Chemical Physics Letters 636 (2015) 163–166

Contents lists available at ScienceDirect

Chemical Physics Letters

journal homepage: www.elsevier.com/locate/cplett

Interaction of metallic clusters with biologically active curcumin molecules

Sanjeev K. Gupta[a,1], Haiying He[b,*], Chunhui Liu[a], Ranu Dutta[c], Ravindra Pandey[a,*]

[a] Department of Physics, Michigan Technological University, Houghton, MI 49931, USA
[b] Department of Physics and Astronomy, Valparaiso University, Valparaiso, IN 46383, USA
[c] Nanotechnology Application Centre, University of Allahabad, Allahabad 211002, India

ARTICLE INFO

Article history:
Received 23 April 2015
In final form 19 July 2015
Available online 29 July 2015

ABSTRACT

We have investigated the interaction of subnano metallic Gd and Au clusters with curcumin, an important biomolecule having pharmacological activity. Gd clusters show different site preference to curcumin and much stronger interaction strength, in support of the successful synthesis of highly stable curcumin-coated Gd nanoparticles as reported recently. It can be attributed to significant charge transfer from the Gd cluster to curcumin together with a relatively strong hybridization of the Gd *df*-orbitals with curcumin *p*-orbitals. These results suggest that Gd nanoparticles can effectively be used as delivery carriers for curcumin at the cellular level for therapy and medical imaging applications.

1. Introduction

Biologically active curcumin shows a remarkable range of pharmacological activity, including antioxidant, anti-inflammatory, and anticancer activity [1–3]. The chemical structure of curcumin enables it to interact with a large number of molecules inside the cell including enzymes and their receptors. However, it has been recognized that the application of curcumin is limited by its bioavailability in the body due to its poor absorption and rapid elimination from the body [4]. Therefore, efforts have been made to deliver curcumin to the body via forming complexes with single metal ions [5], organic assemblies [6], or inorganic nanoparticles [7,8]. The complexation of curcumin with metal ions is by far the most studied. It usually involves strong binding and leads to modification of properties of both the metal ion and the curcumin molecule, such as reducing the toxicity of the metals and varying the medical effects of curcumin. For example, curcumin can easily chelate with Zn^{2+} and Cu^{2+} ions by forming metal complexes, and the Cu(II)–curcumin complex has an ability to scavenge free-radicals [4], act as a reducing agent and a DNA damage agent.

Metallic (e.g. Au) nanoparticles have found applications in diverse health-related areas as they exhibit novel and unique electronic, magnetic, and optical properties [9–11]. The recent development of using metal and oxide nanoparticles as carriers brings a new dimension in the delivery of curcumin in cells, which provides the potential advantages of intact delivery, target specificity and better control of release rate of curcumin [7,8]. Among them, magnetic nanoparticles are attracting special attention as drug delivery systems and magnetic resonance imaging (MRI) contrasting agents owing to the fact that they can be directed via a magnetic field and applied for local hyperthermia. The studies on complexation of curcumin and metal nanoparticles are currently scarce.

In order to assess the effectiveness of nanomaterials for health-related applications, a fundamental understanding of the interaction between nanoparticles and biological molecules appears to be a prerequisite condition. What are the unique features of an inorganic nanoparticle that allows it to bind to a biological molecule and how? Such questions have been addressed previously by our group for subnano metallic clusters (Ag_{13}, Al_{13} and Mn_{13}) interacting with a bioactive molecule, dopamine [12], and various interaction strength and site preference were found for different metals. In this study, we investigate the bioconjugated gadolinium (Gd)–curcumin complex following a recent suggestion from experiment that Gd nanoparticles can act as magnetic carriers for the curcumin molecules [13]. A subnano Gd_{13} cage-like cluster is considered to represent the spherically-shaped Gd nanoparticles. We have also considered interaction of the Au_{13} cluster with curcumin as a reference case to assess the effectiveness of Gd_{13} to form a bioconjugated complex with curcumin. The outline of this letter is as follows: Section 2 describes the computational method. The results are discussed in Section 3. Finally, summary of the results is presented in Section 4.

* Corresponding authors.
E-mail addresses: haiying.he@valpo.edu (H. He), pandey@mtu.edu (R. Pandey).
[1] Current address: Department of Physics, St. Xavier's College, Ahmedabad 380009, India.

http://dx.doi.org/10.1016/j.cplett.2015.07.040
0009-2614/

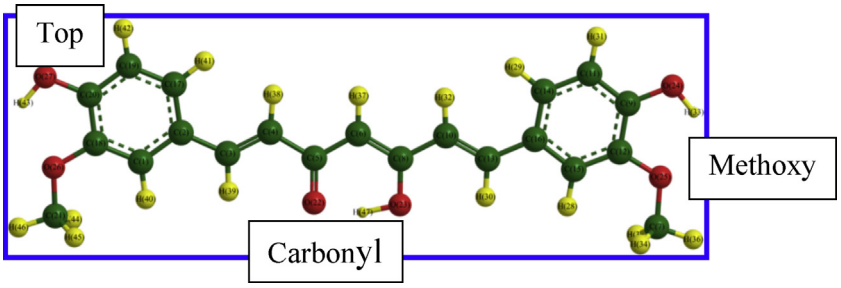

Figure 1. A ball-and-stick model for the enol-curcumin molecule (O: red, C: green and H: yellow). (For interpretation of the references to color in text, the reader is referred to the web version of this article.)

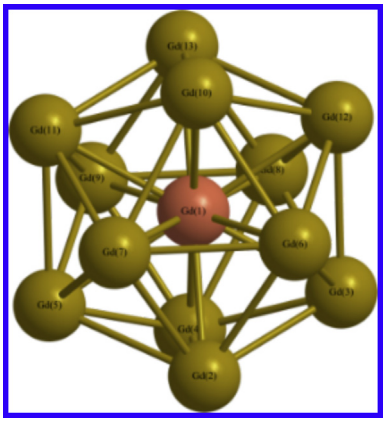

Figure 2. The spin-polarized ground state configuration of Gd_{13}. Atom with spin up is in red. The remaining atoms with spin down are in golden yellow. (For interpretation of the references to color in text, the reader is referred to the web version of this article.)

2. Computational method

Spin-polarized electronic structure calculations were carried out in the framework of density functional theory (DFT). The projector augmented wave (PAW) method with the generalized gradient approximation (GGA) [14] as implemented in the Vienna ab-initio simulation package (VASP) code [15] was used. The valence electronic configurations consisting of ($5s^2$ $5p^6$ $4f^7$ $5d^1$ $6s^2$) and ($4f^{14}$ $5d^{10}$ $6s^1$) were considered for Gd and Au, respectively. The value of the effective on-site coulomb parameter was set to 7 eV for Gd which was found to be reasonable to describe the hcp-Gd crystal [16] and the Gd_2 dimer [17,18]. For example, the calculated magnetic moment of the bulk Gd is 7.6 μ_B/atom, which is in good agreement with the experimental value of 7.63 μ_B/atom [16]. A supercell of $(35 \times 40 \times 20)$ Å^3 was used for the bioconjugated complex involving a 13-atom metallic cluster and the curcumin molecule. The convergence criterion of optimization was set to 0.03 eV/Å for the force on each ion and 10^{-5} eV for the total energy for all calculations. The cutoff energy for the plane wave basis sets was set to 400 eV.

3. Results and discussion

3.1. Curcumin molecule

Curcumin has four different rotation axes involving two C—C single bonds and two C—Ph bonds that give rise to its conformational isomers. Figure 1 shows the equilibrium configuration of the enol-curcumin which is found to be lower in energy than the keto-curcumin. This is in agreement with the previous theoretical study [19].

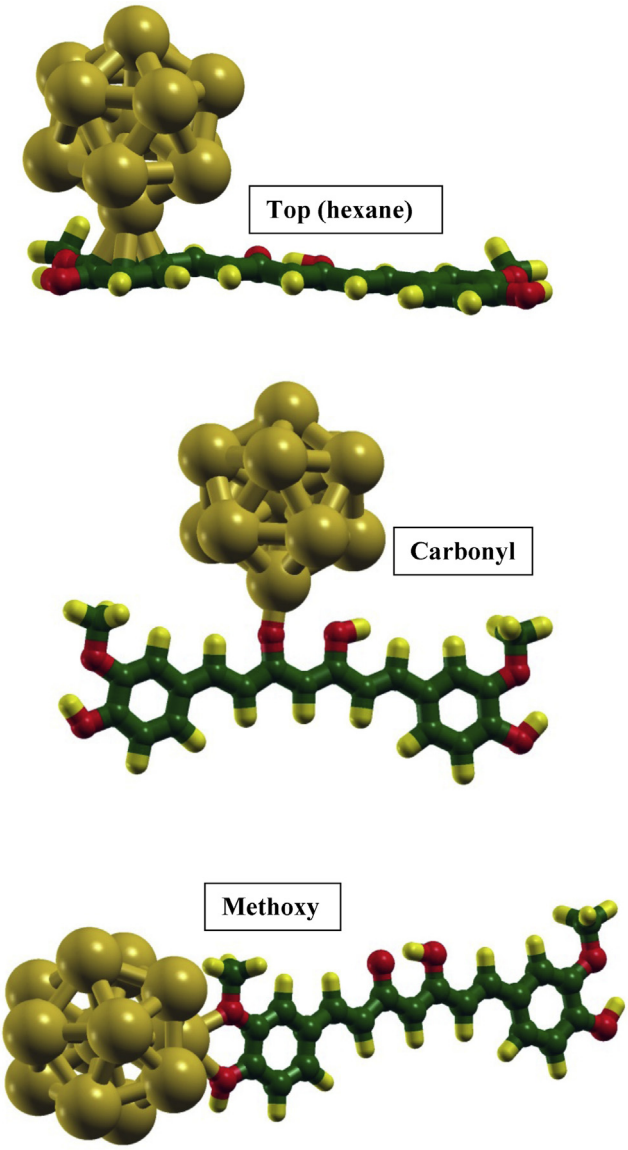

Figure 3. The ground state configuration of the bioconjugated complexes associated with top (hexane), carbonyl and methoxy binding sites.

3.2. Clusters

The spherically-shaped clusters M_{13} (M = Gd, Au) with a diameter of 0.6–0.7 nm are considered to represent metallic nanoparticles in order to reduce computational cost of electronic structure calculations. Although the bonding characteristics of the bioconjugated complex may depend upon the particle size, a comparison of the

Table 1
The calculated binding energy E_b and metal–curcumin bonding distance R of the bioconjugates of Au_{13} and Gd_{13}.

Complex		Top site	Carbonyl site	Methoxy site
$(Au)_{13}$ + curcumin	R (Å)	2.19	2.53	3.43
	E_b (eV)	−0.58	−0.12	−0.10
$(Gd)_{13}$ + curcumin	R (Å)	2.49	2.14	3.63
	E_b (eV)	−0.65	−0.83	−0.28

calculated results for Gd clusters with Au clusters will at least provide a qualitative understanding of the interaction strength of Gd with curcumin in the bioconjugate complex.

Our choice of 13-atom cluster to simulate spherically-shaped nanoparticles is based on the fact that Gd_{13} and Au_{13} clusters are stable in an icosahedral configuration as shown in Figure 2. The cal culated bond lengths are 3.28 and 2.78 **Å** for Gd_{13} and Au_{13}, respectively and are in agreement with the previously reported theoretical studies on these clusters [17,19]. It should be noticed that the bond length of 3.1 Å was reported for the Gd nanoparticles in the experimental study [13]. The icosahedral ground state of Gd_{13} prefers anti-ferromagnetic ordering with the central atom has its net spin pointing to the opposite direction as compared to the remaining atoms (Figure 2).

3.3. Curcumin–metallic cluster bioconjugates

In the bioconjugated complex, the molecular binding sites are considered to be (i) the top of ring (hexane), (ii) carbonyl (—C═O bond) and (iii) methoxy (—C—$COCH_3$) sites as shown in Figure 1. Following the procedure employed for a cluster approaching a dopamine molecule [12], the path taken by the cluster approaching the carbonyl or the methoxy site is constrained on the plane of the molecule whereas the path going to the top site is constrained perpendicular to the plane of the molecule. The potential energy surface is then calculated by keeping the cluster to be rigid retaining its ground state configuration and allowing the curcumin molecule to relax. Here, we have limited our focus to explore single-site binding only, largely because of the size of the clusters considered for Gd and Au. The study of binding of curcumin through multiple active sites simultaneously requires consideration of larger sized metal particles.

Figure 3 displays the calculated equilibrium configurations. Table 1 lists the calculated binding energy and the equilibrium distances of the bioconjugated complexes. The binding energy is defined as the total energy difference between the complex and its constituents, namely molecule and cluster. Negative binding energy suggests the complex to be stable.

Gd_{13} shows higher interaction strength towards curcumin than Au_{13} at all binding sites of the molecule. Moreover, preference for the interaction site is quite different for Gd_{13} and Au_{13}. The calculated results show that Au_{13} prefers the top-site with a binding energy of −0.58 eV. On the other hand, Gd_{13} prefers the carbonyl site with a binding energy of −0.83 eV. For both clusters, the preferred sites show a relatively shorter distance between the cluster and the molecule suggesting a higher degree of overlap of electron densities of the cluster and molecule at the binding site (Figure 4). For example, the top site configuration shows the bonding distance R to be 2.19 Å for Au_{13} and 2.49 Å for Gd_{13}. On the other hand, the carbonyl site configuration shows R to be 2.14 Å for Gd_{13} and 2.53 Å for Au_{13}. The results are consistent with the fact that Au is chemically inert, while Gd acts as a reducing agent and can easily be oxidized. A Gd–O is clearly seen in contrast to the chelate bonding of Au with oxygens at the carbonyl site of curcumin in Figure 4.

The calculated difference between Au_{13} and Gd_{13} is also reflected in their metal–oxygen bond strengths. For instance, the bond enthalpy is found to be 221.8 ± 20.9 kJ/mol and 719 ± 10 kJ/mol for AuO and GdO molecules, respectively [20].

It is well known that the oxygen molecule exhibits strong paramagnetism due to unpaired spins. Gd atoms with unpaired 4*f* and 5*d* states can interact with oxygens facilitating charge transfer in the bioconjugated complex. Bader charge analysis finds the charge transfer of 0.83*e* from the Gd_{13} cluster to the curcumin molecule for the carbonyl site with $R = 2.14$ Å. This is not the case, however, with the Au_{13} complex which shows a significantly smaller charge transfer of 0.03*e*. In the case of the top-site configuration, hybridization of π-orbitals of the molecular hexane ring with Au_{13} yields a charge transfer of 0.20*e* from the molecule to the cluster. It is quite different for Gd_{13} where a charge transfer of 0.80*e* from the cluster to molecule is seen. This is largely due to the much lower electronegativity of Gd (1.20) compared to that of Au (2.54), which tends to donate electrons more than Au. Furthermore, the spin density analysis suggests Gd_{13} retain its magnetic character in the bioconjugated complex with the slightly lower magnetic moment of $\approx 7\ \mu_B$/atom. The calculated magnetic nature of the bioconjugated complex is in agreement with the experiments demonstrating Gd nanoparticles to be acting as magnetic carriers [13], where the observed relaxivity of the curcumin-coated Gd nanoparticles is only slightly below that of the bare Gd nanoparticles. It is also worth noting that the curcumin molecule only undergoes a small conformation change upon binding to the metallic clusters (Figure 3), indicating no change in the nature of the curcumin molecule. These bioconjugates can potentially be used to deliver curcumin to targeted sites for therapy.

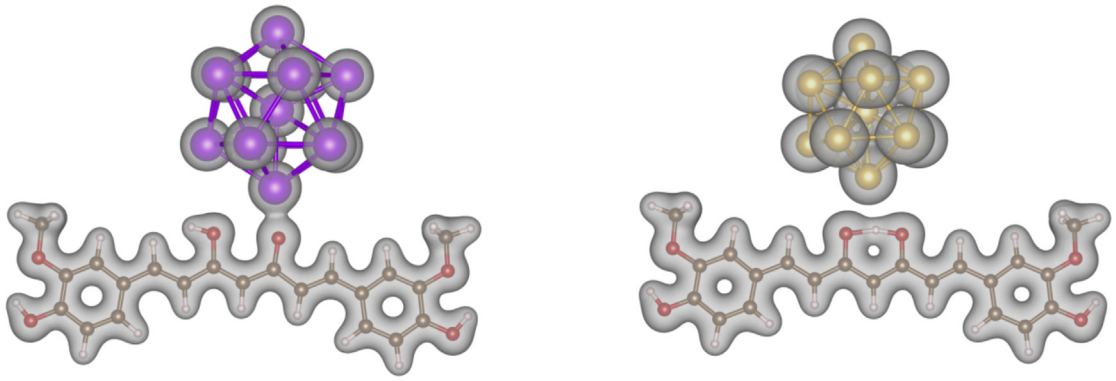

Figure 4. Charge contour plots of Gd_{13} (left) and Au_{13} (right) interacting with curcumin at the carbonyl site with the iso-surface charge density to be 1/30th of the maximum value.

4. Summary

In summary, the interaction strength in terms of the cluster–curcumin binding strength is predicted to be higher for Gd as compared to Au. This is useful to produce stable metal–biomolecule complex for diverse health-related applications. Combining it with their unique magnetic properties, Gd nanoparticles could be potential candidates for magnetic resonance imaging and targeted delivery of curcumin by applying an external magnetic field. The site selectivity and interaction strength of the clusters can be explained by chemical bonding via hybridization. It should be acknowledged that the deprotonation of hydroxyl groups of curcumin is not taken into account in the current study. Consideration of the effect due to the aqueous solution may be an important topic for future studies. We believe that the insights we gained here could pave the way for a full understanding of the bioconjugated material at the atomic level, which will be a key to several biological processes occurring in vitro and in vivo.

Acknowledgments

Helpful discussions with profs. Ashutosh Tiwari and S. Gowtham are acknowledged. SKG acknowledges award of the Fulbright-Nehru Postdoctoral Research Fellowship by United States-India Educational Foundation (USIEF) and Grant No. 1638/FNPDR/2012. RD thanks Department of Physics for the hospitality during her stay at Michigan Tech. RAMA and Superior, high performance computing clusters at Michigan Technological University, were used in obtaining results presented in this letter.

References

[1] A. Brown, Q. Shi, T.W. Moore, Y. Yoon, A. Prussia, C. Maddox, D.C. Liotta, H. Shim, J.P. Snyder, J. Med. Chem. 56 (2013) 3456.
[2] S.M. Bayomi, H.A. El-Kashef, M.B. El-Ashmawy, M.N.A. Nasr, M.A. El-Sherbeny, F.A. Badria, L.A. Abou-Zeid, M.A. Ghaly, N.I. Abdel-Aziz, Med. Chem. Res. 22 (2013) 1147.
[3] (a) Y. Jiao, J. Wilkinson, X.M. Di, W. Wang, H. Hatcher, N.D. Kock, R. D'Agostino, M.A. Knovich, F.M. Torti, S.V. Torti, Blood 113 (2009) 462;
(b) R.A. Sharma, A.J. Gescher, W.P. Steward, Eur. J. Cancer 41 (2005) 1955.
[4] X.Z. Zhao, T. Jiang, L. Wang, H. Yang, S. Zhang, P. Zhou, J. Mol. Struct. 984 (2010) 316.
[5] S. Wanninger, V. Lorenz, A. Subhan, F.T. Edelmann, Chem. Soc. Rev. (2015), http://dx.doi.org/10.1039/C5CS00088B, Advance Article, and references therein.
[6] S. Prasad, A.K. Tyagi, B. Aggarwal, Cancer Res. Treat. 46 (2014) 2.
[7] U. Hani, H.G. Shivakumar, Curr. Drug Deliv. 11 (2014) 792.
[8] K.I. Priyadarsini, Molecules 19 (2014) 20091.
[9] Y.N. Xia, P.D. Yang, Y.G. Sun, Y.Y. Wu, B. Mayers, B. Gates, Y.D. Yin, F. Kim, Y.Q. Yan, Adv. Mater. 15 (2003) 353.
[10] T.T. Xu, F.T. Fisher, L.C. Brinson, R.S. Ruoff, Nano Lett. 3 (2003) 1135.
[11] A. Dykman, N.G. Khlebtsov, Acta Nat. 3 (2011) 34.
[12] C. Liu, H. He, R. Pandey, S. Hussain, S.P. Karna, J. Phys. Chem. B 112 (2008) 15256.
[13] R.A. Dutta, P.K. Sharna, V. Tiwari, V. Tiwari, A.B. Patel, R. Pandey, A.C. Pandey, Appl. Phys. Lett. 104 (2014) 023703.
[14] J.P. Perdew, K. Burke, M. Ernzerhof, Phys. Rev. Lett. 77 (1996) 3865.
[15] G. Kresse, J. Furthmuller, Phys. Rev. B 54 (1996) 11169.
[16] L.W. Roeland, G.J. Cock, F.A. Muller, A.C. Moleman, K.A. McEwen, R.G. Jordan, D.W. Jones, J. Phys. F: Met. Phys. 5 (1975) L233.
[17] G. Kim, Y. Park, M.J. Han, J. Yu, C. Heo, Y.H. Lee, Solid State Commun. 149 (2009) 2058.
[18] H.K. Yuan, H. Chen, A.L. Kuang, B. Wu, J. Chem. Phys. 135 (2011) 114512.
[19] K. Balasubramanian, J. Agric. Food Chem. 54 (2006) 3512.
[20] J.A. Kerr, in: D.R. Lide (Ed.), CRC Handbook of Chemistry and Physics 1999–2000: A Ready-Reference Book of Chemical and Physical Data, 81st edn., CRC Press, Boca Raton, Florida, USA, 2000.