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Burgeoning single atoms as new types of nanozymes and electrocatalysts for sensing, biomedicine and energy conversion

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Abstract

Single atom catalysts (SACs), featured by atomically-level distributed active sites on supports, provide an ideal platform in the fields of energy conversion, and mimic metalloprotease for bridging the gap between natural enzymes and single atom nanozymes by virtue of their maximum atom utilization efficiency, superior selectivity and outstanding catalytic performance. In this review, the recent progress in this field is reported from the perspectives of synthesis routes, which is also a prerequisite for catalytic investigation. Subsequently, we depict their applications in different sensing systems including electrochemical, colorimetric and photoactive sensing, as well as biomedicine such as disease therapy, antibacterial and cytoprotection to demonstrate their nanoenzymatic activity, and their promising applications in electrocatalysis such as water splitting, oxygen and CO₂ reduction reaction are highlighted in more details. Finally, the current challenges and future outlooks of higher loading, more activity and stable in SACs are presented.

1. Introduction

Single atom catalysts (SACs), featuring with atomic-level distributed metal/nonmetal active center over substrates, have been a new frontier in catalysts and exhibit outstanding performance over that of nanoparticles-based catalyst in the field of sensing, biomedicine and energy conversion [1–4]. In contrast to the conventional heterogenous catalysts based on nanomaterials, the reactions generally occur on the surfaces or interfaces of catalysts, thus only a fraction of the surface atoms (rather than the entire particles) participate in the catalytic reaction. Smaller nanoparticles (NPs) possess a higher fraction of surface atoms, downsizing them into separately metal atom with greatly high atom utilization is in demand. The isolated active sites are anchored by ionic interactions or covalent coordination with surrounding atoms, which endow them with multiple advantages of unsaturated metal atoms, unique electronic structure, maximal atom utilization efficiency and strong metal-support interactions. Even before Zhang et al presented the concept of SACs in 2011, there were some works showing the possible discovery of SACs [5]. In 1925, Taylor put forward a theory of the catalytic surface where exists isolated active centers [6]. However, it was not until 1995 that Thomas et al truly realized theory to practical. They synthesized highly dispersed Ti SACs on mesoporous silica via calcination for the epoxidation of cyclic alkynes [7]. Although these early researches have witnessed the evolution and advances for the understanding of single atoms, which suggest that the active center in the reactions may be single atoms, they are limited to characterization methods such as x-ray absorption spectroscopy (XAS) to identify.

Thanks to the considerable progress has been made in advanced characterization techniques over the past decades, the precise microenvironment and understanding of SACs were identified. From scanning tunneling microscope, clear atomic image could be intuitively observed based on the difference between the metal species and the support under the aberration corrected high-angle annular dark-field scanning transmission electron microscope (HAADF) imaging mode. XAS provide information regarding the
Figure 1. Overview of the main topics in this review.

chemical states and coordination environment of SACs, x-ray absorption near-edge structure (XANES) can provide metal oxidation states, and the complementary technique extended x-ray absorption fine structure (EXAFS) gives information about the local coordination environment of central metal atoms, including chemical states and neighboring atoms. X-ray photoelectron spectroscopy (XPS), diffuse reflectance infrared Fourier transform spectroscopy, Mössbauer spectroscopy, etc were also complementary techniques for identifying SACs [8–14]. Moreover, diverse in situ spectroscopies are powerful tools to recognize the true active sites, capture the intermediates and study the reaction mechanisms of SACs such as in situ Raman scattering spectroscopy, attenuated total reflection infrared absorption spectroscopy, etc [15]. The information we obtained from such techniques could be roughly divided into: the geometry and electronic structure of the catalyst surface and the reaction intermediates. The utilization of in situ spectroscopy is indispensable because the structural changes of SACs are often reported under the reaction conditions, which may result in different results compared to in situ characterization. This paper mainly put emphasize on portraying the synthesis of dispersed and coordinated metal sites and note their multiple applications to obtain a comprehensive understanding of SACs. First, we systematically summarize various synthesize methods for the preparation of SACs and discuss how the chemical interactions between the single atoms and their supports can prevent the agglomeration of SACs, which is of great significance for the successful synthesis of SACs. Then the key developments of SACs in sensing, biomedicine, energy conversion, including hydrogen evolution reaction (HER), oxygen evolution reaction (OER), oxygen reduction reaction (ORR), \( \text{CO}_2 \) reduction reaction (\( \text{CO}_2 \text{RR} \)), have been summarized. At the end of the review, the major challenges and future opportunities of SACs are put forward.

Until now, a great progress has been devoted in the development of SACs, including the synthesis methodology, structure characterization, performance modulation, and catalytic mechanism study. In this review, we provide a summary on advances, characterization, applications and main active component of SACs (figure 1).

2. Synthesis of SACs

Considering that the ubiquitous migrate and aggregation of single atoms to NPs in the process of synthesis and subsequent post-treatment due to their high surface energy, it is still challenging to realize atomic dispersion from metal precursors and stabilize them. Aiming to address this issue, several synthetic strategies including wet chemical, atomic layer deposition (ALD), ball milling and etc have been developed.

2.1. Wet chemical

The wet chemical methods, mainly including impregnation [16], ion-exchange [17], electrostatic adsorption, coprecipitation [5], and etc are promising for the preparation of SACs in both research and large-scale practical production. These methods mainly go through two procedures: first introducing metal precursor on the substrate via impregnation, ion exchange, coprecipitation and then post-treatment to remove unwanted ligands by drying, calcination, and etc. Single atom is stabilized by chemical bonding with a
suitable host material. The coordination sites, determined by the number, chemical identity, and arrangement of nearest neighbor atoms as well as their basal environment, are related to the geometric and electronic structure of SACs, which further influence their catalytic activities.

It is worth noting that the coordination design strategy always accompanies with spatial confinement strategy. Metal organic frameworks (MOFs), built upon coordination between inorganic metal-containing nodes and polyfunctional organic ligands, can be characterized with diverse and well-defined structures to uniformly incorporate SACs by additional coordination, adsorption and ion exchange. In the subsequently pyrolysis process, the formation of strong metal-N/S bond represents that the SACs were successfully achieved [18]. For instance, the construction of ultrathin 2D MOF nanosheets incorporated with Pt SACs was prepared by directly using Pt$^{II}$ tetrakis (4-carboxyphenyl) porphyrin as the units and Cu$_2$(COO)$_4$ paddle-wheel clusters as the metal nodes that different from the traditional post-modification strategy. However, the expensive organic linkers and low-concentration utilization in MOFs limited their applications. Lone pairs of electrons exist in heteroatom-doped carbon materials, etc such as S- and N-doped carbon, which can act as coordinating site to anchor metal atoms [19–21]. Zeolite imidazolate framework (ZIF) is considered as an ideal precursor for the synthesis of M-N-C SACs ascribed to the merits of high porosity and simple synthesis [22–24]. For instance, Li et al found a surprising phenomenon of the sintering effects and the conversion of noble metal (Pd, Au, Pt) NPs into thermodynamic stable corresponding single atoms over 900 °C [25]. They used ZIF-8 to encapsulate Pd NPs, capture the migrating metal atoms which recorded by in situ environmental transmission electron microscopy (ETEM). The large Pd NPs formed by sintering, could gradually transform to single atoms via strongly colliding with the matrix. Zhou et al elaborately designed a novel strategy to coordinate ultrahigh concentration of Pt SAs (12.0 wt.%) with 2D MOF nanosheets assisted with polyvinyl pyrrolidone (PVP) (figure 2(a)) [26].

Defects engineering, such as plasma bombardment, chemical etching, template synthesis, dealloying, and heteroatom doping, on substrate is widely employed to tune the electronic, optic, magnetic and chemical structure of SACs, resulting in numerous vacancies and unsaturated coordination sites (such as metal cation, O, S and C vacancies). Zhang et al determined the optimized sulfur vacancy state via high throughout calculations [27]. They incorporated homogeneously distributed single S-vacancies with MoS$_2$ nanosheet via tuning the etching duration, temperature and solution concentration during the H$_2$O$_2$ chemical etching process. Liu et al prepared Pd-based SACs through electrostatic attraction by choosing different vacancies-rich supports, which provide ideal coordination environments for isolated Pd SACs with different metal-support interactions (figure 2(c)) [28].

2.2. Atomic layer deposition

ALD is a thin film growth technique via self-limiting binary reactions between gaseous precursors and the substrate which possesses the advantages of excellent conformity, high atomic-level thickness accuracy and excellent reproducibility [29–32]. In 2013, Sun et al firstly reported the practical synthesis of isolated Pt SAs dispersed on graphene nanosheet by ALD technique [33]. Their group recently devised Pt SACs on ZIF-derived N-doped carbon (NC) support [34]. The morphology, size and loading of the three Pt/ZIF-NC samples with different exposure ALD time (30 s, 1 min and 5 min) showed that the deposited Pt form disperse particles, growing from individual single atoms, sub-nanometer clusters and NPs which was precisely controlled by adjusting ALD cycle time. Lu and co-workers introduced a reliable method for preparing stable high loading Co single atoms on the graphene support (Co/G SACs) via the ALD technique, which can also precisely adjust the density of atomically Co. Firstly, the Co precursor Co(C$_2$H$_3$)$_2$, was exposed to graphene and reacted with epoxy functional groups which produced by exposing graphene to ozone (O$_3$) at elevated temperature. The subsequent O$_3$ exposure in the second pulse of each ALD cycles can remove the remaining ligands of the deposited metal precursors by a combustion reaction and recreate new active sites for loading Co atoms. The two steps complete one cycle of ALD. They managed to fabricate a series of Co/G with Co loadings from 0.4 to 2.5 wt.% by performing 1–5 cycles without any Co NPs or clusters (figure 2(d)) [35].

2.3. Ball milling

Benefiting from the properties of low-cost, easy to large-scalable and ecofriendly, the ball milling method has aroused attraction in preparing SACs [36]. In addition to simple downsize, high-energy ball milling has been demonstrated as a powerful approach to break the covalent or coordination bonds with needed energy input induced by instantaneous high-temperature. The term ‘mechanical-chemistry’ was proposed by W. Ostwald more than 100 years ago. The substrate, activated by milling, will produce defective sites or amorphous surface layer to capture single atom [37]. Many successes have been achieved by Bao’s group, who have synthesized a series of coordination unsaturated metal (i.e. Mn, Fe, Co, Ni, and Cu) SACs embedded in graphene via this method in large quantities, in which embedded Fe loading amount up to 4.0 wt.% [13, 38, 39]. Besides, Kim
et al prepared Pt SACs via ball milling precursors supported on NC, the content of Pt is 1.92 wt.% confirmed by ICP-OES [40]. Ji et al fabricated the kilogram-scale Au SACs via ball milling and calcination treatment of commercial acetate precursors with the quantities more than 1000 g. From the lab-scale (10 g) to the plant-scale (1000 g), the Au SACs on CeO$_2$ support show the same behaviors in preferential oxidation of CO process (figures 2(e) and (f)) [41].

2.4. Other methods
Besides the aforementioned synthesize methods above, some creative strategies have also been intensively studied to prepare SACs, such as photochemical reduction [42–44], chemical vapor deposition (CVD) [45], microwave-assisted method [46, 47], and etc. For example, Tong et al provides general perspectives to design noble-metal-based SACs (such as Au, Pd, Ru, Ag, etc) by adding graphitic carbon wrapped TiO$_2$ nanorods into metal precursor solution (i.e. PtCl$_6^{2-}$) and irradiated them under a 365 nm UV monochromatic lamp [42]. To prevent the aggregation of metal atoms, PVP was introduced to stable noble metal and modulate the
interfacial electronic structure as well by abundant amide functional groups (figures 2(g) and (h)). In addition, Sun et al proposed a facile method involving microwave reduction coupled with aniline anchoring to prepare Pt SACs dispersed on aniline-stacked graphene (AG) [48]. Under the pH 2.6 of the solution, some—NH₂ groups of aniline were protonated to form—NH₃⁺. Graphene was positively charged, and PtCl₆²⁻ ions were electrostatically immobilized on AG to maintain charge balance. Eventually, the anchored PtCl₆²⁻ ions were reduced to single Pt atomic sites by microwave irradiation.

Even though several methods have been developed and widely used for the preparation of SACs, it remains a great challenge to precisely control the coordination and loading amount of single atom sites during the synthesis process. For the wet-chemical strategy, only a small portion of them really participate in and stay stable under the extremely conditions of electrocatalysis; While for ball milling method, the prepared catalysts might be contaminated by the balls and milling additives. ALD and similar technique-CVD, are not appropriate for high-surface-area support or mesoporous support materials, which limits practical industrial applications in SACs synthesis. In addition, SACs always supported by metal oxides, sulfides, LDH, crystalline metal compounds, heteroatom-doped carbon and etc. These substrates suffer from some defects such as low conductivity and poor stability, easy to corrosion, thus rationally designs need to be considered and addressed as a premise. The ubiquitous aggregation to NPs motivated us to require low loading amount of metal and numerous vacancies of support to strengthen their interaction for preparing SACs.

3. Advantages of single atoms over clusters or nanoparticles

It is attractive to explore low-cost and high-efficiency nanozyme and electrocatalysts for practical applications in the past few decades. Metal entities with different size (single atoms, nanoclusters, and NPs) show different catalytic behavior for various heterogeneous catalytic reactions. There is no doubt that all of them exhibit outstanding catalytic properties. SACs not only have the same properties as NPs catalysts, but sometimes even showing unique performance [49, 50]. In the case of supported atomic-level metal species, where reactants are activated, will be regarded as true active sites, while metal NPs are not. Moreover, SACs are much easier to characterization and identify, they can be used as an ideal system in establishing models, and further a rational understanding towards the process and mechanism of catalytic reaction could be formed. It should be noted that theoretical simulations and molecular modeling should match well with the experimental conditions as much as possible in order to obtain a reasonable interpretation of the experimental results. In addition, the active sites of SACs are highly dispersed, their atomic utilization up to 100%, which is impossible for NPs and clusters [51]. Noteworthy, SAC does not mean that a single metal atom with a valence of zero is the active center, the nearby heteroatoms (N, S, P, B, O, and etc) are also key points for catalytic performance. The coordination environments of SACs are more diverse than that of NPs, which gives the structure of SACs more designability. As a conclusion of previous researches, in the catalysis community, the unsaturated surface sites always show higher activity than those surface sites with a saturated coordination environment. For SACs, their electronic and geometric structures have a strongly relationship with the coordination environment. However, in the case of metal clusters and NPs, the situation becomes quite more complicated owing to the orbital overlapping between metal atoms.

4. Applications of single atom nanozymes to sensing

Single atom nanozymes (SAzymes) with atomically dispersed metal sites, ideal atomic structure, superior catalytic activity and uniform catalytic priority have recently attracted significant interest in various sensors [52, 53]. Thanks to these advantages, the detection sensitivity could be greatly enhanced with the merits of the ultrahigh activity of SAzymes. What’s more, the specific detection for bioassays, such as H₂O₂, glucose and ascorbic acid, and etc, could be realized by the SAzymes with sole enzyme activity [54, 55]. Recently, there have been a lot of researches about the applications of SAzymes to sensing, we will mainly discuss them in sequence of electrochemical sensing, colorimetric sensing, chemiluminescence sensing, and photoactive sensing [56].

4.1. Electrochemical sensing

The principle of electrochemical sensor is to determine the concentration of the target analyte mainly through the change of output electrochemical signals (such as potential and current). Electrochemical sensors have been widely used in the quantitative detection of multiple target molecules. For example, Zheng et al have constructed a dodecahedral SAzyme modified by single Fe site to obtain an Fe-N-C SAzyme functionalized solution-gated graphene transistor (SGGT), since the change of the channel current response to the increasing concentration of Hg²⁺ with the Fe-N-C SAzyme and Cs/Au-modified device, the resultant
Figure 3. Electrochemical Sensing: (a) Schematic diagram of a SGGT based on the Fe-N-C SAE and Cu/Au-modified gate electrode for the detection of Hg$^{2+}$. (b) Channel current responses of (a) Fe-N-C SAE-modified gate electrode SGGT to the increased concentration of the Hg$^{2+}$ in 0.01 M Tris–HCl solution. (c) Equivalent gate voltage value variation of Fe-N-C SAE and N-C-modified gate electrode SGGT corresponding to the different logarithmic values of Hg$^{2+}$ concentration [57]. Colorimetric Sensing: (a) schematic presentation of the synthesis of Fe-N/C catalysts. (b) Schematic of colorimetric platform for ALP activity assay. (c) The UV–vis absorption spectra of various reaction systems. (d) Linear plots of $\Delta A_{652}$ vs concentrations of ALP (0.05–100 U L$^{-1}$). Inset: The UV–vis absorption curves and photographs of Fe-N/C/TMB based colorimetric assay with different ALP activity from 0 to 100 U/L. (e) $\Delta A_{652}$ with various interfering substances [60]. Fluorescence Sensing: (a) schematic illustration of this ratio fluorescent sensing strategy for AChE activity sensing. (b) Fluorescence spectra of the ATCh/Fe-SAs/NC/H$_2$O$_2$/OPD/PVP-CuNCs system in the presence of different AChE concentrations (0–90 U L$^{-1}$). (c) Linear relationship between fluorescence ratio $F_{566}/F_{438}$ and AChE concentration. (d) Fluorescence sensing system responses to various species [63]. Photoactive Sensing: (a) illustration of the principle of PS MOF as a photo activated biosensor for glutathione. (b) Synthesis of the PSMOF [64]. Reprinted with permission from [57]. Copyright (2020) American Chemical Society.
sensor has good performance for Hg$^{2+}$ detection (figures 3(a)–(c)) with the detection limit of the detection (LOD) system can reach 1 nM [57] and the linear range of 1 nM to 3 µM. Recently, SAzymes have been used to catalyze the electrochemical process of some substrates, in which highly sensitive current signals are generated. Therefore, some electrochemical biosensors based on these SAzymes have been successfully established for quantitative detection of certain targets [58]. Ebrahimi et al prepared an ultrasensitive electrochemical biosensor based on single atom Mn-doped MoS$_2$ (with Mn $\sim$ 2.15 at. %) for detection of dopamine [45]. The sensors showed a detection limit of 50 pM, 5 nM and 50 nM in buffer solution, 10% serum and artificial sweat, respectively. Isolated Mn atoms incorporated in MoS$_2$ in two forms: on top of a Mo atom and instead of a Mo atom, which can facilitate DA physical or chemical adsorption and activation, and thus leading to an excellent performance towards interfacial electrocatalysis.

4.2. Colorimetric sensing
As one of the most popular sensing methods, colorimetric sensing mode has attracted wide attention due to its simple reading, convenient operation and fast visual detection by naked eye or low-cost portable devices (such as smart phones) and widely used in the detection of a variety of analytes based on the color changes in the chemical reaction process [58, 59]. Through a facile pyrolysis of size controllable Fe-Zn ZIFs precursors, Huang et al successfully prepared the size-controllable Fe-N/C nanozymes containing exclusive single Fe atoms coordinated Fe-N$_2$ sites, which exhibit exceptional high oxidase-mimicking activity able to catalyze oxidation of colorless 3,3′,5,5′-tetramethylbenzidine (TMB) by dissolved oxygen to generate blue product (figures 3(a)–(e)) [60]. In the presence of alkaline phosphatase (ALP), ascorbic acid 2-phosphate (AAP) is hydrolyzed to produce AA, which can completely inhibit the oxidation of TMB, resulting in significant decline in absorbance with a clear color change. Therefore, a novel colorimetric strategy was constructed to detect ALP activity with a good linear relationship between the net absorbance ($\Delta$) and the ALP concentration from 0 to 100 U L$^{-1}$ was obtained. The calculated LOD (3σ) is 0.02 U/L, which is equivalent to the results obtained by redox active nanoceria [61], showing high sensitivity to ALP, the $\Delta$ value of ALP was significantly higher than that of other interfering substances, which confirms that the developed Fe-N/C/TMB/AAP sensing system has satisfactory selectivity for ALP detection. Similarly, Guo’s group synthesized a kind of B-doped Fe-N-C single-atom enzyme to detect the small molecule [62], Based on the principle that organophosphorus pesticides (OPs) can inhibit AChE activity and lead to the decrease of acetic acid production in ahe system, OPs were detected by using paraoxon-ethyl as a model with a good linear relationship from 8 to 1000 ng ml$^{-1}$ and the LOD was 2.19 ng ml$^{-1}$. OPs biosensor also showed satisfactory specificity for some potential interferences, and it was feasible in tap water. They also show that boron doped Fe-N-C enzyme with intrinsic charge transfer can play a better role and significantly enhance the peroxidase like activity and selectivity.

4.3. Fluorescence sensing
Fluorescence based sensors have attracted significant attention due to their high sensitivity, short response time and simplification. Their progress can be achieved by modifying materials with fluorescent sensory properties, which is also critical to respond to the fluorescent ‘turn on/off’ signals. Su et al constructed a ratio fluorescence method for AChE activity sensing [63]. With AChE present, the produced TCh with sulphydryl group will inhibit the Fe-SAs/NC activity and block the oxidation of OPD, resulting in the fluorescence recovery of PVP-CuNCs at 438 nm and fluorescence decrease of DAP at 566 nm. Then the research displayed that fluorescence intensity ratio $F_{566}/F_{438}$ was proportional to the concentration of AChE from 2 U L$^{-1}$ to 70 U L$^{-1}$ and the detection limit was determined to be 0.56 U L$^{-1}$. These obtained results were comparable to previously existing technologies and materials for AChE activity determination. Additionally, the specificity of this Fe-SAs/NC/PVP-CuNCs based system was measured by studying the responses of the system to common ions, amino acids, biomolecules and bio-enzymes (figures 3(a)–(d)).

4.4. Photoactive sensing
The photoactive technique has been widely applied for sensitive and selective detection. Developing materials with high photoactive ability play a key role in the improvement of analytical performances of photoactive sensing system. Recently, Wei et al developed a light-responsive mental-organic framework with oxidase-like activity (figures 3(a) and (b)) [64]. An organic dye of Ru(bpy)$_3^{2+}$ with a stronger visible-light absorption was used as a photosensitized (PS) linker for the construction of PSMOF. The PSMOF showed excellent oxidase-like activity under light irradiation, and the enzyme-like activity could be controlled by switching light on and off. Mechanistic studies indicated that the dissolved oxygen could be activated by the PSMOF under light irradiation to form ROS including •O$_2$ and •OH. Based on the production of ROS, the PSMOF nanozyme was used to detect the reducing molecule of glutathione in both normal and cancer cells.
5. Applications of single atom nanozymes to biomedicine

In recent years, as a new type of high-performance nanoenzymes, SAzymes have been widely used in biomedical fields, such as disease treatment, neuroprotection, bioassay, biofilm elimination, cell protection and antibacterial, due to their similar catalytic activity and uniform distribution of active centers [65–67]. The unsaturated coordination structure and well dispersed active center of the SAzymes make them have high catalytic activity and good stability. Herein, we summarize several representative biomedical applications of SAzymes.

5.1. Disease therapy

Although some progresses have been made in nanoenzymes, effective antioxidant therapy is still challenging. The potential toxicity of nanomaterials is mainly related to dissolved ions. Therefore, small amount of metal below the threshold is almost nontoxic. This encouraged us to develop nanocatalysts with high therapeutic efficacy, relatively low metal concentrations, and negligible side effects [68, 69]. Herein, an enzyme-mimicking SACs, features atomically dispersed coordinatively unsaturated active Co-porphyrin centers, which can quickly eliminate multiple RONS to alleviate sepsis [70]. Co/PMCS can eliminate O$_2^-$ and H$_2$O$_2$ by simulating superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase. At the same time, the activity of Co/PMCS is significantly higher than that of nanoenzyme. It can also scavenge NO by forming nitrosol-metal complexes. Finally, it can reduce the level of pro-inflammatory cytokines, protect organs from damage, and give the mice infected with sepsis obvious survival advantages as shown in figures 4(a)–(d). Li et al found a synthetic material, Fe-N doped graphene (FeNGR), which can effectively catalyze the conversion of NADPH to NADP$^+$ and trigger the formation of oxygen radicals to simulate nitrogen oxide, as well as demonstrated its biological function in immune activation NOX-deficient cells [71]. As a transmembrane enzyme complex, NADPH oxidase (NOX) controls the generation of superoxide and plays an important role in immune signal transduction. Inactivation of NOX can cause immune deficiency and chronic granulomatous disease (CGD). Therefore, as prepared biocompatible synthetic materials with NOX like activity are of great significance as therapeutic and/or preventive methods in the absence of NOX. Shi et al fabricated single-atom Fe nanocatalysts and subsequent surface engineering of PEGylation (PSAF NCS). The PSAF NCS were initially investigated for cell internalization upon fluorescein isothiocyanate conjugation, and the effective localization could be visualized by confocal laser scanning microscopy imaging clearly. Then conducted with a single tail-vein injection in vivo, the biodistribution profile show the favorable biodegradability and biocompatibility which guarantee their desirable biosafety. It could efficiently trigger the in-situ tumor-specific Fenton reaction to generate large quantities of toxic ·OH under the acidic tumor microenvironment. These radicals could apoptotic cell against malignant tumor cells. In addition, the injectable PSAF NCS could suppress tumor via ferroptosis, a programmed cancer apoptosis induced by iron and lipid peroxidation [72].

5.2. Antibacterial

In order to retard the drug resistance evolution and reduce the side effects caused by nonspecific bactericidal action, some selective bactericidal methods have been successfully developed. At present, antibacterial nanozymes are mainly based on their OXD- or POD-like catalytic activity to produce ROS from H$_2$O$_2$ and O$_2$, SAzymes has also been used as a new fungicide [66, 73]. For instance, Dong et al found a new class of SAzymes of FeN$_5$ SA/CNF, which has a catalytic behavior similar to the axial coordination heme of oxidoreductase [74]. They evaluated the practical antibacterial efficacy of FeN$_5$ SA/CNF through in vivo antibacterial experiments in Balb/c mice with actual wound infection. As shown in the results, compared to the control group, which coincided with the hematoxylin and eosin (H and E) staining of infected wounds, they observed the clear remission of ulceration and accelerated wound healing in the mice treated with FeN$_5$ SA/CNF within the 4 d observation of the wound after E. coli infection and therapy. The results of staining showed that keratinocytes migrated from normal tissues to the wound site, and the epidermis gradually became complete and thick in the normal skin sections after treatment. In general, these results indicate that the synthesized FeN$_5$ SA/CNF were highly biocompatible bactericidal nanozymes.

5.3. Cytoprotection

ROS (such as H$_2$O$_2$, ·OH, and ·O$_2^-$) are intermediates in cell metabolism. ROS at low level can act as a second messenger and play an extremely important role in signal transmission [75]. However, excessive reactive oxygen species can cause many adverse reactions. For example, excessive ROS can cause oxidative damage to cell biomolecules such as nucleic acids, lipids and proteins. In addition, excessive ROS can also cause apoptosis [53, 76]. Liu et al has demonstrated that Fe–N/C SACs prepared by mechanical method and
pyrolysishaveavarietyofenzymemimickingproperties,includingPOD-like, OXD-like, CAT-like, and GPx-likeactivities [77]. Based on CAT-like and GPx-like activities, Fe–N/CSACshasbeen successfully applied to HeLa cells to removeintracellular ROS. This study extends the types of enzymes mimicked by sacs. Moreover, these findings may provide opportunities for SACs to be used in biomedical and other bioengineering applications, such as the treatment of neurodegenerative diseases and the diagnosis and treatment of cancer (figures 4(a)–(c)).

6. Applications of single atom catalysts to energy conversion

6.1. Hydrogen evolution reaction

Hydrogeneconomy, originally proposed by John Bockris, depicts a pollution-free and sustainable energy system [78, 79]. Reduction of water into hydrogen through electrocatalysis holds great promise for clean energy while its widely application restricts by the development of low-cost and efficient catalysts. First, a deep understanding of HER mechanism is essential for design the electrocatalyst [80]. HER is a multistep electrochemical process, which may follow pH-dependent formula.

In acid solution it follows the sequence of Volmer–Tafel or Heyrovsky:

Volmer: \( H^+ + e^- + * = H_{ad} \)

Tafel: \( H_{ad} + H_{ad} = H_2 + 2* \) (at a high \( H_{ad} \) coverage is high)

Heyrovsky: \( H_{ad} + H^+ + e^- = H_2 + * \) (where the \( H_{ad} \) coverage is relatively low)

In alkaline solution, the step can be adapted as (Tafel is the same as above):

Volmer: \( H_2O + e^- + * = H_{ad} + OH^- \)

Heyrovsky: \( H_{ad} + H_2O + e^- = H_2 + OH^- + * \)
SACs may shed light on research to replace noble metals by nonprecious-metal catalysts for dramatically accelerating the reaction kinetics of HER due to the adjustable coordination environment engineering, which can bring about unique electronic and structure properties.

6.1.1. Precious-metal-based SACs for HER

Till now, Pt-based catalysts provide the maximum exchange current density for HER, thus are the most active ones. It is highly desirable to maintain or improve their HER performances with as few doses as possible [21, 42, 81]. Wang et al proposed a scalable, precisely-controlled templating strategies to prepare vertically aligned N-doped graphene nanomesh arrays (VNGNMAs) to bridge the gap between 2D nanosheets and 3D architectures [82]. This VNGNMAs could serve as a prominent scaffold to anchor Pd and Pt SACs via ALD technique, such a strong metal–matrix interaction between Pt SACs and graphene is imperative for HER. The Pt1 SAC-VNGNMA electrode shows negligible onset overpotentials, and the Tafel slope is 49 mV dec$^{-1}$. As a relatively cheaper PGM, Ru has been considered to be the most potential substitute since it has similar geometric and electronic structures with Pt (figures 5(a)–(f)) [83, 84]. Recently, Zhang et al reported the utilization of amine-functionalized MOF (NH$_2$-MIL-125) as supports to encapsulate Ru species [85]. Worthy of note, the much stronger signal at $g = 2.003$ of Ru-SAs@N-TC indicates that the atomic-scale Ru must favor creating more Ti$^{3+}$-Ov defective sites compared to Ru NPs. These Ti$^{3+}$-Ov defects could hence provide more trapping sites to boost separation and transform of electrons. As expected, the Ru-SAs@N-TC sample delivers a $\eta_{10}$ value of only 97 mV and a smaller Tafel slope of 58 mV dec$^{-1}$. It still needs furthermore precise control on atomic coordination environments and coordination numbers of metal species that are very important for catalysis (figures 5(g)–(i)) [86, 87]. Li et al designed a novel substrate, amorphous phosphorus nitride imide nanotubes, to stabilize Ru SAs [88]. DFT simulations revealed that more electrons

![Figure 5](image_url)

Figure 5. (a)–(d) Images show the formation processes of hollow graphene wall pores, scale bar: 20 nm; (e) HER polarization curves and (f) Tafel plots of Pd$_1$ or Pt$_1$-SAC VNGNMAs, benchmark Pt/C, Pt$_1$-SAC VGNMA powder and carbon cloth. Reproduced from [82] with permission of The Royal Society of Chemistry. (g) Schematic illustration for preparation of Ru-NPs/SAs@N-TC and Ru-SAs@N-TC samples. (h) Linear sweep voltammetry (LSV) curves. (i) Tafel plots. Reprinted from [85], Copyright (2020), with permission from Elsevier.
are transferred between Ru SAs and HPN nanotubes compared to C₃N₄ and carbon paper, resulting in more positively charged Ru SAs within RuSAs@PN which facilitate the HER.

6.1.2. Non-noble metal-based SACs for HER

On accounts of their rich reserves and distinct catalytic activities, transition metals-based SACs, especially Ni [89, 90], Co [91], Fe [92], Mo, and W [93] based SACs are regarded as superior HER electrocatalysts and even surpass that of Pt/C. In earlier research, N-doped graphene with negligible H₂-evolving activity when encountered with very small amounts of Co single atoms can function as a highly catalyst represents the first example of SAC achieved in inorganic solid-state catalysts for HER [94]. Later, Jiang et al anchored single Ni atom on vacancy defects of a hybridized graphene–boron nitride monolayer (BCN), to act as a highly active HER catalysts [95]. Atoms of 11 different TMs (i.e. Fe, Co, Ni, Cu, Cr, Mn, Mo, Pd, Ag, Pt, and Au) were tested by first-principle simulations. As a result, Ni@BCN offers best HER activity with a ΔG₅₇° value of only 0.02 eV. Despite Fe-N, SACs have attracted special interest for electrocatalysis due to their high conductivity and noble-metal-like feature, there are few related papers reported for HER. Qian and coworkers rationally tuned the electronic coupling between Fe₂N and H₆ad via a simple N-vacancy-mediated orbital steering strategy [96]. The vacancy-modified Fe₂Ni nanowires exhibited a minimum overpotential of 54 mV in 0.5 M H₂SO₄ outperforms the ever-reported iron nitrides. Importantly, the real-time XAFS studies decipher the electronic state evolution of Fe sites during the HER catalysis may be originated from the surface hydronium ion adsorption in aqueous solution. This work could provide meaningful insights into the current understanding on the catalyst design for acidic HER and beyond.

6.1.3. Non-metal based SACs for HER

Since Qiao et al firstly reported non-metal single-iodine-atom electrocatalysts for HER in 2019. Non-metal-based SACs features as low cost, easy to synthesis while there are few works focus on this aspect up to now [97]. The SANi-I is fabricated via a simple calcination step in a vacuum-sealed ampoule and subsequent CV activation. AC-HAADF-STEM and XAS results strongly prove the successful formation of atomic-level dispersed iodine atoms and detailed structural information of SANi-I. Iodine SAs are found to bond with Ni and O atoms, and evenly dispersed on the nickel hydroxide support. In situ Raman spectroscopy discovered that the H₆ad is adsorbed by one iodine SA, forming the I-H₆ad intermediate, thus accelerate the dissociative adsorption of H₂O and promotes the HER process. A 100 mA cm⁻² current density was achieved at an overpotential of 60 mV, lower than those of benchmark Pt-C (61 mV) and A-Ni-OH (285 mV) in 0.1 M KOH (figures 6(a)–(c)). Recently, Wang et al employed carbon sheet as a support to disperse P single atom on Mo₃C-based hexagonal nanosheet arrays to form HER electrocatalyst [98]. They developed a simplified pressurized gas-assisted process under PH₃ atmosphere with low-temperature treatment followed by a facile two-step solid state reaction to form single atom P-Mo₂C-carbon sheet. DFT confirmed the stable configuration of atomically dispersed P on Mo₂C surface, and collaboration effect with their adjacent Mo atoms to form a high-active ‘window’ which shows the ΔG₅₇° nearly to zero for H⁺ desorption. This SAP-Mo₂C-CS achieved a quite low overpotential of 36 mV at η₁₀, and a Tafel slope of 38.1 mV dec⁻¹ in 0.5 M H₂SO₄ (figures 6(f) and (g)).

6.2. Oxygen evolution reaction (OER)

OER, which involves multiproton-coupled electron transfer steps, is the counter reaction to HER in water electrolyzer and a fundamental half-reaction for rechargeable metal-air battery [99–101]. In view of the sluggish kinetics compared to the rather fast rate of HER suppressing the OER process, which is regarding as a critical bottleneck of water splitting, there is an urgent need to develop effective catalysts. Among various OER catalysts reported, SACs are promising alternatives with well-defined structures and unique electronic properties.

6.2.1. Noble-metal based SACs for OER

The most commonly popular OER catalysts are noble metal-based materials (i.e. RuO₂ and IrO₂) while their high cost and low abundance limit large-scale requirements. Downsizing the noble-metal NPs into atomic-level is a promising approach to reduce their content in OER catalysts [102, 103]. Wu et al introduced atomic Ru species into a hybrid amorphous/crystalline (AC) FeCoNi-LDH via a facile self-templating cation-exchange method to lower overpotential for OER kinetics [104]. Synergistic interactions were also found in Ru SAs/AC-FeCoNi, which endow the electrocatalyst with robust stability and excellent OER activity. As Ru doping accelerates the M-OH* process, subsequently boosting the OER activity. For Ru SAs/AC-FeCoNi with a loading content of 0.67 wt.%, only an overpotential (η₁₀, OER) of 205 mV was required to reach 10 mA cm⁻² and display a Tafel slope of 40 mV dec⁻¹ in 0.1 M KOH. After 2000 CV scans,
Figure 6. (a) XRD patterns of SANi-I and SANi-I96. (b) K\(^{3}\)-weighted $\chi$ (k) function of EXAFS spectra. (c) Iodine K edge XANES spectra and (insert) enlarged absorption-edge. In situ Raman spectra of (a) SANi-I and (b) A-Ni-OH at OCP and constant potentials (vs. RHE). [97] John Wiley & Sons. © 2019 WILEY-VCH Verlag GmbH&Co. KGaA, Weinheim. (f) Bader charge analysis of Mo\(_2\)C-CS and SAP-Mo\(_2\)C-CS, and their differences to purely ionic models ($\Delta Q$) (inset: isosurfaces of local charge density difference of SAP-Mo\(_2\)C-CS interface). (g) Calculated PDOS of the d-band of Mo\(_2\)C-CS and SAP-Mo\(_2\)C-CS. [98] John Wiley & Sons. © 2020 WILEY-VCH Verlag GmbH&Co. KGaA, Weinheim.

Ru SAs/AC-FeCoNi sustains its performance with negligible change in the polarization curve (figure 7). Yan et al incorporated Ir SAs into ultrathin NiCo\(_2\)O\(_4\) porous nanosheets containing oxygen vacancies via a co-electrodeposition method to improve the OER activity, which exhibited an overpotential of 240 mV at a current density of 10 mA cm\(^{-2}\), a Tafel slope of 60 mV dec\(^{-1}\) with a low Ir loading about 0.41% in acid media [105]. DFT simulations suggest atomic Ir anchored Co species adjacent to V\(_0\) achieve higher electron exchange and transfer activities. Specifically, the surface Ir species provide abundant sites for bonding with lower coordinated Ni and Co sites, which not only facilitated the adsorption of initial H\(_2\)O and further splitting activation but also enhance the valence stability of Co sites.

Au NPs were found to exhibit very poor current density even at very large overpotentials, while individual Au atoms can enhance the OER efficiency of Ni\(_2\)P [106]. Interestingly, Ni\(_2\)P is more active than pure Au for OER which demonstrated the efficient charger transfer in Au@Ni\(_2\)P yolk shell depends on the structural and electronic state of Ni\(_2\)P. The decreased Tafel slope from Au@Ni\(_2\)P (70 mV dec\(^{-1}\)) to Au@Ni\(_2\)P-350 °C (58 mV dec\(^{-1}\)) indicated that the activated state of Ni\(_2\)P was originated from atomically Au and clusters not bulk Au. The authors observed the Au yolk can diffuse into and even completely dissolve in Ni\(_2\)P at elevated temperature to form Au SAs or clusters by in situ TEM and ex situ heating. Pt is also previously regarded as an inert OER electrocatalyst, while individual Pt atoms can remarkably improve the OER activity [107]. Liu et al introduced isolated Pt into the bulk crystalline lattice of NiO. 0.5 wt% Pt/NiO possesses the lowest Tafel slope of 33 mV dec\(^{-1}\), much lower than that of NiO, ALD-Pt/NiO, and 1 wt.% Pt/NiO. DFT simulations reveals Pt actually does not reduce the overpotential of OER. Combined with experimental phenomena, they draw to conclude that Pt SAs can promote rocksalt NiO to active layered NiOOH phase formation which is truly beneficial to OER process.
6.2.2. Non-noble-metal based SACs

Nowadays, non-precious-metal based SACs, such as Fe [108, 109], Co [110], Ni [111], Mn [112, 113], Cu, Zn, etc based SAs coordinated with heteroatoms (e.g. N, O, P, S) have been intensively designed as superb OER catalysts owing to its maximal atom utilization. For instance, high valence Ni SAs coordinated to oxygen sites supported on graphene-like carbon (Ni-O-G SACs) were reported by Bao’s group [114]. Individual Ni atoms, Ni-O configuration and high valence state of >Ni(II) species were distributed over 3D interconnected porous framework consisted of 2D ultrathin sheet structure. The Ni-O-G SACs showed an overpotential of 224 mV at the current density of 10 mA cm$^{-2}$ and 42 mV dec$^{-1}$ Tafel slope lower than NiO, Ni-N-G SACs and the state-of-the-art OER SACs, indicating the vital contribution from Ni-O coordination to boost the OER activity and durability (figure 8). Lou et al fabricated an isolated Ni species decorated N-doped hollow carbon matrix via the Ni-N coordination [115]. In addition, atomically dispersed Fe with Co carbonate hydroxide hydrate grown on nickel foam constructed by Wang et al were active for OER in 1 M KOH, which achieved an overpotential of 200 mV (vs RHE) at $\eta_{10}$ and a small Tafel slope of 50 mV dec$^{-1}$ with a low loading of stabilized single Fe atoms (0.28 wt %) [116]. Single atom Fe-N-C catalysts possesses a
high performance compete with noble metal benchmarks for binding oxygen-containing intermediates. Chen’s group devised a self-sacrificed templating approach to obtain edge-enriched Fe$\text{N}_\text{4}$ sites over highly graphitic nanosheet architecture. The as-synthesized catalysts behaved unprecedented catalytic activity and stability, and can be assembled into rechargeable Zn-air battery [117]. Generally, TM-SACs are anchored on carbon or metal oxide substrate through coordination with nitrogen dopants or oxygen vacancies [118]. However, the strong electronegativity of N/O atoms not favors to modulate the electronic properties of metal active sites and increase the adsorption energy of reaction intermediates. To address this problem, the secondary heteroatom substitutes with weaker electronegative (S and P) could be incorporated to improve their local coordination environment and facilitate OER kinetics [95, 119, 120]. Chen et al prepared atomically dispersed N, S-codoped Co atoms (denoted as Co SA/ N, S-HCS), which exhibits outperforming OER performance. DFT demonstrated density-of-states distribution and electron transfer of Co active center was optimized by near-range coordination with N (Co-N$_4$) and long-range interaction with S (electron-donation) [20].

6.3. Oxygen reduction reaction (ORR)
ORR, occurs at the cathode, plays a critical role in proton exchange membrane fuel cells (PEMFCs) and metal-air batteries. ORR process can be categorized into 2 e$^-$ and 4 e$^-$ reduction, and the corresponding products are hydrogen peroxide and water, respectively [121].

6.3.1. Noble-metal-based SACs for ORR
Over the past years, Pt and its alloy play a pivotal role in the heterogeneous ORR electrocatalysis [122, 123]. In the work conducted by Sun et al, isolated Pt dispersed on MOF-derived N-doped carbon was synthesized via adjusting the ALD exposure time of the Pt precursor to study the effect of size-controlled Pt catalysts (from Pt single atoms, subclusters to NPs) for ORR [34]. DFT revealed that Pt SAs inclines to be anchored by pyridinic N-doped carbon sites and the electronic structure of them can be adjusted due to different adsorption species. The ORR prefers to occur in multichannel rather than single pathway of the Pt NPs, which lower the free energy for the rate-determining step and further promote the ORR activity (figure 9) [26]. Maximizing the platinum utilization in electrocatalysts toward ORR is quite desirable for sustainable application of Pt in energy systems [122]. A cost-effective carbon-supported carbon-defect-anchored Pt SACs (Pt$_1$/C) with remarkable ORR performance is reported by Xu’s group. Physical characterization and

![Figure 8.](image-url)
DFT computations reveal that single Pt atoms anchored stably by four carbon atoms in carbon divacancies (Pt-C$_4$) are the main active centers for the observed high ORR performance.

6.3.2. Non-noble-metal based SACs for ORR

PGM catalysts can significantly improve the sluggish ORR kinetics, while their high-cost, material scarcity and easy to poison which restricts their commercialization. Recently, transition metal SACs have been developed as promising alternatives for efficient electrochemical ORR. Numerous efforts have been devoted into revealing the intrinsic SAC active sites for ORR follows the order of Fe > Co > Cu > Mn > Ni [124]. Fe SACs have been regarded as the potential candidate to substitute PGM catalysts [125–128]. For instance, Wang et al fabricated isolated transition metals SAs dispersed on honeycomb-like nitrogen-doped carbon substrate. (M$_1$-HNC, M = Fe, Co, Ni) and compared their performance for ORR. The half-wave potential of M$_1$-HNC followed the order of Fe$_1$-HNC > Co$_1$-HNC > Ni$_1$-HNC, owing to the strong p–d-coupled spatial charge separation results in the Fe-N$_4$ effectively elevating d-band activity in a van-Hove singularity like trait [129]. Baek’s group also prepared a series of atomically dispersed TMs on N-doped nanosheets (MNCss, M = Fe, Co, or Cu), the obtained catalysts displayed excellent activity in the order of Fe$_3$N$_2$C$_2$ > Co$_3$N$_2$C$_2$ > Cu$_3$N$_2$C$_2$. C atoms in the M-N$_3$C$_1$ served as extra collaborative adsorption sites for providing dual site which is more thermodynamically conducive for ORR [130]. Combined with DFT calculations, Chen et al concluded five coordinated Fe-N$_x$ moieties could serve as ORR active sites through significantly decrease the reaction energy barrier and lower the adsorption energy of intermediate OH among Fe-N$_x$ (x = 2–6) active sites [131]. However, Fe ions are easy to induce the generation of radical oxygen species (ROS) via their strong Fenton reactions when they meet H$_2$O$_2$, the unwanted products lead to carbon corrosion and performance decay. Co-N-C SACs have attracted much attention since their weaker Fenton reaction [132, 133]. Lu et al revealed that Co-N$_3$C$_1$ site is more energetically favorable compared to Co-N$_2$C$_2$ and Co-N$_4$ via engineering local and global structures of Co SAs for ORR [134]. Wu et al innovatively proposed a lysozyme (Lys)-modified Co-ZIF-8 approach to obtain atomically Co implanted into dominated pyridinic-N doped porous carbon [135]. The Co-pyridinic N-C catalyst exhibits a remarkable stability in both alkaline and more challenging acidic media, and exceptional ORR activity with positive $E_{1/2}$ of 0.87 and 0.83 V, respectively. Another heteroatom coordinated into M-N-C can also be an effective strategy to induce charge redistribution and spin density changes of SACs, such as B [136, 137], S [138], F [139], P [140, 141]. Li et al rationally design optimal Co$_3$-N$_2$PS active sites incorporated into a hollow carbon polyhedron (Co$_3$-N$_2$PS/HCC) guided by DFT simulations. A rational design strategy of SA Co catalysts for ORR is developed, which achieves the optimal electronic density distribution to enhance ORR activity and kinetics through modulating slightly the coordination and electronic structure surrounding the metal center Co-N$_4$ moiety by synergistic coordination of the heteroatom of P and S. The obtained materials
achieved superior alkaline ORR performance with a $E_{1/2}$ of 0.920 V, a relatively low Tafel slope of 31 mV dec$^{-1}$, and record-level kinetic current density as shown in figure 10 [142]. High performance Fe/Co-free TM-N-C (TM = Ni, Mn and Cu) catalysts also have been intensively discussed [143, 144].

6.4. CO$_2$ reduction reaction (CO$_2$RR)
An uncontrolled emission of CO$_2$ has provoked environmental greenhouse impacts and resource depletion since the advent of industrial revolution. Electrocatalytic CO$_2$ reduction is an efficient means to generate
renewable energy, precious value-added chemicals and fuels. Compared to above electrochemical reactions, the large-scale application is hindered by the chemical inertness of CO$_2$ and CO$_2$RR is more complicated owing to it involves either two-, four-, six-, or eight-electron reduction pathways for generating numerous products widely distribute from C$_1$ (carbon monoxide, formic acid, methane and methanol), C$_2$ (ethene, ethane, ethanol, and etc), C$_3$ (acetate, and etc) and (methanol, n-propanol, etc). Furthermore, the equilibrium potentials of the CO$_2$RR to various major products are quite similar, and close to that of the HER. Therefore, it is critical to selective catalyze CO$_2$RR to certain desired products without the occurring of HER. Different central metal tends to show unique preference for CO2RR products, apart from N and C coordinated atoms, O and S can also be bonded with single metal atoms and further endow them with different electronic and geometric properties [145–147]. Jagvaral et al. found SACs dispersed on graphene with defects is favorable for CO2RR over HER. Five representative metals Ag, Cu, Pd, Pt, and Co improve the rate limiting potentials to generate C1 hydrocarbons. Ag has the lowest overpotential, and isolated Cu atoms prefer to produce CH3OH via screening of 28 d-block transition metals conducted by computational [148]. Through the precise electronic and coordination structure adjustment, the products distribution towards SACs could also be effectively controlled. In summary, more advanced characterization techniques and researches devoted into unveiling the structure-activity relationship of SACs.

6.4.1. Noble-metal based SACs for CO$_2$RR

Noble metal such as Au [150], Ag [151], and Pd [152] based electrocatalysts have shown superb activity for CO$_2$RR. Li et al. synthesized Ag$_x$/MnO$_2$, via a simply thermal transformation of Ag NPs driven by surface reconstruction of MnO$_2$ [149]. The evolution process of large Ag NPs to Ag SAs was clearly observed by in situ ETEM with XRD, the size of Ag NPs become smaller until it totally disappears from the substrate ascribed to temperature-induced the transformation of MnO$_2$ crystal facets from (211) to (310). The Ag$_x$/MnO$_2$ achieved high CO$_2$RR performance, with a FE$_{CO}$ of 95.7% at −0.85 V vs RHE and long-term stability. DFT reveals Ag possesses high electronic density, thus reduces the adsorption energy of intermediates *COOH (figure 11). Similarly, considering that the crystal facet of CeO$_2$ is highly correlated to
Figure 12. (a) Synthetic route towards single-atom FeN$_4$ and FeN$_5$ catalysts. (b) Free-energy profile with the optimized intermediates for the electroreduction of CO$_2$ to CO. The asterisk (*) denotes the free adsorption site, and $^\ast$M (M = COOH, CO, CHO) indicates the adsorbed chemical species. (c) Local DOS of the FeN$_4$ and FeN$_5$ system with adsorbed CO; the Fermi level is taken as the zero-energy point. (d) LSV scans (20 mVs$^{-1}$) for the FeN$_5$ catalyst (H-M-G) in Ar- and CO$_2$-saturated KHCO$_3$ solution (0.1 m). (e)–(g) Comparison of the electrocatalytic activity of as-synthesized catalysts: Faradaic efficiency (e), partial current density (f), and production rate of CO versus potential (g). [155] John Wiley & Sons. [Copyright © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim].

its morphology, four structurally well-defined different shapes, including rods expose (110) and (111) facets, cubes expose (100) facet, polyhedrons expose (111) facet, and octahedrons expose (111) facet, as the substrate for anchoring Pd SAs was synthesized by Liu et al [153]. Their influences in the reduction of CO$_2$ to CH$_3$OH have been detailed studied. They draw to conclude that CeO$_2$ morphology greatly affects the catalytic activity of Pd/CeO$_2$ materials owing to the various crystal facets exposed. The Pd/CeO$_2$-R (rods) display the best-performance among the four catalysts which possesses the highest density and numerous oxygen vacancies, originating from low oxygen vacancies formation energy promoted by SA Pd and the (110) facet of CeO$_2$-R with high oxygen mobility. Wang et al fabricated a series of photo-coupled electrocatalysts via mimicking the structure of chlorophyll (HNTM-Au-SA) [154]. Single porphyrin-Au atom possesses a FE$_{CO}$ of 94.2% at −0.9 V and a TOF of 37 069 h$^{-1}$ at −1.1 V.

6.4.2. Non-noble-metal based SACs for CO$_2$RR
Earth-abundant first-row transition metals (mainly Fe, Co, Ni) are active for HER and easy adsorption of CO, hampered their usage for CO$_2$RR. A number of transition metals have been shown to produce CO (e.g. Au, Ag, Zn). Isolated transition metals coordinated with N in carbon matrix (M-N-C) have been exploited as promising alternatives for nonprecious SACs in CO$_2$RR [156, 157]. Wang et al developed a facile approach to obtain atomically dispersed FeN$_5$ active sites integrated on N-doped graphene via thermal pyrolysis of hemin and melamine coadsorbed on graphene [155]. The EDS and XANES analysis demonstrated the individual distribution of Fe sites with presumable five N atoms to form pentacoordinated iron (FeN$_5$), which exhibited the maximum FE$_{CO}$ of 97.0% at moderate overpotential of 0.56 V. The excellent activity for CO$_2$-to-CO conversion can be ascribed to an additional axial pyrrolic N ligand coordinated with FeN$_5$, thus consumes the electron density of Fe 3d orbital and decrease the Fe-CO $\pi$ back-donation, and further facilities to high selectivity of CO via fast CO desorption. Ni-N-C was regarded as the state-of-the-art for CO$_2$RR (figure 12)
For example, atomically 3d metals implanted in N-doped carbon were synthesized from a series of isostructural multivariate MOFs constructed from M-TCPP (tetrakis(4-carboxyphenyl) porphyrin) (M = Fe, Co, Ni and Cu) [159]. When employed as ideal model electrocatalysts in CO$_2$RR, Ni-N-C showed the highest FE$_{CO}$ of 96.8% at −0.8 V in pure CO$_2$, that far superior to those of Fe$_{1}$, Co$_{1}$, and Cu$_{1}$-N-C. Theoretical results illustrated that Ni$_{1}$-N-C possesses the most positive value of U$_L$(CO$_2$)-U$_L$(H$_2$), elucidating its efficiently and high selectivity for CO$_2$RR and suppression of the competitive HER. This group also studied the coordination environment of MOF-templated Ni SACs for promoting CO$_2$RR [160]. They proposed a general host-guest cooperative protection strategy to fabricate Ni SACs by in situ polymerization of pyrrole into 1D channels of a bimetallic non-nitrogenous MOF, i.e. MgNi-MOF-74. Single atom dispersed Ni with different N atoms were obtained via regulating the pyrolysis temperature. The optimal catalysts, NiSA-N$_2$-C, achieves high CO Faradaic efficiency of 98% and turnover frequency of 1622 h$^{-1}$. Theoretical simulations suggest that the NiSA-N$_2$-C possesses the lowest free-energy barrier of forming COOH$^*$ intermediates for the rate-determining step and poorly CO$^*$ desorption energy on accounts of the reduced coordination number of N atoms in Ni SA.

### 7. Conclusions and future prospects

In virtue of the rapid development of advanced characterization techniques and theoretical calculations, many high-performance SACs have been successfully designed and prepared in the past decade. SACs provided vast opportunities for various electrochemical catalytic reactions, such as HER, OER, ORR, CO$_2$RR, etc owing to their unique electronic and structure properties. Moreover, they can show enzyme-mimicking activities including CAT$^-$, SOD$^-$, etc for biomedicine and biosensing. Overall, despite the great and encouraging achievements achieved, there are still many challenges to be solved in the practical applications and research, which are mainly divided into the following two questions from the perspectives of future outlooks and possible solutions.

(a) The low mass loading of the isolated metals on substrate (typically below 5%) greatly blocked their performance to satisfy the demand in large-scale industrial applications. Since their extremely surface free energy, resulting in aggregation into NPs, there could be thresholds of individual atoms loading ratios in SACs. Various strategies towards fabricating high loading SACs were still highly desired, a suitable support with abundant defects or numerous coordination numbers are favors to form a strong metal-support interaction, such as M-metal oxide, M-N$_x$-C$_y$ (N can be replaced by S, P, Cl), M-metal, M-other supports (Mxene, MoS$_2$, etc).

(b) Deeply insight into the relationship of catalytic performance and mechanism based on the interactions between active SACs and supports is indispensable but challenging, which can guide researchers to rational design efficient catalysts. The structure of active sites changes dynamically under realistic reaction needs to be investigated by advanced in situ/operando measurements. The information obtained from those techniques combined with DFT simulations reveals that SACs may catalyze in distinct routes compared to the corresponding NPs by recognizing reaction intermediates, and monitoring the dynamic behaviors of their electronic microenvironment and geometric structure while they are still in infancy. Of particular interestingly is SACs tends to possesses unique properties compared to corresponding bulk metal. Further study should be focused on finding the optimal doping heteroatoms species and ratios, and adopting multiple active sites, i.e. dual atoms or clusters even including nonmetal SACs.

(c) When it comes to the biomedical applications of SACs, the long-term biocompatibility of the nanozymes is one of the crucial issues but still has not been well elucidated. Compared with small biomolecules, SACs always require longer blood circulation time and even manifest toxicity owing to their larger size and higher stability. Therefore, it is very critical to precisely develop biocompatible SASs and comprehensive evaluate their biosafety for the future clinical applications. Surface modifications with profuse functional groups could diversify the functionalities of SACs, which enables tumor targeting, and therapy of cancer or bacteria.

(d) Some strategies are easy to scale up (the highest recorded value of metal loading in SAC is 30 wt%), which pave ways to practical applications. With the advantages of heterogeneous catalysis, SAC is widely applied in almost all heterogeneous catalysis fields. Individual atoms are regarded as active centers for heterogeneous SACs. Most studies focus on electrochemical catalysis, such as ORR, HER, OER, CO2RR. In the recently reported works, the catalytic mechanism and performance regulation were also explored based on the ideal single-atom simulation platform. Through the development of green large-scale synthesis strategy, characterization technologies and theoretical calculation, significant progresses will be achieved in understanding the catalytic properties (activity, selectivity and stability) and mechanism of SACs, so as to realize the ultimate goal of industry application references.
Data availability statement

No new data were created or analysed in this study.

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