On shape dependence of the toxicity of rutile nanoparticles

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Abstract Using DFT treatment based on the B3LYP hybrid functional, the nearly spherical structure of \([\text{Ti}_7\text{O}_{28}\text{H}_{26}]^{2-}\), the rod-like structures of \([\text{Ti}_2\text{O}_{10}\text{H}_{10}]^{2-}\), and \([\text{Ti}_7\text{O}_{30}\text{H}_{10}]^{2-}\) chains in singlet ground spin states and the structures of their neutral complexes with \(\text{Cu}^{2+}\) ions coordinated at various terminal or bridging oxygen sites in doublet ground spin states are optimized in order to assess the toxicity of rutile nanoparticles of various shapes. For this purpose \(\text{Cu}-\text{ligand interaction energy parameters and } \text{Cu charges in the above systems under study are evaluated. Spherical structures are more reactive than the rod-like chains of the (nearly) same size. The reverse relation holds for the degree of their toxicity as indicated by the extent of the electron density transfer to a } \text{Cu}^{2+} \text{ probe. The experimentally observed higher cytotoxicity of the rod-like nanoparticles in comparison with the spherical ones might be explained by the higher electron density transfer to the interacting cells.}

Keywords Protonated rutile nanoparticle · DFT method · \(\text{Cu(II)}\) probe · Electron density transfer · Interaction energy

Introduction

Biochemical and molecular mechanisms of cytotoxicity include oxidative stress-induced cellular events and alteration of the pathways pertaining to intracellular calcium homeostasis (Huang et al. 2017). All the stresses lead to cell injuries and death. The physicochemical properties of nanoparticles influence their interaction with cells and, thus, their overall potential toxicity. Understanding these properties can lead to the development of safer nanoparticles.

Recent studies have begun identifying various properties that make some nanoparticles more toxic than others (Huang et al. 2017). The properties of nanoparticles that contribute to cytotoxicity include, but are not limited to, surface, particle size, particle morphology, and dissolution of ions. As oxidative stress is elevated and intracellular calcium homeostasis is perturbed due to exposure to nanoparticles, subsequent actions lead to cell injury and death, and deregulation of the cell cycle.

i) Particle size is likely to contribute to cytotoxicity (Huang et al. 2017; Jiang et al. 2008). Given the same mass, smaller nanoparticles have a larger specific surface area and thus more available surface area to interact with cellular components such as nucleic acids, proteins, fatty acids, and carbohydrates. The smaller size also likely makes it possible to enter the cell, causing cellular damage.

ii) Particle surface charge may affect the cellular uptake of particles as well as how the particles interact...
with organelles and biomolecules. Consequently, particle surface charge influences cytotoxicity.

iii) Shape also affects levels of toxicity. Rod-shaped Fe$_3$O$_3$ nanoparticles were found to produce much higher cytotoxic responses than sphere-shaped Fe$_3$O$_3$ nanoparticles in a murine macrophage cell line (RAW 264.7) (Lee et al. 2014). Rod-shaped CeO$_2$ nanoparticles were found to produce more toxic effects in RAW 264.7 cells than octahedron or cubic particles (Forest et al. 2017). Nanorod ZnO particles are more toxic toward human lung epithelial cells (A549) than the corresponding spherical ones (Hsiao and Huang 2011). The reason why the physical shape of a nanoparticle affects cytotoxicity is not elucidated yet.

Theoretical model studies based on quantum-chemical calculations are capable to shed more light on these problems. The relation between activity of some antioxidants and their copper coordination ability based on B3LYP calculations of their metal ion affinity (MIA) values has been investigated recently.
The stability order of the antioxidant ligands with metals bonded at various coordination sites strongly depends on their position and nature. The spin density of the Cu$^{2+}$ cation upon ligand coordination becomes vanishingly small, whereas the ligand spin density approaches 1. Thus, the ligand is oxidized to a radical cation (Ligand$^+$), while Cu(II) is reduced to Cu(I). In agreement with experimental investigations, the higher antioxidant activity of individual compounds and their reaction sites may be assigned to higher MIA values and higher reducing character toward Cu(II). Another modification of the abovementioned method has been used for both N centers of a series of para-phenylene diamine (PPD) antioxidants (Puškárová and Breza 2016). Nearly linear dependence of the experimental antioxidant effectiveness on Cu(II)-PPD interaction energies, Cu atomic charges, and other electron density parameters has been deduced. This method might be used to estimate the level of oxidation stress caused by nanoparticles and thus of their cytotoxicity.

Nano-sized TiO$_2$ particles can be found in a large number of foods, cosmetic goods, and consumer products. Their nanotoxicity has been drawn an increasing attention because human bodies are potentially exposed to this nanomaterial either by inhalation, oral, or dermal route. Numerous studies have tried to characterize their in vivo biodistribution, clearance, and toxicological effects (see, e.g., Olmedo et al. (2002), Wang et al. (2007), Fabian et al. (2008), Xie et al. (2011), Wang et al. (2013), Geraets et al. (2014), Elgrabli et al. (2015)).

Rutile is the most stable polymorph of TiO$_2$ at all temperatures exhibiting lower total free energy than the metastable phases of anatase or brookite (Hanaor et al. 2012a). Rutile has a tetragonal unit cell (space group $P4_2/mnm$) (Diebold 2003). The titanium cations are surrounded by an octahedron of 6 oxygen atoms while the oxygen anions have a coordination number of 3. Rutile crystals are most commonly observed to exhibit a prismatic or acicular growth habit with preferential orientation along their $c$-axis, the [001] direction. This growth habit is favored as the {110} facets of rutile exhibit the lowest surface free energy and are therefore thermodynamically most stable (Hanaor et al. 2012b).

The rutile (110)–aqueous solution interface structure was measured in deionized water (DIW) at 25 °C by the X-ray crystal truncation rod method (Zhang et al. 2007).
The rutile surface consists of a stoichiometric (1:1) surface unit mesh with the surface terminated by bridging oxygen (BO) and terminal oxygen (TO) sites, with a mixture of water molecules and hydroxyl groups (OH) occupying the TO sites.

Very recently, scanning tunneling microscopy and surface X-ray diffraction were used to determine the structure of the rutile (110) – aqueous interface, which is comprised of an ordered array of hydroxyl molecules with molecular water in the second layer (Hussain et al. 2017). A combination of experimental data with interpretation aided by DFT calculations implies that the rutile TiO$_2$ (110) surface has terminal hydroxyls in the contact layer. The ideal coverage by terminal OH groups is half a monolayer, but this is decreased to approximately 0.4 monolayers by absences at domain wall boundaries.

The liquids in human body are, in principle, aqueous solutions which imply a possible protonation of the negatively charged surface of the rutile nanoparticles. For the sake of simplicity, only hexacoordinated Ti atoms and full protonation of non-bridging O atoms may be supposed in model systems. The aim of this study is to compare the toxicity of small idealized protonated rod-like and sphere-like rutile nanoparticles based on their Cu(II) complexation ability and electron density transfer to Cu at DFT level of theory.

**Method**

Geometries of the model systems under study in their lowest ground spin states (denoted by spin multiplicity as the left superscript) were optimized using B3LYP functional (Becke 1993) with standard 6-311G* basis sets for all atoms (McLean and Chandler 1980; Raghavachari et al. 1980; Wachters 1970). Stability of the optimized structures was confirmed by vibrational analysis (no imaginary vibrations). Atomic charges...
were evaluated in terms of Mulliken population analysis (MPA) (Mulliken 1955), atomic polar tensor (APT) derived charges (Cioslowski 1989), and natural population analysis (NPA) (Reed et al. 1988). All the calculations were performed using Gaussian09 program package (Frisch et al. 2013).

Fig. 5 Optimized structures and models notation of $^{2}$(Ti$_7$O$_{30}$H$_{30}$Cu)$_2$–C1 model series (Ti green, O red, H gray, Cu blue)
The metal-ligand interaction energy $\Delta_{\text{int}}E$ is defined as

$$\Delta_{\text{int}}E = E_{\text{Complex}} - E_L - E_{\text{ion}}$$

where $E_{\text{Complex}}$ and $E_L$ are the energies of the $[\text{L...Cu}]^{n+}$ complex and of the isolated rutile nanoparticle $L^q$ model cluster in their optimized geometries, respectively, and $E_{\text{ion}}$ is the energy of the isolated $\text{Cu}^{2+}$ ion (Alagona and Ghio 2009a, b; Mammino 2013; Puškárová and Breza 2016). Metal-ligand interaction enthalpy $\Delta_{\text{int}}H_{298}$ and Gibbs free energy $\Delta_{\text{int}}G_{298}$ data at 298 K were evaluated analogously.

Results and discussion

In the first step, it was necessary to build suitable model systems based on experimental rutile structure (Diebold...
2003) with fully protonated surface oxygen atoms of nearly spheric and rod-like shapes which are small enough to be treated by DFT methods. This task is complicated by additional requirements on equal charges and (nearly) the same number of atoms in order to eliminate charge and size effects.

The nearly spherical structure of $^{1}[\text{Ti}_7\text{O}_{28}\text{H}_{26}]^{2-}$ (model A) in the singlet ground state consists of a single TiO$_6$ octahedron surrounded by six lateral TiO$_6$ octahedra (see Fig. 1 for the optimized geometry).

A rod-like chain structure consists of TiO$_6$ octahedra bonded by double $\mu$-OH bridges as the single bridged structures disintegrate after protonation (into fragments consisting of mostly two TiO$_6$ units). For comparative purposes, we investigate both the dimeric $^{1}[\text{Ti}_2\text{O}_{10}\text{H}_{10}]^{-}$ (model B) and heptameric $^{1}[\text{Ti}_7\text{O}_{30}\text{H}_{10}]^{2-}$ (model C) chains in the singlet ground state (see Fig. 2 for the optimized geometries). It may be seen that only up to three TiO$_6$ units are bonded by double OH bridges after protonation and these trimers are bonded by the single ones only. The reason of such behavior is unknown.

In the next step, we placed a Cu$^{2+}$ ion in the neighborhood of the oxygen atom (ca 1.7 Å distance) of various terminal (TO) hydroxyl (models A1, B1, and C1) or bridging (BO) hydroxyl (models A2, B2, and C2) groups. In this way, optimized structures are presented in Figs. 3, 4, 5, and 6 and Tables 1 and 2. As our model systems contain many oxygen atoms, Cu atoms in the optimized structures are bonded at least to two O atoms and at least one of them is TO. In A model series, Cu atoms are always bonded to BO whereas in B and C models, the Cu-BO bonding is rare (see B2a and C2b models). In some cases, Cu$^{2+}$ ions can cause splitting terminal hydroxyl groups (A1a and B1c models) or even Ti(OH)$_4$ units (C1b, C1d, and C1e models). Adding Cu$^{2+}$ ions to TO or (more frequently) to BO sites can cause hydroxyl bridges splitting. No Ti(OH)$_4$ unit removal proceeds due to Cu–BO bond formation. As expected, in all optimized structures, the Cu–BO bonds are longer than the Cu–TO ones whereas the shortest Cu–O bonds belong to free hydroxyls (A1a and B1c models) (Chart 1).

Positive Cu charges in all model systems (Tables 1 and 2) are always significantly lower than +2 (i.e., the free Cu$^{2+}$ ion charge in all types of population analysis). The highest average Cu charge (i.e., the lowest electron density transfer from the ligand) is observed for nearly spherical A models whereas these ones for B and C models are nearly equal (i.e., within their standard deviations). The highest Cu charges are in model systems with the highest number of Cu–O bonds (A2a, B1c, and C2b models). MPA charges are lower than the APT ones whereas the NBO ones are the highest ones. Nevertheless, all these population analysis types preserve the same trends in Cu charges. In agreement with Alagona and Ghio (2009a, b), Mammino (2013), and Puškárová and Breza (2016), only vanishing spin density remains at Cu atoms in optimized structures (not presented).

Metal-ligand interaction energies (Table 3) evaluated in terms of DFT energies, and Gibbs free energies are practically equal whereas these ones in terms of enthalpies are lower. Nevertheless, in all three cases, the same trends are preserved. Their average absolute values for model systems under study decrease in the sequence B > A > C. The highest energy is released for the systems with maximal numbers of Cu–O bonds.

![Table 1](https://example.com/table1.png)

| Compound | Model | q(Cu)$_{\text{MPA}}$ | q(Cu)$_{\text{APT}}$ | q(Cu)$_{\text{NBO}}$ | d$_{\text{Cu-O}}$ [Å] |
|----------|-------|---------------------|---------------------|---------------------|---------------------|
| $^{2}[\text{Ti}_7\text{O}_{28}\text{H}_{26}]^{2-}$ | A1a   | 0.518               | 0.829               | 0.957               | 1.764 (TO), 1.996 (BO) |
|         | A2a   | 0.684               | 1.054               | 1.048               | 1.902 (TO), 1.970 (TO), 2.026 (BO) |
|         | A2b   | 0.403               | 0.541               | 0.710               | 1.935 (TO), 1.958 (BO) |
|         | Average | 0.53 ± 0.14        | 0.81 ± 0.26         | 0.90 ± 0.18         |         |
| $^{2}[\text{Ti}_2\text{O}_{10}\text{H}_{10}]^{2-}$ | B1a   | 0.406               | 0.585               | 0.719               | 1.976 (TO), 1.956 (TO) |
|         | B1b   | 0.286               | 0.507               | 0.629               | 1.918 (TO), 1.923 (TO) |
|         | B1c   | 0.540               | 0.959               | 1.001               | 1.818, 1.939 (TO), 1.941 (TO) |
|         | B2a   | 0.330               | 0.565               | 0.710               | 2.074 (TO), 2.095 (TO), 2.154 (BO) |
|         | Average | 0.39 ± 0.11        | 0.65 ± 0.21         | 0.76 ± 0.16         |         |

a) Terminal oxygen atoms bonded to the same Ti center.
(A2a and B1c models) or with a maximal number of broken OH bridges (C2c model). Coiled C chains around Cu atoms are important for the energy effects as well.

**Chart 1** Ti centers notation in \( [\text{Ti}_{2}O_{33}H_{35}]^{2-} \)-model C

**Table 2** MPA (q(Cu)\text{MPA}), APT (q(Cu)\text{APT}) and NBO (q(Cu)\text{NBO}) copper atomic charges, the lengths of Cu-O bond to (d_{Cu-OH}) oxygen atoms of terminal (TOi), and bridging (BOij) hydroxyl groups bonded to the i-th and j-th Ti centers (see Chart 1), respectively, and the indices of broken \( \mu_{ij}-\text{OH} \) bridges of the C model series

| Compound | Model | q(Cu)\text{MPA} | q(Cu)\text{APT} | q(Cu)\text{NBO} | d_{Cu-OH} [Å] \(^3\) | i-j |
|----------|-------|----------------|----------------|----------------|-------------------|-----|
| \( [\text{Ti}_{7}O_{28}H_{26}]^{2-} \)| C     |                |                |                |                   | 1-2 |
| \( [\text{Ti}_{7}O_{30}H_{30}]^{2-} \)| C1a  | 0.382          | 0.632          | 0.711          | 1.951(TO1) 1.969(TO1) | 1-2 |
|         | C1b  | 0.408          | 0.579          | 0.734          | 2.003(TO2) 1.951(TO2) | 1-2 |
|         | C1c  | 0.368          | 0.546          | 0.659          | 1.986(TO1) 1.883(TO2) | 1-2 |
|         | C1d  | 0.379          | 0.533          | 0.630          | 1.888(TO2) 1.878(TO3) | 1-2 |
|         | C1e  | 0.314          | 0.520          | 0.652          | 1.886(TO3) 1.900(TO4) | 1-2 |
|         | C1f  | 0.437          | 0.533          | 0.686          | 1.885(TO6) 1.898(TO5) | 1-2 |
|         | C1g  | 0.343          | 0.513          | 0.653          | 1.891(TO7) 1.932(TO6) | 1-2 |
|         | C1h  | 0.383          | 0.617          | 0.720          | 1.964(TO7) 1.971(TO7) | 1-2 |
|         | C2a  | 0.369          | 0.529          | 0.619          | 1.892(TO1) 1.870(TO2) | 1-2 |
|         | C2b  | 0.550          | 1.250          | 1.009          | 1.943(TO2) 2.011(TO3) 1.939(TO7) 2.096(BO23) | 1-2 |
|         | C2c  | 0.270          | 0.500          | 0.596          | 1.868(TO2) 1.870(TO4) | 1-2 |
|         | C2d  | 0.435          | 0.564          | 0.679          | 1.911(TO4) 1.911(TO5) | 1-2 |
|         | C2e  | 0.437          | 0.531          | 0.685          | 1.884(TO6) 1.896(TO5) | 1-2 |
|         | C2f  | 0.360          | 0.512          | 0.666          | 1.911(TO6) 1.912(TO7) | 1-2 |
| Average |       | 0.388 ± 0.066  | 0.60 ± 0.19    | 0.693 ± 0.099  |                   |     |

\(^{a3}\)Bonded oxygen atoms in parentheses
Conclusions

Our results show that the electron density removal from model rutile nanoparticles is connected with significant changes in their structure and may cause their degradation as well. Unfortunately, we cannot obtain any structure with only one Cu–O bond, but terminal hydroxyls seem to be more reactive than the bridging ones as indicated by the geometries and interaction energies of the optimized structures. Spherical structures are more reactive than the rod-like chains of the (nearly) same size. The reverse relation holds for the degree of their toxicity as indicated by the extent of the electron density transfer to a Cu\(^{2+}\) probe. Experimental proof of these conclusions might be based on cytotoxicity comparison of rutile nanoparticles of various shapes (and of similar size distributions). Nevertheless, in the light of our results, the higher toxicity of the abovementioned rod-shaped Fe\(_2\)O\(_3\), CeO\(_2\), or ZnO nanoparticles in comparison with the spherical ones (Lee et al. 2014; Forest et al. 2017; Hsiao and Huang 2011) may be explained by the higher electron density transfer to the interacting cells.

In our study, the most popular B3LYP hybrid functional (Becke 1993) is used in analogy with previous studies on the relation between activity of antioxidants and their copper coordination ability (Alagona and Ghio 2009a, b; Mammino 2013; Puškárová and Breza 2016). We suppose that the results should not depend on this choice crucially as indicated by our very recent toxicity study of a [Ti\(_{40}\)O\(_{124}\)H\(_{81}\)]\(^{-}\) model cluster using its Cu\(^{2+}\) coordination ability (Breza and Šimon 2019) which is based on a semiempirical PM6 method. Nevertheless, further theoretical studies in this field are desirable.

Although the scientific community has made considerable strides in understanding nanotoxicity in the recent past, the future research needed to decipher nanotoxicity

| Compound | Model | \(\Delta_{\text{int}}E\) [kJ/mol] | \(\Delta_{\text{int}}G_{298}\) [kJ/mol] | \(\Delta_{\text{int}}H_{298}\) [kJ/mol] |
|----------|-------|-----------------|-----------------|-----------------|
| \(2[\text{Ti}_{2}\text{O}_{10}\text{H}_{10}\text{Cu}]^0\) | A1a | −2586.4 | −2589.3 | −2568.5 |
| | A2a | −2675.8 | −2671.6 | −2635.0 |
| | A2b | −2516.5 | −2517.1 | −2486.4 |
| | Average | −2593 ± 80 | −2593 ± 77 | −2563 ± 74 |
| | B1a | −2695.6 | −2694.7 | −2665.0 |
| | B1b | −2757.2 | −2758.4 | −2726.3 |
| | B1c | −2906.6 | −2903.2 | −2865.4 |
| | B2a | −2696.0 | −2696.7 | −2661.8 |
| | Average | −2764 ± 99 | −2763 ± 98 | −2730 ± 95 |
| | \(2[\text{Ti}_{2}\text{O}_{10}\text{H}_{30}\text{Cu}]^0\) | C1a | −2401.9 | −2396.7 | −2343.5 |
| | C1b | −2483.4 | −2476.7 | −2429.0 |
| | C1c | −2387.1 | −2384.3 | −2350.7 |
| | C1d | −2396.9 | −2394.8 | −2346.2 |
| | C1e | −2470.5 | −2467.5 | −2422.4 |
| | C1f | −2453.9 | −2444.9 | −2405.1 |
| | C1g | −2494.4 | −2492.4 | −2445.7 |
| | C1h | −2451.8 | −2454.1 | −2424.6 |
| | C2a | −2453.7 | −2476.0 | −2412.7 |
| | C2b | −2419.1 | −2417.8 | −2381.0 |
| | C2c | −2722.8 | −2720.2 | −2656.1 |
| | C2d | −2453.6 | −2444.4 | −2406.1 |
| | C2e | −2486.5 | −2487.0 | −2457.6 |
| | C2f | −2415.6 | −2410.2 | −2383.8 |
| | Average | −2464 ± 82 | −2462 ± 83 | −2419 ± 77 |
remains significant (Huang et al. 2017). For instance, what are the properties of the nanoparticle that induce oxidative stress? How do nanoparticles interact, physically and chemically, with biomolecules such as nucleic acids, proteins, and lipids leading to alteration of gene expression? The answer on the last question in Huang et al. 2017—what is the basic scientific principle that dictates the shape-dependent cytotoxicity?—might be based on the results of our study. Besides size, charge, and shape, also the mixing of different elements in a nanoparticle and its chemical ordering may greatly change its cytotoxicity (see e.g., Benetti et al. 2019).

We are convinced that quantum-chemical modeling is necessary for answering all these questions. As quantum-chemical calculations of larger model systems are connected with serious technical problems at DFT level of theory, an ONIOM (our own n-layered integrated molecular orbital and molecular mechanics) treatment (Dapprich et al. 1999) combining DFT, semiempirical and molecular mechanics calculations would be advisable to use.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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