Supporting Information

Computer-Aided Design of Nanoceria Structures as Enzyme Mimetic Agents: The Role of Bodily Electrolytes on Maximising Their Activity.

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Details of Models

Quantum Mechanics. Density Functional Theory (DFT) calculations were performed using the Vienna Ab initio Simulation Package (VASP),\(^1\)\(^-\)\(^2\) within which projector augmented wave pseudopotentials and a plane wave cutoff of 500 eV were used. Calculations were carried out using the generalized gradient approximation (GGA) exchange-correlation functional of Perdew, Burke and Ernzerhof revised for solids (PBEsol)\(^3\), with the +U correction of Dudarev\(^4\) to account for on-site Coulombic interactions. A U value of 5eV is applied to Ce f states.\(^5\)

The structures were geometrically optimized until the residual forces on each atom were less than 10 meV Å\(^-1\). All calculations were spin polarized and a ferromagnetic ordering was used throughout, which was shown to bare no difference in the energetic of CeO\(_2\) systems.\(^6\)

CeO\(_2\) bulk was optimized at constant pressure using a 4 CeO\(_2\) unit fluorite structure with a k-point grid of \(\Gamma\)-centred 4 x 4 x 4 Monkhorst-Pack grid. Upon optimization bulk CeO\(_2\) retain the fluorite crystal structure (space group \(\text{\Gamma}m\overline{3}m\)) despite a small expansion of the unit cell, which is well-documented effect for the ab initio methodology used in this study.\(^5\) The simulated lattice parameters (\(a=0.544\text{nm}\) and \(\alpha=\beta=\gamma=90^\circ\)) compares well with the experimental lattice parameters (\(a=0.541\text{nm}\) and \(\alpha=\beta=\gamma=90^\circ\)).

The three most stable surfaces of CeO\(_2\) were generated by cleaving the optimized bulk structure along the Miller indices \{111\}, \{110\} and \{100\}. The surfaces were modelled at constant volume using 6 repeat crystal layers (24 CeO\(_2\) units) via the introduction of a 15 Å vacuum gap perpendicular to the surface to minimize the interaction between images. Crystal thickness and vacuum depth were checked and deemed converged. According to Tasker the \{110\} surface is a type I, the \{111\} surface is a type II whereas the dipolar \{100\} surface is a type III. In the latter the dipole is removed by shifting half of the surface oxygen atoms to the opposite side of the structure. This is an approximation for the structure of the \{100\} surface, which was found to have a complicated potential energy surface.\(^7\)\(^8\)

The \{100\} and \{110\} surfaces are a p (2 x 2) expansion, whereas the \{111\} surface is a p(2 x \(\sqrt{3}\)) expansion of the surface primitive unit cells. The k-point grid of \(\Gamma\)-centred 2 x 2 x 1 with the third
vector perpendicular to the surface plane was used. The slab method was used to calculate the surface energy of the stoichiometric surface. This method generates two identical surfaces and does not require a dipolar correction to the energy of the system. The surface method was used to evaluate the adsorption of phosphates on the surface. This method uses a two region approach and therefore a dipolar correction to the energy is required. In our calculations, 2 crystal repeat units are kept fixed to their equilibrium bulk position whereas the remaining crystal layers are allowed to relax. As the number of configurations for adsorbed phosphate on surfaces of ceria is extremely large, we have limited the choice to structures that maximize the hydrogen bonding between the adsorbate and the surface. Few configurations were computed, but only the most stable are reported. All structural models were made using the METADISE code.

Using the slab method, the surface energy ($\gamma_s$) is calculated from the energy of slabs ($E(CeO_2)_s$), the energy of ceria stoichiometric bulk ceria ($E(CeO_2)_b$), and the surface area ($S$), according to Equation S1.

$$\gamma_s = \frac{E(CeO_2)_s - E(CeO_2)_b}{2S}$$  \hspace{1cm} (S1)

The relative stability of the three stoichiometric surfaces is expressed in terms of surface energy ($\gamma_s$) follows the order 0.85 Jm$^{-2}$, 1.23 Jm$^{-2}$ and 1.72 Jm$^{-2}$ for the {111}, {110} and {100} surfaces, respectively, in agreement with the literature.

The heat of reduction associated with creating an oxygen vacancy at the surfaces of ceria, i.e. by removing an oxygen ion from the surface leaving two electrons localised onto 4f states of neighbouring cerium ions, can be calculated using Equation S2, where $E(CeO_{2-x})_s$ and $E(CeO_2)_b$ are the energies of the oxygen deficient and stoichiometric surfaces and $E(O_2)$ is the energy of a diatomic $O_2$ molecule in the gas phase.

$$E_{\text{red}} = E(CeO_{2-x})_s + \frac{1}{2}E(O_2) - E(CeO_2)_s$$  \hspace{1cm} (S2)

The heat of reduction of the three surfaces ($E_{\text{red}}$) follows the order {111}, {100} and {110} with values of 254.72 kJ/mol, 192.01 kJ/mol and 177.53 kJ/mol, respectively, in agreement with the literature.
Nanoceria like other inorganic materials is a nanozyme.\textsuperscript{10-11} The interaction of phosphates at the surfaces of nanoceria was studied following Scheme S1, Scheme S2 and Scheme S3. Scheme S1 considers hydroxylated, oxygen stoichiometric surfaces of nanoceria. Scheme S2 considers oxygen deficient surfaces of nanoceria. Scheme S3 considers hydroxylation of oxygen deficient surfaces of nanoceria. The surface concentration (in molar fraction) of hydroxyl groups, oxygen vacancies and Ce\textsuperscript{3+} are calculated within the surface repeat unit layer for each type of surfaces using the products as reference state. Although pH may vary depending on the local cellular environment, at physiological pH only $H_2PO_4^-$ and $HPO_4^{2-}$ are relevant species at a 4:1 ratio. For this reason, we present data for $H_2PO_4^-$ adsorbing at the surfaces of nanoceria, showing the schematic representation of each reaction in Scheme S1, Scheme S2 and Scheme S3, respectively. For each reaction, the snapshot of the final product (i.e. the phosphate adsorbed on the {111}, {100} and {110} surfaces of nanoceria) is presented in Fig. S1, Fig. S2 and Fig. S3, for Scheme S1, Scheme S2 and Scheme S3, respectively.

**Classical Mechanics.** A model nanoparticle of CeO\textsubscript{2} comprising 18849 atoms was generated using simulated amorphisation and crystallisation, details of this strategy can be found in reference.\textsuperscript{12} During crystallisation the structure of the nanoparticle evolves exposing {111}, {110} and {100} surfaces in accord with the real nanomaterial. 628 oxygen vacancies (together with 1256 Ce\textsuperscript{3+} for charge balance) were then randomly introduced into the model nanoparticle and MD simulation was run, at 2000K, for 2.5 ns. This was to enable the oxygen vacancies to locate to low energy positions within the nanoparticle; the nanoparticle was then cooled. Inspection of the model revealed the presence of oxygen vacancies, which reside throughout the nanoparticle and also on the surface, Fig. 1 in main manuscript.
Scheme S1. The adsorption of phosphate ions ($H_2PO_4^-$, green) on hydroxylated, oxygen stoichiometric surfaces of nanoceria. The concentration of surface hydroxyl groups (OH, blue) governs the concentration of surface Ce$^{3+}$ ions (red), and whilst it increases, the ratio Ce$^{4+}$/Ce$^{3+}$ decreases from equations 1a to 1c.

Scheme S2. The adsorption of phosphate ($H_2PO_4^-$, green) on oxygen deficient surfaces of nanoceria. The concentration of surface oxygen vacancies governs the concentration of surface Ce$^{3+}$ ions (red), and whilst it increases, the ratio Ce$^{4+}$/Ce$^{3+}$ decreases from equations 2a to 2b.
Scheme S3. The adsorption of phosphate ($H_2PO_4^-$, green) on hydroxylated and oxygen deficient surfaces of nanoceria. Oxygen deficiency is kept constant in the reactant. Thus, the concentration of hydroxyl groups governs the concentration of surface Ce$^{3+}$ ions (red), and whilst it increases, the ratio Ce$^{4+}$/Ce$^{3+}$ decreases from equations 3a to 3b. This scheme also include Equation 2a in Scheme S2 as this provides the starting point for comparison.
Fig. S1. Adsorption site of phosphate ions on hydroxylated (a, b, c) (111), (d, e, f) (110), and (g, h, i) (100) surfaces of nanoceria at different hydroxylation content. Cerium in cream, hydrogen in white, and oxygen in red respectively. Phosphate anions shown as grey polyhedra.
Fig. S2. Adsorption site of phosphate ions on oxygen deficient (a, b) {111}, (c, d) {110}, and (e, f) {100} surfaces of nanoceria at different oxygen stoichiometry. Cerium in cream, hydrogen in white, oxygen in red, and oxygen vacancies in grey respectively. Phosphate anions shown as grey polyhedra.
Fig. S3. Adsorption site of phosphate ions on hydroxylated, oxygen deficient (a, b, c) \{111\}, (d, e, f) \{110\}, and (g, h, i) \{100\} surfaces of nanoceria at different hydroxylation content and oxygen stoichiometry. Cerium in cream, hydrogen in white, oxygen in red, and oxygen vacancies in grey, respectively. Phosphate anions shown as grey polyhedra.
Details of Experimental Methodology

**Nanoparticle preparation.** Bare Nanoceria particles were synthesized according to the procedure described in the paper.\textsuperscript{13,14} Typically, an appropriate amount of Cerium (IV) ammonium nitrate was dissolved in the DI water and the reaction was carried out at 100 °C under reflux conditions with continues stirring. An appropriate amount of ammonium hydroxide was added slowly to the equilibrated solution mixture and the reaction was continued for 24 h to obtain CeO\textsubscript{2} nanoparticle dispersion.

**Phosphate Ion Treatment.** The phosphate ion buffer solution was prepared by mixing the 1:1 ratio of a 50 mM aqueous solution of Na\textsubscript{2}HPO\textsubscript{4} and 50 mM aqueous solution of NaH\textsubscript{2}PO\textsubscript{4}. The molar ratio of phosphate ion buffer solution and nanoparticle was maintained as 4:1 and incubated period was 24 h. The approximate concentration of ceria was determined by drying, at moderate temperature (70°C) under vacuum overnight, sample aliquots of known volume. Ceria molarity was calculated (under the assumption that the dried mass was purely CeO\textsubscript{2}; MW = 172.1 g/mol) from the dried weight and the initial sample volume. Measurements were performed in replicate and an averaged concentration was determined. The treated nanoparticles were separated by multiple centrifugation for XPS analysis.

**Characterization details.** The particle size was measured using High-Resolution Transmission Electron Microscopy (HRTEM) (FEI Technai F30 TEM), at a potential of 300 kV. The selected areas electron diffraction (SAED) pattern was used to analyse the crystallinity of nanoparticles. The analysis of the electronic/vacancy state of nanoceria was completed with the use of an X-ray Photoelectron Spectrophotometer. The Instrument used was a Physical Electronics 5400 ESCA using unmonochromatized Mg K\textsubscript{x} \textsubscript{1} (1253.6 eV) ray sources. The experiments were all conducted at ultrahigh vacuum (UHV) with a maximum internal pressure of $5 \times 10^{-8}$ Torrs within the instrument. The spectra observed are comparative standards that we have used to analyse the change in the surface chemistry of cerium, oxygen and phosphorous under their new chemical configuration. The spectra have all been referenced and shifted to the carbon peak position at 284.5 eV in order to compensate for charging due to irradiation.
The fitting of XPS spectra for Ce (3d) for Ceria before and after phosphate ion treatment produces deconvoluted peaks. The characteristic peaks are for Ce$^{3+}$ and Ce$^{4+}$. The deconvoluted Ce (3d) spectrum is relatively complex due to the presence of Ce in 3+ and 4+ oxidation states as well as multiple d-splitting. The peaks in the spectrum of Ce were deconvoluted using the PeakFit (4.0) software. XPS results indicate that Ce is in mixed valence states of 3+ (880.61, 885.12, 898.94, 903.40 ± 0.3 eV) and 4+ (882.25, 888.71, 897.92, 900.73, 907.13, 916.40 ± 0.3 eV). The integrated area under the curve of each deconvoluted peak was used to calculate the concentration of Ce$^{3+}$ ions as $[\text{Ce}^{3+}] = \Sigma \text{IA of Ce}^{3+} / \Sigma \text{IA of Ce}$, where, IA of Ce$^{3+}$ is the integrated area of the Ce$^{3+}$ state and IA of Ce is the total integrated area of all Ce peaks.

Details of peaks in XPS spectra O1s is given in Table S1.

![Table S1: peak position of XPS spectra O1s. Area % in brackets.](image-url)
References


