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Theoretical design of magnetically ultrasensitive two-dimensional ZnO biosensor for *in vivo* NO detection by electron paramagnetic resonance technique

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ABSTRACT

Nitric oxide (NO) is an important messenger molecule in physiological activities. *In vivo* detection of NO by the electron paramagnetic resonance (EPR) and electrochemistry is based on the variation of magnetization and conductivity in the presence of NO, respectively. In this paper, we focus on the adsorption of NO on the non-toxic zinc oxide with the intriguing two-dimensional structure, which is named as graphene-like zinc oxide (g-ZnO). According to our first-principles calculations, NO is physisorbed on the pristine g-ZnO with the binding energy of 0.24 eV. In order to improve the sensitivity of the NO detection, we employ the transition metal (TM) elements (Cr, Mn, Fe, Co, Ni, and Cu) to decorate g-ZnO, obtaining the TM-g-ZnO systems. It was found that the incorporation of TM significantly increases the binding energy of NO. Due to the coupling between the NO:2*p* orbital and the TM:3*d* orbitals, the variation of the total magnetization of TM-g-ZnO is as high as 0.62–3 μ_B per TM atom with the adsorption of NO, thus showing the sensibility to NO in terms of the magnetization. Furthermore, the calculated band structures show that the conductivity of TM-g-ZnO can be modulated in the presence of NO due to the hybridization between the NO molecular orbitals and the TM defective state in the band gap. Based on our results, the TM-g-ZnO systems show the promising application in NO sensing by the electron paramagnetic resonance (EPR) or electrochemistry.

1. Introduction

Nitric oxide (NO) takes the role of the messenger molecule in various physiological activities, such as neurotransmission [1], vasodilation [2] and immune responses [3]. Therefore, the *in vivo* detection of NO by microsensors is essential for real-time diagnosis. Extensive material engineering has been conducted to fabricate the NO sensors based on the electron paramagnetic resonance (EPR), electrochemistry, and fluorometry [4] approaches. The detection of NO in biological systems based on the EPR has comprehensively utilized the transition-metalloproteins, where NO molecules bond with the transition metal (TM) atoms of transition-metalloproteins, forming the TM-nitrosyl complexes [5]. Since both the NO and TM atoms possess unpaired electrons, an external magnetic field applied on the sample induces the splitting of energy levels of unpaired electrons. When the microwave radiation is shined on the sensor, the EPR spectrometer quantifies the NO by measuring the adsorption of radiation as a function of externally applied magnetic field [6]. The major advantage of EPR over the other forms of spectroscopy is the unique ability to make observations in complex, nonhomogeneous, and optically opaque solutions, thus making it possible to achieve the *in vivo* detection and three-dimensional imaging of NO [7]. On the other hand, the electrochemical approach has been also widely studied and shows the promising ability to detect NO mainly based on the cyclic voltammetry, where the presence of NO results in a variation of the electric current.

It has been shown that the employment of nanomaterials is able to significantly improve the sensitivity of the microsensors [8,9], such as the metal nanoparticles [10], nanowires [11], nanotubes [12] and monolayers [13]. Meanwhile, the transition-metalloproteins are attached to the low dimensional nanomaterial-based substrates as the adsorbent to further enhance the selectivity and sensitivity [14]. In short, the nanomaterial and the transition metal atoms play important role in both approaches, which relied on the variation of magnetization or conductivity in the presence of NO.

However, in contrast with the selection criteria of gas sensor material used in industrial production, one key paradigm in biological and biomedical fields is that safety research must be part of the development of new nanotechnologies. On one hand, the protein containing

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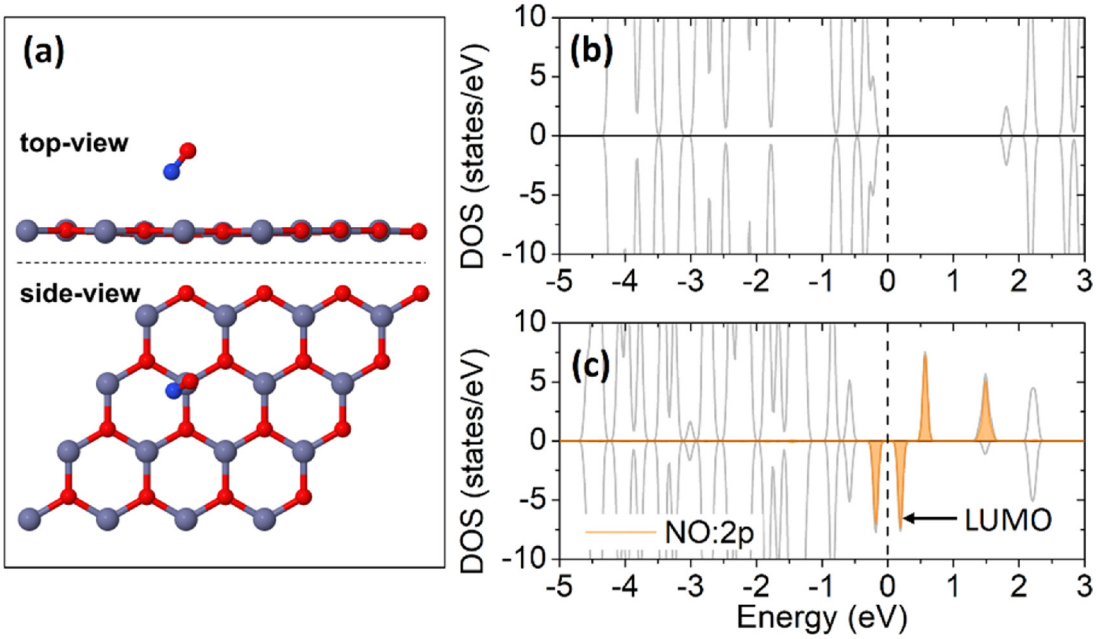

Fig. 1. (a) Crystal structure of NO-g-ZnO (Blue: nitrogen; red: oxygen; dark gray: zinc); Density of states of (b) pristine g-ZnO and (c) NO-g-ZnO. Gray lines represent the total DOS and orange ones for the 2*p* states of NO. Fermi level is represented by the vertical dash line. The lowest unoccupied molecular orbital (LUMO) of NO-g-ZnO is marked by the arrow.

Table 1
Binding energy of NO adsorbed on TM^{sub}-g-ZnO (E_b), total magnetization of TM^{sub}-g-ZnO and the magnetic moment of TM ion before and after NO adsorbed.

Element	E_b (eV)	Total magnetization (μ_B)		Magnetic moment of TM (μ_B)	
		before	*after*	*before*	*after*
Cr	1.20	4	1	3.73	1.99
Mn	0.70	5	4	4.62	4.16
Fe	1.27	4	3	3.59	3.64
Co	1.03	3	2	2.64	2.47
Ni	1.22	2	1	1.54	1.34
Cu	0.62	1	0	0.64	0

transition-metal atoms used in the NO detection is the target of nitrosative stress, which results in impairment and apoptosis [15]. On the other hand, the biological safety issues of graphene used in NO nanosensor also caused a lot of concern [16]. Some *in vitro* and *in vivo* studies show no particular risks [17], while the recent investigations have indicated that graphene and graphene-based nanomaterials might become health hazards [18,19]. Direct evidence for the toxicity of graphene has been reported by Biris et al. based on the lactate dehydrogenase test [20]. Furthermore, graphene has been predicted to be damaging to mammalian fibroblasts [21], and the growth rate of HepG2 cells may be disturbed after exposure to graphene by proteome analysis [22]. Therefore, novel safe nanomaterials for NO *in vivo* detection are desired.

Zinc oxide (ZnO) is a common nutrition enhancer in food. Therefore, ZnO is believed to be risk-free in biosecurity. Recently, a new ZnO specie with planar graphene-like structure (named as g-ZnO) has been predicted [23] and later successfully synthesized [24–26]. The g-ZnO monolayer possesses much higher surface-to-volume ratio as compared with its bulk counterpart. Therefore, the g-ZnO expected to be an excellent candidate for gas sensing. To date, numerous molecules have been considered, for example, H_2 [27], H_2S [28], SO_2 [29], CO_2 [30], CO [31], NO [32] et al., as the detecting targets based on the pristine g-ZnO system.

In view of the sensitivity and biosecurity for NO detection, in this paper, we study the adsorption of NO on both the pristine and transition metal elements (Cr, Mn, Fe, Co, Ni, and Cu) decorated g-ZnO (TM-g-ZnO) by performing the first-principles calculations. We focus on the variation of magnetic moment and electrical conductivity induced by the adsorption of NO. We found that: (i) the TM decoration induces the strong interaction between NO and g-ZnO; (ii) The magnetization and the conductivity of TM-g-ZnO can be significantly modulated by NO adsorption. Based on the results, the TM-decorated g-ZnO could be potential candidate for the *in vivo* NO detection.

2. Calculation details

The first-principles structure optimizations and self-consistent ground state calculations have been performed by the Vienna ab-initio simulation package (VASP) [33]. Projector-augmented wave (PAW) method [34] with the PBE [35] type exchange-correlation potentials was adopted. The optimized lattice parameters of g-ZnO (a = 3.232 Å) were used to build a 4 × 4 × 1 slab model (see Fig. 1a) with a vacuum layer of 20 Å to minimize the interaction between the neighboring slabs. The structure optimization and the ground state calculations were performed with a cut-off energy of 400 eV for basis set and a 2 × 2 × 1 Monkhorst-Pack grid for Brillouin zone sampling. The atomic positions were optimized until the forces were less than 0.02 eV/Å. The orbital-dependent on-site Coulomb repulsion of TM:3*d* electrons was taken into account by using DFT + U method [36] with $U_{TM\&Zn}$ = 3.0 eV [37]. To properly take into account the van der Waals (vdW) interactions in the structures, the DFT-D2 method [38,39] was used throughout all the calculations. The charge and the magnetic moment of TM ions was calculated by the Bader analysis algorithm [40].

3. Calculation results

3.1. NO adsorption on pristine g-ZnO

We first study the adsorption of NO adsorbed on the pristine g-ZnO monolayer. To evaluate the stability of NO adsorbed on the pristine g-ZnO, we calculated the binding energy (E_b) of NO which is defined as: