional theory (DFT) as implemented in DMOl³ code in Materials Studio software [12,13]. The electronic exchange-correlation functional was described by Perdew-Burke-Ernzerhof (PBE) in generalized gradient approximation (GGA) [14]. The localized double-numerical basis sets with polarization functions (DNP) were used to expand the Kohn-Sham orbitals. The core electrons of the metal atoms were treated using density functional semicore pseudopotentials (DSPP) [15]. The DSPP methods is an efficient way which replaces core electrons by a single effective potential and introduces some degree of relativistic correction into the core. A real-space cutoff of 4.5 Å was used, which is sufficient for accurate evaluation of the energies. The self-consistent field (SCF) calculations were conducted with the spin-polarization Kohn-Sham formalism, with the spin multiplicity relaxed during the optimization. Molecular symmetry was not enforced to allow for full geometry relaxation. The transformation pathways and transition state (TS) search were performed by using the complete LST/QST method [16]. The solvent effect was taken into account in our calculations with the conductor-like screening model (COSMO) using water as solvent (ε=78.5) to simulate the experimental solvent environment.

3. Results and discussion
In this study, small-sized Au$_{138}$ cluster is constructed as the model of AuNPs. The Au$_{138}$ cluster is a three-dimensional truncated octahedron with O$_h$ symmetry. The surface of Au$_{138}$ cluster is consisted of six planar squares alternating with eight planar hexagons, corresponding to the (100) and (111) planes of stable face-centered cubic (fcc) bulk single crystal gold, respectively. The Au atoms occupy two distinct adsorption sites, the five-coordinated top site and six-coordinated center site. In view of several low molecular weight RSNOs compounds, including S-nitroso-penicillamine (SNAP), S-nitroso-N-acetyl-DL-penicillamine (SNAP), and S-nitrosothiogluthione (GSNO) have been utilized to react with AuNPs for NO release in previous literature [10], herein SPEN compound and Au$_{138}$ cluster are selected as representative reactant models to elucidate the mechanism of NO generation and the Au-thiolate complexes formation via the ligand exchange reaction of AuNPs induced catalyzing decomposition of RSNOs. The solvent effect was considered in the following calculations.

Typical reaction pathway is proposed accordingly on the basis of the original reactants and final products, which may proceed along the following postulated multistep process. Firstly, the reaction starts with the adsorption of RSNO on AuNPs by the S atom to form the intermediate. Next, RSNO decomposes into thyl radical (RS•) and NO, the catalytic reaction proceeds in such a way that NO dissociates from RSNO, thereafter thyl radical bonds to AuNPs surface to form the products. The main pathway (1) can be divided into two steps (1a-1c), involving RSNO adsorption, NO dissociation from RSNO and Au-thiolate complex formation.

The overall reaction can be described as follows:

\[
\text{RSNO} + \text{AuNPs} \rightarrow \text{RS-AuNPs}_{\text{ad}} + \text{NO}_{\text{g}} \quad (1) \\
\text{RSNO} + \text{AuNPs} \rightarrow \text{RSNO-AuNPs}_{\text{ad}} \quad (1a)
\]

\[\text{RSNO} + \text{AuNPs} \rightarrow \text{RS-AuNPs}_{\text{ad}} + \text{NO}_{\text{g}} \quad (1b)\]

\[\text{RS-AuNPs}_{\text{ad}} + \text{NO} \rightarrow \text{RSNO-AuNPs}_{\text{ad}} \quad (1c)\]
RSNO$_{(ad)}$ → RS$^*_{(ad)}$ + NO$_{(g)}$  \hspace{1cm} (1b)
RS$^*_{(ad)}$ + AuNPs → RS-AuNPs$_{(ad)}$ \hspace{1cm} (1c)

Where R group represents C(CH$_3$)$_2$CH(NH$_2$)COOH.

To testify the above presented two-step reaction process, the optimized structures of reactants, intermediate, products, and TS are shown in figure 1, respectively. The potential energy profile along the reaction pathway is depicted in figure 2. As mentioned above, the formation of Au-thiolate and S-Au bond during experiments are supported by XPS and SERS measurements[9,10], indicating the existence possibility of thiol radical species and S-Au bond in the reaction process. Thus, we reasonably assume in the first step of the reaction that SPEN adsorbs on the top site of Au$_{38}$ cluster by S atom to form the intermediate and that SPEN would decompose into two species, i.e., thiol radical and NO. In the intermediate, the S atom is surrounded by C, N and Au atoms. The S-N bond length is enlarged from 1.847 Å in SPEN to 2.141 Å and the newly formed S-Au bond is 2.414 Å. The first step of the reaction is an exothermic process with the calculated energy release of -16.1 kcal/mol (figure 2). Also, we found this step is barrierless, indicating the adsorption of SPEN is kinetically favorable for the catalytic process.

![Figure 1. (Color online) Optimized structures of the reactants (R), the intermediate (IM), the transition state (TS), and the products (P) (unit: Å).](image)

In the following, the intermediate undergoes NO dissociation from SPEN to form the final product and NO via TS. As one of the species produced, reactive thiol radical has the possibility to bond to different adsorption sites of Au$_{38}$ cluster, thereby mediating the formation of several different low-lying isomer structures of Au-thiolate complex with distinct S-Au bond linkages. Among them, the one with S-Au single bond formed in the intermediate is energetically less stable than that with S atom bridges two Au atoms at equivalent top sites in a trilateral arrangement in the product (figure 2). As we know, the S-Au bond has higher dissociation energy relative to that of the S-N bond. Therefore, the S-N bond cleavage would occur under the catalysis of Au$_{38}$ cluster and afterwards S atom bonds to the neighbor Au atom, leading to a dissociation of NO from SPEN and finally to a new formation of the Au-S-Au bridge. The S-Au bonds eventually change to 2.499 Å and 2.504 Å in the product. Although the step of dissociation is endothermic by 0.38 kcal/mol, it shows that the reaction process is kinetically feasible to the product side. For the dissociation of NO from SPEN, a substantially low barrier of 3.77 kcal/mol is obtained (figure 2). It is obviously facile to overcome such a low barrier.
even at room temperature. This result may be due to mainly the role of AuNPs in reducing the barrier for the catalytic reaction and in part to the solvent effect. Also, AuNPs acts as a catalyst for SPEN decomposition towards NO release. The formation of Au-thiolate complex is a crucial step in the catalytic reaction for NO release.

4. Conclusions
In summary, to theoretically clarify the mechanism of NO release, Au-thiolate complexes formation and intrinsic catalytic role of AuNPs, the reaction of AuNPs-induced decomposition of SPEN compound has been investigated by using DFT methods. A two-step reaction pathway for NO release is proposed, in which SPEN firstly adsorbs on Au$_{38}$ cluster surface by the S atom to form the intermediate. Subsequently, NO dissociates from SPEN under the catalysis of Au$_{38}$ cluster then S atom bonds to the neighbor Au atom to form stable Au-thiolate complex as final product. The proposed microscopic mechanism was further elucidated by searching low-energy reaction pathway. The results reveal that the first step of the reaction is found to be barrierless and exothermic, therefore feasible at room temperature. The second step of the reaction is an endothermic process with a small activation barrier, confirming the catalytic reaction would happen easily. The Au-thiolate complex readily produced in the reaction course plays a significant role in the catalytic cycle. Our results verify specific catalytic roles of AuNPs for facilitating SPEN decomposition and NO release and reducing the energy barrier of the reaction.

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