Accelerated discovery of superoxide-dismutase nanozymes via high-throughput computational screening

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The activity of nanomaterials (NMs) in catalytically scavenging superoxide anions mimics that of superoxide dismutase (SOD). Although dozens of NMs have been demonstrated to possess such activity, the underlying principles are unclear, hindering the discovery of NMs as the novel SOD mimics. In this work, we use density functional theory calculations to study the thermodynamics and kinetics of the catalytic processes, and we develop two principles, namely, an energy level principle and an adsorption energy principle, for the activity. The first principle quantitatively describes the role of the intermediate frontier molecular orbital in transferring electrons for catalysis. The second one quantitatively describes the competition between the desired catalytic reaction and undesired side reactions. The ability of the principles to predict the SOD-like activities of metal-organic frameworks were verified by experiments. Both principles can be easily implemented in computer programs to computationally screen NMs with the intrinsic SOD-like activity.
The principles governing the activity of nanomaterials (NMs) in the catalytically scavenging superoxide anion (O$_{2}^{\cdot-}$) underlie many biological effects of the materials, which are of great importance in both basic chemistry and therapeutic applications of the materials. O$_{2}^{\cdot-}$ is an unavoidable byproduct of oxygen metabolism. An excess amount of O$_{2}^{\cdot-}$ triggers many severe diseases, such as heart disease, cardiovascular disease, cancer, diabetes, Alzheimer’s disease, and Parkinson’s disease. To protect cells from O$_{2}^{\cdot-}$, biosystems have evolved a specific family of metalloenzyme called superoxide dismutases (SOD), which catalyze the dismutation of O$_{2}^{\cdot-}$ to form biologically less harmful species, hydrogen peroxide (H$_{2}$O$_{2}$) and O$_{2}$ (Fig. 1a). Intriguingly, recent studies have demonstrated that some inorganic NMs possess the activity of scavenging O$_{2}^{\cdot-}$, which mimics SOD (Table 1). Compared to SOD, NMs are usually more stable and less expensive. Moreover, such enzyme-like NMs (collectively called nanozymes) can simultaneously possess unique electronic and magnetic properties, which are not exhibited by SOD. Therefore, NMs with SOD-like catalytic activity has shown the potential to develop novel therapeutic strategies in the area of radiation protection and the treatment of diseases such as vascular calcification, immunodeficiencies, and neurodegenerative diseases.

However, the activities of these NMs in catalytically scavenging O$_{2}^{\cdot-}$ are much weaker than those of SODs, hindering their widespread applications. Lacking a general prediction theory, the rational design of NMs with sufficiently high activities along with other desired properties is particularly challenging. Dugan and coworkers suggested a two-step mechanism for water-soluble C$_{60}$ fullerene catalytically scavenging O$_{2}^{\cdot-}$. The catalyst is first reduced by accepting an electron from O$_{2}^{\cdot-}$, followed by transferring the electron to another O$_{2}^{\cdot-}$; these two steps generate O$_{2}$ and H$_{2}$O$_{2}$, respectively, in the presence of protons in the solution. This mechanism has been verified by later studies on the SOD-like properties of other C$_{60}$ derivatives, sp$^{2}$-carbon nanoparticles, and perylene diimide. Self and coworkers experimentally demonstrated that the SOD-like activity of nanoceria increases with the ratio of Ce$^{3+}$ to Ce$^{4+}$ in the material. Using density functional theory (DFT) calculations, we computationally studied the rearrangements of H$_{2}$O$_{2}$ radicals on the surfaces of nanoceria and noble metals in the gas phase, which suggested that the catalyst surfaces influence the catalytic activity by tuning the kinetic stability of the intermediate structures involved in the rearrangements. Although these results have provided insights into the catalytic mechanisms and have revealed structure-activity relationships for some specific types of NMs, the general principles determining the activity are still elusive. On the other hand, previous studies have established a powerful principle, which is shown in Fig. 1b, for the activity of SOD.

In this work, by learning from the principle of SOD and considering the differences between the NMs and SOD, we develop and verify a new energy level principle and adsorption energy principle for the SOD-like activity of NMs on the basis of their electronic band structures and surface adsorption energies, respectively. The energy level principle reveals the critical role of the intermediate frontier molecular orbital (iFMO), which is defined as the FMO of the NM with energy located in between $\varphi_{1}$ and $\varphi_{2}$, where $\varphi_{1}$ and $\varphi_{2}$ are the potentials of the half-reactions of O$_{2}^{\cdot-}$ dismutation, in transferring electrons for catalysis. The adsorption energy principle quantitatively describes the competition between the target catalytic reaction and possible side reactions for O$_{2}^{\cdot-}$ on the catalysts. Therefore, the combination of both principles provides not only systematic and in-depth insight into the mechanisms of the SOD-like properties of NMs but also a general guide for the computational design and screening of SOD-like NMs.

### Results and discussion

#### Energy level principle

We first developed a theoretical model to predict the activity of NMs catalyzing the dismutation of O$_{2}^{\cdot-}$. In nature, SOD is the enzyme that specifically catalyzes this reaction, and previous studies have achieved a thermodynamics-based model (Fig. 1b). According to this model, the reduction potential order $\varphi_{1} < \varphi_{\text{SOD}} < \varphi_{2}$ is the sufficient and necessary condition for the activity of SOD. This condition ensures that both half-reactions of the dismutation are thermodynamically spontaneous and that the maximized activity is reached when $\varphi_{\text{SOD}} = (\varphi_{1} + \varphi_{2})/2$. Because all reaction steps involved in SOD catalysis have low energy barriers and the catalyzes are under

#### Table 1 Nanomaterials catalytically scavenging O$_{2}^{\cdot-}$ and having atomistic-level structural information for the computational investigation.

| Material       | Type       | Exposed facets | Ref. |
|----------------|------------|----------------|------|
| sp$^{2}$-carbons | Carbon     |                | 9-13 |
| Au             | Metal      | (111), (100)   | 15   |
| Pd             | Metal      | (111)          | 16   |
| Pt             | Metal      |                | 17   |
| MnO            |            |                | 18   |
| MnO$_{2}$      |            |                | 19,20|
| Mn$_{3}$O$_{4}$| Spinel     | (211), (103), (101) | 21-23|
| Co$_{3}$O$_{4}$| Inverse spinel | (220), (311), (400) | 24   |
| NiO            |            | (111), (200)  | 25   |
| CeO$_{2}$      | Fluoride   | (111), (200)  | 26   |
| Mo$_{2}$       | TMDC       |                | 27   |
| V$_{2}$C       | MXene      |                | 28   |
| Nb$_{2}$C      | MXene      |                | 29   |

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**Fig. 1 Metalloenzyme catalytically scavenging O$_{2}^{\cdot-}$.** a. The superoxide dismutase (SOD) that scavenges O$_{2}^{\cdot-}$ by catalyzing its dismutation reaction. b. The reduction potential model predicting the catalytic activity of SOD. In b, $\varphi_{1}$ and $\varphi_{2}$ are the reduction potentials of O$_{2}$/O$_{2}^{\cdot-}$ and O$_{2}^{\cdot-}$/H$_{2}$O$_{2}$, respectively, and their values at pH = 7 are given in the parentheses.
thermodynamic control, such a purely thermodynamics-based theoretical principle of SOD has stood the test of time.\textsuperscript{14}

To develop a prediction model for NMs by learning from SOD, the following two differences between the NM and SOD must be considered. First, the electron energy levels responsible for electron transfer in catalysis are different. In SODs, the level is $\phi_{\text{SOD}}$, i.e., the potential of Mn\textsuperscript{1+}/MnSOD. In contrast, those of NMs are FMOs, which include the conduction band minimum (CBM), valence band maximum (VBM), or mid-gap impurity level (MGIL). For bandgap NMs, the MGILs are associated with structural imperfections; for metal NMs, the MGILs are Fermi energy levels ($E_F$). Second, the possibilities of side reactions in the two cases are different. Because of its protein scaffolds, SOD catalyzes the dismutation of O$_2$\textsuperscript{−} with high specificity. By contrast, side reactions may compete with the target catalytic reaction occurring on the NMs. These two differences suggest the necessity of developing new principles for the SOD-like activity of NMs.

Because FMOs are responsible for electron transfer in the case of NMs, we hereby adjust $\phi_{\text{SOD}}$ in the model of SODs to the FMO energy ($E_{\text{FMO}}$) to fit with the NMs. A similar idea of using FMO energies as activity descriptors has been proposed for the oxidative dehydrogenation reactions catalyzed by CeO$_2$-based catalysts.\textsuperscript{35,36} Therefore, we obtain the energy level principle for NMs (Fig. 2a). According to this principle, we propose Eq. (1)

$$\phi_1 < E_{\text{FMO}} < \phi_2$$

(1)

to be the first criterion for screening NMs as O$_2$\textsuperscript{−} scavenging catalysts. Thereafter, we will denote the FMO satisfying Eq. (1) as iFMO. Similar to the case of SOD, when $E_{\text{FMO}} = (\phi_1 + \phi_2)/2$, the maximized catalytic efficiency of the NM will be anticipated when the other factors influencing the activity are the same. With this principle, it is easy to predict whether a NM is a potential SOD mimic. Figure 2b illustrates XI types of electronic band structures of NMs: I – VIII are characteristics of bandgap NMs, and IX – XI are those of metal NMs. Among them, I, II, IV, V, and IX have a VBM, a CBM, an occupied MGIL (OMGIL), an unoccupied MGIL (UMGIL), and an $E_F$ in the range ($\phi_1$, $\phi_2$), respectively; III has both a VBM and a CBM in this range. Accordingly, these NMs have iFMOs and thus are potential catalysts. In contrast, VI, VII, VIII, X, and XI have no iFMOs and thus are not the potential catalysts. Because the FMO energies of NMs can be measured by experiments or calculated by DFT, this energy level principle could be easily implemented for screening NMs toward O$_2$\textsuperscript{−} scavenging catalysts.

To verify the energy level principle, we have calculated the electronic density of states (DOs) for all materials listed in Table 1, whose SOD-like catalytic activities have been experimentally confirmed before. For these calculations, graphene has been used as the model of sp$^2$ carbons. Reportedly, MoS$_2$ contains sulfur vacancies.\textsuperscript{37} Therefore, MoS$_{2-x}$ with a reduced number of sulfur has been used for the calculation (for computational method, see Supplementary Fig. 2, Supplementary Table 1, and Supplementary Method). The calculated results are shown in Fig. 2c and Supplementary Fig. 3a. NiO, MoS$_{2-x}$, Mn$_3$O$_4$, Co$_3$O$_4$, V$_2$C, Nb$_2$C, Au, and Pd indeed have FMOs located in the energy window (~0.16 V, 0.94 V). The Fermi level of graphene is ~0.19 V, which is close to ~0.16 V. These results excellently support the energy level principle. The CBM of MnO$_2$ has energy more positive than $\phi_2$; therefore, MnO$_2$ will probably oxidize O$_2$\textsuperscript{−} to form O$_2$, H$_2$O, and MnO$_{2-x}$ in the presence of H$^+$ rather than catalyze the disproportionation of O$_2$\textsuperscript{−}. In contrast, the VBM of MnO has energy more negative than $\phi_1$; therefore, MnO will probably reduce O$_2$\textsuperscript{−} to form H$_2$O and MnO$_{2-x}$ in the presence of H$^-$? We reason that the SOD-like activities experimentally found for them are actually originated from the modified structures MnO$_{2-x}$ and MnO$_{1+x}$, respectively. Similarly, the SOD-like activity of CeO$_2$ is originated from the modified structure CeO$_{2-x}$.\textsuperscript{26,32} Pt does not have any iFMO, which can be ascribed to that Pt particles practically expose irregular surfaces unlike the Pt(111) used for the calculation. These results suggest the potential power of the principle to investigate the in-situ active structures for the catalysts.

Besides the support by computation, such an energy level principle has also been supported by previous experimental results on the redox potentials of the materials. For example, Tsai et al. reported the SOD-like activity of sp$^2$ carbon NMs, including single-walled carbon nanotubes and nanographene.\textsuperscript{11} These researchers found that the reduction potential of nanographene was 0.40 V, which was exactly located in the range from ~0.16 V to 0.94 V (Fig. 1b), supporting our energy level principle.\textsuperscript{11} Recently, Wei et al.\textsuperscript{28} have reported the SOD-like activities for V$_2$C MXene. The reduction potential of V$_2$C has been determined to be ~0.11 V,\textsuperscript{28} which is in good agreement with our energy level principle.

The energy level principle provides not only the criterion to screen out NMs as potential catalysts but also new insight into the catalysis mechanism. Because the iFMOs of NMs II and V are the unoccupied FMOs (i.e., the lowest unoccupied molecular orbitals, LUMOs), the catalysis follows a LUMO-mediated mechanism (Fig. 2d):

$$\text{O}_2\textsuperscript{−} + \text{NM} = \text{O}_2 + \text{NM}\textsuperscript{−}$$

$$\text{O}_2\textsuperscript{−} + 2\text{H}^\text{+} + \text{NM}\textsuperscript{−} = \text{H}_2\text{O}_2 + \text{NM}$$

The NM is first reduced by one O$_2$\textsuperscript{−} and then oxidized back to its original state by another O$_2$\textsuperscript{−}, with negatively charged NM$^-$ as the intermediate. This CBM-mediated mechanism has been experimentally observed for the SOD-like activity of sp$^2$ carbon NMs\textsuperscript{11} having unoccupied iFMOs, which agrees with this prediction. By contrast, the activity of NM-I and NM-IV is mediated by occupied FMOs (i.e., the highest occupied molecular orbitals, HOMOs) and thus follows a HOMO-mediated mechanism (Fig. 2e):

$$\text{O}_2\textsuperscript{−} + 2\text{H}^\text{+} + \text{NM} = \text{H}_2\text{O}_2 + \text{NM}$$

$$\text{O}_2\textsuperscript{−} + \text{NM} = \text{O}_2 + \text{NM}\textsuperscript{−}$$

The NM is first oxidized by one O$_2$\textsuperscript{−} and then reduced back by another with positively charged NM$^+$ as the intermediate. Having both occupied and unoccupied FMOs as the iFMOs, the activities of NM-III and NM-IX follow both mechanisms with the overall neutral intermediate. The HOMO-mediated mechanism has not been experimentally reported before and deserves attention in the future.

Using the energy level principle, we now analyze the iFMOs for the NMs in Table 1 to predict the mechanisms of their SOD-like activities, which have been rarely studied at the microscopic level. The results of Fig. 2c and Supplementary Fig. 3a predict the following new knowledge. The iFMO of NiO is its VBM; those of MoS$_{2-x}$, Mn$_3$O$_4$, and Co$_3$O$_4$ are their CBMs. Therefore, NiO has an occupied iFMO, following the HOMO-mediated mechanism. MoS$_{2-x}$, Mn$_3$O$_4$, and Co$_3$O$_4$ have unoccupied iFMOs, following the LUMO-mediated mechanism. For metals, the Fermi energies with respect to the vacuum energy are known as work function ($W_0$). Therefore, a $W_0$-version of the energy level principle has been further derived, which also supports the principle (Supplementary Note 1 and Supplementary Fig. 3b).

To computationally verify the above-predicted mechanisms, we located the key intermediate and transition state structures involved in the dismutation of O$_2$\textsuperscript{−} on the surfaces of NiO(100) and MoS$_{2-x}$ using DFT calculations. As can be seen from Fig. 2f and 2g, the kinetically favorable pathways for the dismutation of O$_2$\textsuperscript{−} on NiO(100) and MoS$_{2-x}$ indeed follow the HOMO-
LUMO-mediated mechanisms, respectively. On NiO(100), the first protonated $O_2^\cdot$ (i.e., $HO_2^\cdot$) takes the hydrogen atom from the $H_2O$ adsorbate to form the $H_2O_2$ molecule, which oxidizes the NM by forming the intermediate $NM^+\cdot$ $O_2^\cdot$ transfers its hydrogen to the HO adsorbate to generate the $O_2^\cdot$ molecule, which reduces the NM back to the original state (Fig. 2f).

On MoS$_2$-$x$, $O_2^\cdot$ first passes its hydrogen to the sulfur of MoS$_2$-$x$, reducing the NM by forming the intermediate $NM^-\cdot$ $H^\cdot$). The second $HO_2^\cdot$ takes the hydrogen away, oxidizing the NM to its original state (Fig. 2g). Therefore, the results of Fig. 2f, g excellently support the predicted mechanisms. The energy profiles in Fig. 2f, g also suggest that the SOD-like catalysts have only very small energy barriers (<0.50 eV), which means that the catalysts are controlled by thermodynamics. This explains why the energy level principle, which only reflects the thermodynamics of the half-reactions, can successfully predict the catalytic activity of NMs.

**Adsorption energy principle.** We now develop a model to describe the competition of the side reactions with the target dismutation of $O_2^\cdot$ on NMs. In Fig. 3a, the target reaction is illustrated as (i), and the possible side reactions are illustrated as (ii–v). Denoting the Gibbs free energy ($G$) changes in these five reactions as $\Delta G_i$ (i = 1–5), the molar fraction $x_i$ for $O_2^\cdot$ to
undergo reaction (i) when reaching thermodynamic equilibrium can be expressed with the following partition function:

\[ x_1 = \frac{\Delta G_1}{R T} \sum_{i} \frac{\Delta G_i}{RT} \]  

(2)

In Eq. (2), \( e, R, \) and \( T \) are Euler’s number, the universal gas constant, and temperature, respectively. The target reaction is dominant, meaning that over 50% of \( O_2^{2-} \) undergoes reaction (i). Therefore, we propose \( x_1 > 0.5 \) as the second criterion for screening NMs as \( O_2^{2-} \) scavenging catalysts.

To derive a simpler screening criterion from Eq. (2), the mathematical descriptions in the Method and Supplementary Method sections were conducted. Briefly, the calculation of \( x_1 \) at any pH needs to calculate \( \Delta G_i \) (\( i = 1 \rightarrow 5 \)) at the pH. To calculate \( \Delta G_i \) (\( i = 1 \rightarrow 5 \)) using the standard thermodynamic data that can be consulted from the chemistry handbooks, the Hess cycles of Fig. 3b have been constructed. The result suggests that \( x_1 \) is a function of three variables, \( E_{ads,HO}, E_{ads,OH}, \) and \( E_{ads,H} \) which represent the energy changes for the adsorptions of \( HO^\bullet, O^\bullet, \) and \( H^+ \) on the material surfaces, respectively. Because of the linear relationship between \( E_{ads,HO} \) and \( E_{ads,OH} \) shown in Fig. 3c, \( x_1 \) turns to a function of only two variables, \( E_{ads,HO} \) and \( E_{ads,H} \). Figure 3d plots the variation in \( x_1 \) with \( E_{ads,HO} \) and \( E_{ads,H} \). From Fig. 3d, the criterion \( x_1 > 0.5 \) becomes

\[ E_{ads,HO} > -2.7 \text{ eV} \quad \text{and} \quad E_{ads,H} > -3.4 \text{ eV} \]  

(3)

Therefore, Eq. (3) is the second criterion for screening NMs as \( O_2^{2-} \) scavenging catalysts under the condition that \( T = 298.15 \text{ K} \) and \( pH = 7 \).

The adsorption energy principle reasonably explains the SOD-like activity for Au15, Pd16, Pt17, NiO25, and MoS227, which are located in the region with \( x_1 > 0.5 \) (Fig. 3d). However, CeO226, MnO18, MnO220, Mn3O422, and Co3O424 are beyond the region, although their SOD-like activities have been experimentally demonstrated. Such inconsistency may be ascribed to the that the practical surfaces of these NMs exhibiting activity are different from the slab models used for calculating the \( E_{ads,HO} \) and \( E_{ads,H} \). Unfortunately, the exact surface structures of NMs in water are usually difficult to characterize because they may simultaneously expose multiple surfaces40, and surface reconstructions may drastically occur in water41. We believe that NMs such as CeO2, MnO, MnO2, Mn3O4, and Co3O4 will enter the region \( x_1 > 0.5 \) when their exact surface structures are determined and used for calculating the adsorption energies. This point is already supported by the case of CeO2. The \( E_{ads,H} \) of CeO2 calculated using the defect-free (111) surface is \(-3.68 \text{ eV} \), however, practical nanoceria contains oxygen vacancies38,39 and thus are more chemically reductive. Therefore, the practical value of \( E_{ads,H} \) is more positive, pushing CeO2 into the region with \( x_1 > 0.5 \). These results suggest that Eq. (3) is a simple but powerful criterion that is able to screen our NMs on which the target catalytic reaction is more thermodynamically competitive than unwanted side reactions.

Experimental verification. To verify the above screening principles, metal-organic framework (MOF) compounds MIL-53(Fe)X (X = NH2, CH3, H, HO, F, Cl, Br, and NO2) were synthesized and their activities of scavenging \( O_2^{2-} \) were investigated by the combination of experiments and computations. As seen from Fig. 4a, the structures of these MOFs differ from each other in the linker substituents X. The Hammett \( \sigma_m \) values, which characterize the electron-withdrawing ability of the substituents, increase in the order \( NH2 < CH3 < H < HO < F < Cl < Br < NO2 \). To determine whether these MOFs satisfy the energy level criterion
(Eq. (1)), their reduction potentials were measured using the cyclic voltammetry technique. Fig. 4b plots the measured reduction potentials as a function of the Hammett σm values. The reduction potentials and the σm values have similar variation tendencies, which is in agreement with the knowledge that a stronger electron-withdrawing substituent leads to a high electron affinity of the material. Importantly, the reduction potentials vary from 0.28 V (for X = NH2) to 0.31 V (for X = NO2), which are exactly located in the range from −0.16 V to 0.94 V. Therefore, all the eight MOFs satisfy the energy level criterion. To determine whether these MOFs satisfy the adsorption energy criterion Eq. (3), the $E_{\text{ads,H}}$ and $E_{\text{ads,HO}}$ values at the defective sites of the MOFs were calculated using the DFT method. The most energetically favorable adsorption sites for H• and HO• are the bridge oxygen and iron atoms, respectively (Fig. 4c, d). All the calculated $E_{\text{ads,HO}}$ values are more negative than −2.3 eV, and those of $E_{\text{ads,H}}$ more negative than −2.7 eV. Namely, all the eight MOFs also satisfy the adsorption energy level criterion, and thus all the MOFs are predicted to have the activity of catalytically scavenging O2•−.

The above prediction encouraged us to further investigate the SOD-like activities of MIL-53(Fe)-X MOFs experimentally. The O2•− scavenging abilities of MIL-53(Fe)-X MOFs were characterized by monitoring the fluorescent spectra of ethidium, the product of O2•− and its specific probe hydroethidine. As shown in Fig. 4f, in the absence of MIL-53(Fe)-X MOFs, the fluorescent intensity of ethidium significantly decreased, whereas the one with MIL-53(Fe)-NO2 gave the lowest intensity. This result illustrated that the addition of these MIL-53(Fe)-X MOFs could eliminate O2•− amount, and thus reducing the fluorescent intensities of ethidium. The SOD-like activities of MIL-53(Fe)-X MOFs were also plotted as a function of Hammett σm values (Fig. 4g). And a similar change tendency as the one in Fig. 4b was observed, where MIL-53(Fe)-NH2 with the reduction potential farthest and MIL-53(Fe)-NO2 with the reduction potential closest to the midpoint of $\varphi_1$ and $\varphi_2$ (0.39 V) gave the worst and best...
SOD-like activities. This activity order supported the prediction that NMs with $E_{\text{ads}}(\text{H}_2\text{O}) = (\varphi_1 + \varphi_2)/2$ have the maximized catalytic efficiency. While for another MIL-47(V)-X (X = H, NH$_2$, and Br) MOF, their reduction potentials were even lower than that of MIL-53(Fe)-NH$_2$ (Supplementary Fig. 5). And our previous work showed that MOFs including MIL-47(V)-NH$_2$, MIL-47(V)-H, and MIL-47(V)-Br indeed exhibited much weaker and even negligible SOD-like activities$^{33}$. Furthermore, DFT calculations suggested that the $E_{\text{ads,HO}}$ and $E_{\text{ads,Br}}$ of these MIL-47(V) MOFs were about $-0.76 \text{ eV}$ and $-4.25 \text{ eV}$ (Supplementary Method and Supplementary Figs. 6 and 7), respectively, disobeying the adsorption energy criterion Eq. (3). This finding confirmed the negligible SOD-like activities of MIL-47(V)-X (X = H, NH$_2$, and Br) MOF, consistent with the guidance of the above principle. The principle was further verified by the different SOD-like activities of ceria particles that were synthesized under the same condition except at different temperatures: 0, 30, 60, and 90 °C. The former two ceria particles had markedly stronger activities than the latter, which exactly agreed with the experimental result that the former had no iFMO but the latter had one (see Supplementary Note 2 and Supplementary Figs. 8-11). Therefore, the results here not only demonstrated the above screening principles could predict the SOD-like activities of MOFs, but also verified the validity and generality of the principles.

Computational screening of antioxidants from 2D materials. We now use the above screening principles, Eq. (1) and Eq. (3), to screen NMs with intrinsic SOD-like catalytic activity. Because two-dimensional (2D) materials have large surface areas, which will serve as potential catalytically active sites, we focus our attention on 2D materials. Thygesen and coworkers established the Computational 2D Materials Database (C2DB), which deposits structural, elastic, thermodynamic, electronic, optical, and magnetic properties for a total of 3814 2D materials obtained by DFT calculations$^{44}$. This database provides an excellent platform for the modeling and design of 2D materials without redundant calculations.

Here, we will screen out stable NMs belonging to type I or II from the 2D material library. We further restrict our screening within the subset composed of no more than two elements because NMs consisting of fewer elements will be more suitable for mechanistic studies in the future. The screening procedure is shown in Fig. 5. A total of 370 materials among the 3814 passed the first-step screening. These materials are all composed of no more than two elements ($N_{\text{element}} \leq 2$), have considerable thermodynamic stability ($\Delta H_{\text{null}} < 0.2 \text{ eV/atom}$) and kinetic stability ($\sigma_{\text{kin}}^\text{min} = 10^{-5} \text{ eV/Å}^2$), and have nonzero electronic bandgaps calculated with the Heyd–Scuseria–Ernzerhof (HSE) method ($E_{\text{HSE}} > 0$)$^{44}$. A total of 126 of the 370 passed the second-step screening. These materials have only one type of iFMO, either a CBM or a VBM, whose energy is located in the range $(\varphi_1, \varphi_2)$. 121 among the 126 passed the third-step screening, which had $E_{\text{ads,HO}} > -2.7 \text{ eV}$ and $E_{\text{ads,Br}} > -3.4 \text{ eV}$. These 121 materials are thus predicted to have intrinsic SOD-like catalytic activities. These results have demonstrated that the screening principles can be easily implemented in computer programs for the high-throughput screening of NMs with intrinsic SOD-like activity. Among these materials, T-phase transition metal dichalcogenides (TMDCs), PtS$_2^{45}$, ZrS$_2^{46}$, ZrSe$_2^{46}$, SnS$_2^{47}$, HfS$_2^{48}$ and H-TMDCs (MoTe$_2^{49}$, WS$_2^{50}$, WTe$_2^{31}$, VS$_2^{52}$) have been experimentally reported. They existed in the form of single layers supported on substrates or a few layers in solutions$^{33-37}$. The SOD-like activities of these nine single-layer TMDC structures have been computationally investigated, and the results match well with the prediction (see Supplementary Table 2, Supplementary Note 3, and Supplementary Figs. 12-14). Therefore, the screening performed on 2D materials is likely to stimulate the application of these materials as novel SOD mimics provided that the high-yield synthesis of these single layers is achieved.

It’s worth noting that the principles are proposed for ideal material surfaces with explicit atomic structures. However, real NMs usually have inhomogeneous morphologies and ambiguous structural configurations. In addition, because the SOD-like catalysis occurs in aqueous solutions, other molecules present in the solvents may cause irreversible structural modifications to the materials, changing their FMO energies and surface affinities. The different aqueous dispersibility of materials may also influence their practical catalytic performances. This complexity of NMs in real situations should be considered when linking the predicted results to experiments.

In summary, two principles governing the catalytic activity of NMs mimicking that of SOD have been revealed by computationally studying the microscopic thermodynamics and kinetics of the catalytic processes. The energy level principle suggests the critical role of the iFMO in transferring electrons for the catalysis, which can be used to predict whether a given half-reaction of the catalytic dismutation of $\text{O}_2^-$ are thermodynamically favorable. This principle suggests the first criterion for screening NMs with the SOD-like activity: the NMs should have at least one iFMO, namely, the FMO with energy located in between $(\varphi_1, \varphi_2)$. Because the catalytic mechanism critically depends on whether the iFMO is occupied by electrons or not, this principle determines whether the SOD-like catalysis of NMs follows the HOMO- or the LUMO-mediated mechanism. The adsorption energy principle is based on the thermodynamic partition function and determines whether the target catalytic reaction occurring on the NMs is more thermodynamically competitive than the undesired side reactions. This principle suggests the second criterion for the screening, $E_{\text{ads,HO}} > -2.7 \text{ eV}$ and $E_{\text{ads,Br}} > -3.4 \text{ eV}$ at pH 7 and at the level of theory used for the computations. Both principles have received support from the previous results of NMs showing the SOD-like catalytic activity, giving an in-depth explanation of the results. The ability of the principles to predict the SOD-like activities of MOFs was further verified by our experimental results. The screening criteria derived from the principles can be easily implemented into computer programs, and they are used to computationally screen the NMs with the intrinsic SOD-like activity from the database of 2D materials. The results provide a systematic view of the antioxidant property of NMs and the method for the computational design and screening of NMs as novel SOD mimics.

Methods

DFT calculations. All NMs were computed using the projector augmented wave (PAW) method$^{30}$ implemented in the Vienna Ab initio Simulation Package (VASP)$^{39}$. The Perdew–Burke–Ernzerhof (PBE)$^{90}$ exchange-correlation functional with the generalized gradient approach (GGA) was applied. The plane-wave energy cutoff was set to 500 eV for the former and 400 eV for the other NMs. The GGA + U$^{51}$ corrections using the formalism of Dudarev et al$^{52}$, were also used to accurately describe the distribution of electrons on the NMs surfaces. When calculating the reaction energy profiles for NiO(111) and MoS$_2$–$\omega$–, the water solvent effect was considered by an implicit solvation model using the VASP code developed by Kiran Mathew and Richard G. Hennig$^{64}$. A vacuum value of 15 Å along the z-direction was set to separate the slab with an upward unit cell to avoid inveracous interactions. Gaussian smearing with a width of 0.05 eV was used for the Fermi level. The total energy and force convergences were $10^{-5} \text{ eV}$ and 0.02 eV/Å for the local minimum of all potential surfaces. Some small molecules, such as $\text{H}_2\text{O}$, $\text{H}_2\text{O}_2$, $\text{O}_2^-$, $\text{HO}^-$, $\text{HO}_2^-$, and $\text{O}_2$ were calculated in a 15 Å cubic lattice using the same parameters and convergence criteria as those for the rutile slabs. For the transition state search, the climbing image nudged elastic band method$^{65}$ was used in conjunction with partial atomic fixation with a convergence of $10^{-4} \text{ eV}$ and 0.05 eV/Å. More computational parameters, such as the model of every nanomaterial, the effective value of $U(\text{C}_\text{slab})$, and the Brillouin zone k-points, are shown in Supplementary Data 1.

The adsorption energy ($E_{\text{ads}}$) of a molecule on the slab is defined as follows:

$$E_{\text{ads,mol}} = E_{\text{mol/ slab}} - (E_{\text{slab}} + E_{\text{mol}})$$

where $E_{\text{ads,mol}}$, $E_{\text{mol/ slab}}$, and $E_{\text{mol/ slab}}$ are the total energies for the isolated ceria slab, isolated...
molecule, and ceria with the adsorbed molecule, respectively. The source data obtained by DFT calculations for Figs. 2–4 are present in Supplementary Data 2.

**Derivation of the adsorption energy criterion.** To calculate the partition function \(x_i\) with Eq. (2), the values of \(\Delta G_i (i = 1 - 5)\) should be calculated first. According to the Hess cycles of Fig. 3b, the \(\Delta G_i\) at any pH can be expressed as follows:

\[
\Delta G_1 = \Delta G_6 + 0.0592pH + \Delta G_f
\]  

(4a)

\[
\Delta G_2 = \Delta G_6 + 0.0592pH + \Delta G_f + E_{ads,HO} + \Delta G_{ads,HO}
\]  

(4b)

\[
\Delta G_3 = \Delta G_6 + 0.0592pH + \Delta G_f + E_{ads,HO} + \Delta G_{ads,HO} + E_{ads,HO}
\]  

(4c)

\[
\Delta G_4 = \Delta G_6 + 0.0592pH + \Delta G_f + E_{ads,HO} + \Delta G_{ads,HO} + E_{ads,HO} + E_{ads,HO}
\]  

(4d)

\[
\Delta G_{11} = \Delta G_6 + 0.0592pH + \Delta G_f + E_{ads,HO} + \Delta G_{ads,HO} + \Delta G_{ads,HO} + \Delta G_{ads,HO}
\]  

(4e)

The detailed procedures to derive Eq. (4a–e) are presented in Supplementary Method. In the above equations, \(\Delta G_i\) (\(i = 6 - 11\)) are defined in Fig. 3b and also in the Supplementary Method. \(S_1, S_2, S_3\), and \(S_4\) are standard entropies of the radicals \(HO^*, O^*, \) and \(H^*\), respectively, \(\Delta G_{ads,HO}, \Delta G_{ads,HO}, \Delta G_{ads,HO}, \) and \(\Delta G_{ads,HO}\) are the changes in the standard G value associated with the solvation of adsorbates \(HO^*, O^*, \) and \(H^*\), respectively, from the gas phase in water (for their definition, see the Supplementary Method). All these standard thermodynamic data necessary for the calculation of \(\Delta G_i (i = 1 - 5)\) are summarized in Table 2. These results suggest that \(\Delta G_i (i = 1 - 5)\) at any given pH are functions of three variables, \(E_{ads,HO}, E_{ads,HO}\), and \(E_{ads,HO}\). Namely, the partition function \(x_i\) is the function of these three variables.

To reduce the number of variables, the relationship between \(E_{ads,HO}, E_{ads,HO}\), and \(E_{ads,HO}\) was further studied. We calculated the \(E_{ads,HO}, E_{ads,HO}\), and \(E_{ads,HO}\) for a series of material surfaces, which include the (100), (110), and (111) surfaces of transition metals and the (111) surfaces of the fluorides MO2 and the rutiles MX2 (for parameter settings of the calculations, see Supplementary Data 1). The results are plotted in Fig. 5c. As seen from this figure, \(E_{ads,HO}\) and \(E_{ads,HO}\) have a good linear relation,

\[
E_{ads,HO} = 1.87E_{ads,HO} + 1.42
\]  

(5)

A similar linear relation between \(E_{ads,HO}\) and \(E_{ads,HO}\) has been reported previously by Norskov et al., Liu et al., and coworkers, which can be ascribed to both \(HO^*\) and \(O^*\) preferring the same adsorption sites on the surfaces. Substituting \(E_{ads,HO}\) in Eq. (4d) and Eq. (4e) by Eq. (5), plugging the values of Table 2 into Eq. (4a–e), and taking \(T = 298.15\) K and \(pH = 7\), \(\Delta G_i (i = 1 - 5)\) can be simplified as follows:

\[
\Delta G_i = -1.3
\]  

(6a)

\[
\Delta G_2 = E_{ads,HO} + 1.4
\]  

(6b)

\[
\Delta G_3 = E_{ads,HO} + 2.1
\]  

(6c)

\[
\Delta G_i = 2.87E_{ads,HO} + 8.54
\]  

(6d)

\[
\Delta G_i = 3.74E_{ads,HO} + E_{ads,HO} + 16.4
\]  

(6e)

Substituting \(\Delta G_i (i = 1 - 5)\) in Equation (4) with Eq. (6a–e), \(x_i\) becomes a function of only two variables, \(E_{ads,HO}\) and \(E_{ads,HO}\). Figure 3d plots the variation in \(x_i\) with \(E_{ads,HO}\) and \(E_{ads,HO}\). From Fig. 3d, the criterion \(x_i > 0.5\) becomes the adsorption energy criterion of Eq. (3). Using a similar method, the adsorption energy criterion at any other pH can be obtained.

**High-throughput calculations.** The high-throughput calculations of \(E_{ads,HO}\) and \(E_{ads,HO}\) for the 2D materials were performed by the python script (Supplementary
than 5 Å, both vortexed, and kept for another 30 min. At last, the solution was taken out and

| Item | Value | Item | Value |
|------|-------|------|-------|
| $\Delta G_i$ | $-0.86a$ | $\Delta G_{i3}$ | $4.92b$ |
| $\Delta G_0$ | $-0.86b$ | $\Sigma_{mol}$ | $1.9 \times 10^{-3}c$ |
| $\Delta G_0$ | $0.12b$ | $\Sigma_D$ | $1.7 \times 10^{-3}c$ |
| $\Delta G_0$ | $1.87b$ | $\Sigma_H$ | $1.2 \times 10^{-3}c$ |
| $\Delta G_{20}$ | $2.52b$ | $\Delta_{mol} \Sigma G_{mol}$ | $1.20d$ |
| $\Delta G_1$ | $6.68b$ | $\Delta_{mol} \Sigma G_{mol}$ | $1.20d$ |
| $\Delta G_{12}$ | $3.59b$ | $\Delta_{mol} \Sigma G_{mol}$ | $0.81d$ |

*aThe data were obtained by DFT calculations using the method described in the Supplementary Method section (unit: eV/particle).
*bThe data were directly taken from the chemistry handbook (unit: eV/particle/K).
*cThe data were obtained by DFT calculations using the method described in the Supplementary Method section (unit: eV/particle).
*dThe data were estimated from the combination of experiment and computation using the method described in the Supplementary Method section (unit: eV).

The authors declare that all other data supporting the findings of this study are available within the paper, the Supplementary Information/Source Data file.

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Author contributions

X.G. conceived the project and performed the high-throughput calculations. Z.W., J.J.Z., and X.G. prepared the initial manuscript with approval from all the authors. Z.W., J.J.Z., H.W. and Y.Z. advised on the experimental data. Z.W. and J.J.Z. drafted the initial manuscript, X.G. and H.W. synthesized the samples, then X.G. prepared the initial manuscript with approval from all the authors.

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Competing interests

The authors declare no competing interests.

Additional information

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