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Perspective

Structure−Property−Activity Relationships in Carbon Dots

Yiqun Zhou,[‖] Wei Zhang,[‖] and Roger M. Leblanc*

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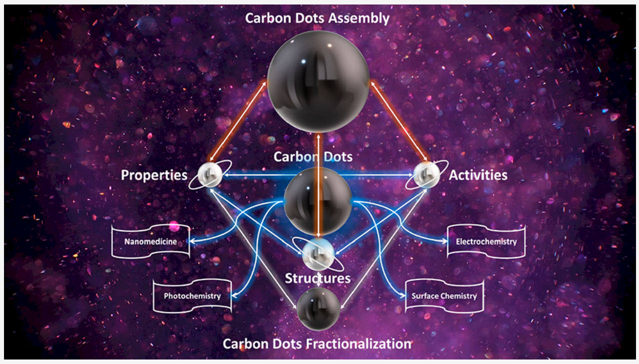
ABSTRACT: Carbon dots (CDs) are one of the most versatile nanomaterials discovered in the 21st century. They possess many properties and thus hold potentials in diverse applications. While an increasing amount of attention has been given to these novel nanoparticles, the broad scientific community is actively engaged in exploring their limits. Recent studies on the fractionalization and assembly of CDs further push the limits beyond just CDs and demonstrate that CDs are both a mixture of heterogeneous fractions and promising building blocks for assembly of large carbon-based materials. With CDs moving forward toward both microscopic and macroscopic levels, a good understanding of the structure−property−activity relationships is essential to forecasting the future of CDs. Hence, in this Perspective, structure−property−activity relationships are highlighted based on the repeatedly verified findings in CDs. In addition, studies on CD fractionalization and assembly are briefly summarized in this Perspective. Eventually, these structure−property−activity relationships and controllability are essential for the development of CDs with desired properties for various applications especially in photochemistry, electrochemistry, nanomedicine, and surface chemistry. In summary, in our opinion, since 2004 until the present, history has witnessed a great development of CDs although there is still some room for more studies. Also, considering many attractive properties, structure−property−activity relationships, and the building block nature of CDs, a variety of carbon-based materials of interest can be constructed from CDs with control. They can help reduce blind trials in the development of carbon-based materials, which is of great significance in materials science, chemistry, and any fields related to the applications.



■ INTRODUCTION

Carbon-based nanomaterials have always been of great interest in the field of materials science in the past 30 years since the first report of fullerene that was formed by the laser ablation of graphite.[1−4] The following discoveries of carbon nanotubes in 1991, graphene in 2004, and carbon dots (CDs) in 2004 drew the public's attention to a wide array of zero-, one-, two-, and three-dimensional carbon-based nanomaterials due to their unique structures, properties, and applications.[5−7] Among the diverse allotropes, due to excellent photoluminescence (PL), biocompatibility, water dispersion ability, low cytotoxicity, small particle size (<10 nm), and abundant and tunable surface functional groups and electron donors/acceptors, CDs are widely applied in biomolecular detection and recognition, disease diagnosis and detection, drug delivery and bioimaging, and catalysis.[3,8,9] CDs were serendipitously discovered during the purification of single-walled carbon nanotubes and reported for a particle size dependent fluorescence in 2004.[7] Two years later, Sun and co-workers synthesized fluorescent carbogenic nanoparticles (NPs) via laser ablation of a mixture of graphite powder and cement and named these NPs as CDs for the first time,[10] which subsequently triggered extensive studies on the synthesis, purification, separation, characterizations, and applications of CDs.[7,11] As one of the most intriguing properties of CDs, PL has been widely studied and the fluorescence quantum yield (QY) of CDs has increased over the years. In 2013, Yang and co-workers reported a great increase in the fluorescence QY of CDs to 80% by using a one-step hydrothermal method with citric acid and 1,2-ethylenediamine as the precursors.[12] With citric acid and tris(hydroxymethyl)aminomethane as precursors, Zheng et al. further raised the fluorescence QY of CDs to 93.3% in 2015,[13] which is even higher than that of many fluorophores such as Alexa (10−92%) and fluorescein (79%).[14]

Broadly speaking, CDs can include graphene quantum dots (GQDs), carbon quantum dots (CQDs), and polymer dots (PDs).[11] CQDs are a class of carbon-based quasi-spherical NPs with a crystalline graphitic lattice or an amorphous structure.[15] The precursors for synthesizing CQDs seem to be

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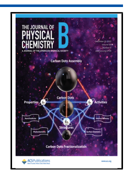

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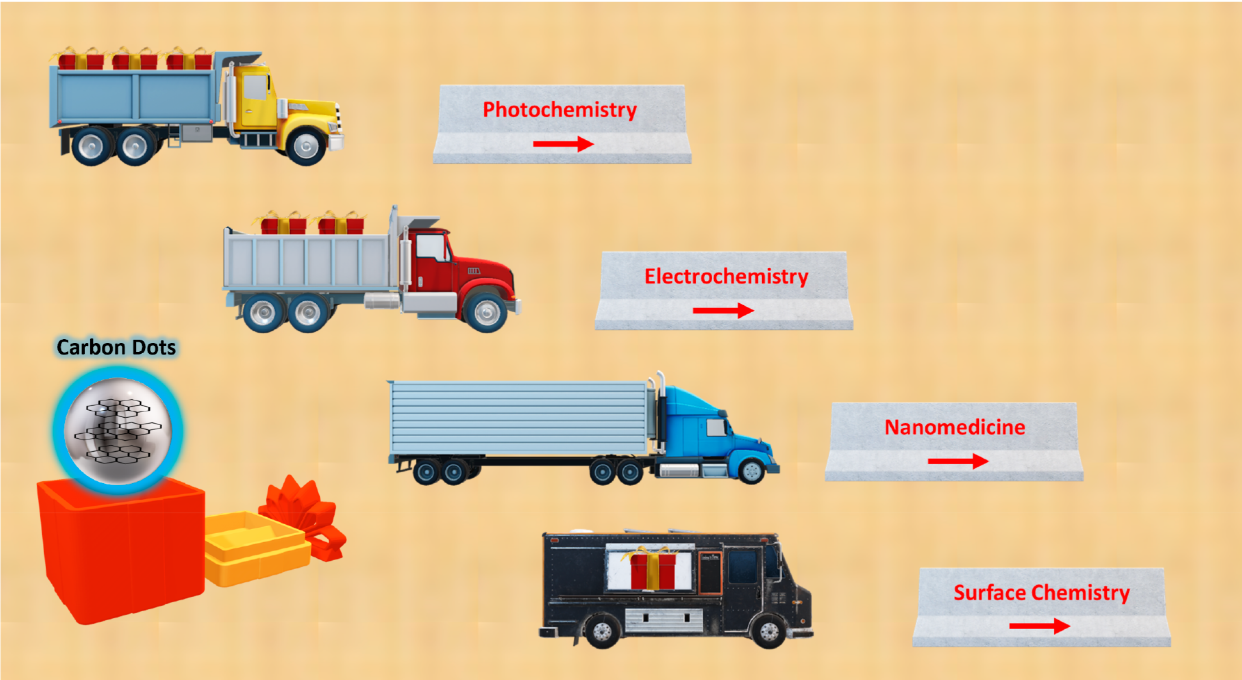

Figure 1. Graphical illustration of carbon dots studied and applied in four major fields, namely surface chemistry, electrochemistry, photochemistry, and nanomedicine.

more available than those for GQDs and PDs.[16] In comparison, GQDs were first reported in 2008 and they are graphene-based NPs with a diameter less than 100 nm and a few graphene layers in the core.[17,18] Because of these graphene layers, GQDs possess a large surface area and rich π electrons. Also, due to both the quantum confinement and edge effects occurring once the particle size falls below 10 nm, GQDs exhibit interesting electrical and optical properties.[19−21] In addition, studies have demonstrated that the band gaps of conduction/valence bands and optoelectronic properties of GQDs can be tuned by adjusting their morphology and edges.[22−24] In comparison to CQDs and GQDs, PDs are synthesized by aggregation and cross-linking of small organic molecules, linear polymers, or monomers.[11,25] The polymer/carbon hybrid structures grant PDs abundant functional groups and polymer chains on the surface and unique optical properties.[26]

Since the discovery of CDs, their properties have been extensively studied and they are widely applied in diverse property-associated fields where most nanomaterials are studied.[27−29] Among them, photochemistry, electrochemistry, nanomedicine, and surface chemistry are of particular interest (Figure 1). First of all, photochemistry is the most intriguing and unique area to study in CDs considering their excellent light harvesting ability and photoluminescence (PL).[30,31] Due to the light harvesting ability and mostly blue PL emission, CDs are favor photosynthesis.[32] Also, photon absorption stimulates CDs to generate abundant electron donors (electrons) and acceptors (holes) on the surface, which allows CDs to induce the formation of singlet oxygen and various reactive oxygen species (ROS) such as hydroxyl radicals (•OH) and superoxide anion radicals (•O_2^-) that play key roles in photocatalysis.[33] As for the PL of CDs, although the mechanism is generally prone to the surface state theory,[34] namely the PL of CDs is determined by surface functional groups and energy levels, other mechanisms including molecular, core state theories, and quantum confinement effect also apply, which heavily depends on the CD species.[35] However, compared to the theoretical studies, implementation of PL seems to have attracted much more attention. For instance, the PL of CDs is typically excitation dependent, which offers more options in the applicable excitation wavelength in bioimaging.[36] The PL of CDs can be quenched by interactions with the surrounding substances, so CDs are often reported for various sensing application potentials, especially in the detection of metal ions.[37−39] For another example, phosphorescent CDs have great application potentials in energy, information, biomedicines, and other fields due to their long lifetime and low background interference.[40]

Furthermore, due to a biocompatible and nontoxic nature, CDs are considered as an ideal alternative for diverse metal-based nanomaterials, especially in electrochemistry and nanomedicine.[41,42] The electrochemistry of CDs, in this study, primarily centers on electrochemical properties and thermoelectric effect (TE). Although there are few related studies, CDs were observed to enhance the TE properties of many well-characterized materials.[43,44] In nanomedicine, CDs are often applied as drug nanocarriers for targeted therapies. For instance, CDs were observed to cross the blood−brain barrier (BBB),[45−47] the most essential barrier in the treatment of various brain diseases and disorders. Once CDs enter the brain, CDs incorporating contrast agents enable magnetic resonance imaging (MRI). In addition, certain CD species were observed to target bones[48] and inhibit both the replication and cell entry of viruses such as human immunodeficiency virus (HIV) and SARS-CoV-2.[49] Most significantly, the singlet oxygen and ROS generated in the aforementioned photocatalysis have promoted the applications of CDs in photodynamic therapies, which are often accompanied by photothermal therapies.[50,51] Compared to the other areas, studies on the surface chemistry of CDs are insufficient. For example, Langmuir monolayers are commonly

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used to mimic cell membranes to investigate the effects of pharmaceuticals, but the Langmuir monolayers of CDs so far have only been reported by our group.[52]

Herein, in this Perspective, based on extensive experimental results and literature studies, a variety of structure−property−activity relationships of CDs are summarized. In particular, these relationships were revealed via CD fractionalization and assembly. Also, CD fractionalization and assembly demonstrate that CDs are versatile. Between them, the summary of applying CDs as building blocks for the assembly of many one-, two-, and three-dimensional carbon-based materials is new. In addition, the progresses in the elucidation of some CD-related research topics such as structures and PL are reported. We also introduce some new discoveries on the properties, applications, and the structure−property−activity relationships of CDs in photochemistry, electrochemistry, nanomedicine, and surface chemistry, by combining the experimental results acquired in our group and reported by others. At the conclusion of this Perspective, the expectations for and outlook on the future development of CDs are proposed. For example, more endeavors should be made toward the development of red/NIR-emitting or chiral CDs with a controlled synthesis, clear structure (both core and shell), and energy levels (surface states, conduction/valence bands, and band gap). Regarding applications, the metabolisms of CDs *in vitro* and *in vivo* are insufficiently investigated. Also, considering the abundant surface functional groups, are CDs biomimetic materials?

■ FRACTIONALIZATION OF CARBON DOTS

CDs are a mixture of heterogeneous fractions, which can be simply proved by electron microscopy results.[45,53] In addition, fractionalization, separation, or isolation of CDs has been achieved by controlling the particle size, hydrophilicity, and molecular weight,[14,54] while surface charge is less used for CD separation. The fractions often exhibit properties that are different from the collective characteristics of overall CDs.[14,55] Most significantly, fractionalization is often applied to elucidate basic principles in the properties of CDs such as PL and various structure−property relationships.[14,55]

The most common approach for fractionalization of CDs is chromatography.[56] In our previous studies, many chromatographic techniques including reversed-phase column, thin-layer, and size-exclusion chromatography (SEC) were employed to separate CDs into different fractions based on their differences in hydrophilicity and particle size.[14,54] It is worth noting that most CDs applied were hydrophilic or amphiphilic, so whether column or thin-layer chromatography, reversed phase was applied. The developing solvents are usually more polar than those used for normal-phase counterparts. Since CDs are not uniform, fractionalization often enables us to observe some novel characteristics from certain CD fractions. For instance, many CDs display excitation-dependent PL,[36] which means the PL emission shifts with the applied excitation wavelengths. However, in one of our early studies mentioning the fractionalization of gel-like CDs via thin-layer chromatography, two fractions were observed to exhibit excitation-independent PL.[55] Thus, the study demonstrated that the excitation-dependent PL of gel-like CDs was a collective characteristic of many fractions displaying excitation-independent PL that reveals a few different energy levels on the surface of CD fractions. A structure−property relationship in the hydrophilicity of CDs was revealed by a recent study.[14] In this study, a type of CDs was separated via column chromatography and five fractions with similar particle sizes and surface charges but different structures were obtained. Interestingly, thermogravimetric analysis (TGA) suggested that the increase of surface hydrophilic functional groups such as hydroxyl and amine groups was consistent with the enhanced hydrophilicity of CDs. However, other hydrophilic functional groups could not be estimated due to their connections to alkane chains or triple-heptazine layers of the core, which was a flaw of this work. It also urges a table for TGA such as Fourier transform infrared (FTIR) and nuclear magnetic resonance (NMR) spectroscopies that can help accurately identify different functional moieties and structures. For another example, another type of highly photoluminescent CDs was separated into three fractions via size-exclusion chromatography.[54] The changes in particle size and PL emission were found to be inconsistent. Nonetheless, the variation of PL emission synchronized with that in the elemental compositions including carbon, nitrogen, and oxygen. Thus, the study suggested that the PL of this type of CDs was determined by the surface state theory instead of the quantum confinement effect. On the basis of extensive literature records,[57−59] the surface state theory is the mainstream mechanism hypothesis for CDs' PL, which is very different from the traditional metal-based quantum dots.[60]

In addition, fractionalization of CDs has also been achieved via other techniques such as electrophoresis and dialysis.[47,61] CD fractionalizations via electrophoresis are based on the difference in surface charge among different fractions. A major drawback of this fractionalization approach is low yield. Meanwhile, although dialysis can be exploited to separate CDs with different molecular weights, it is more often considered as a purification strategy.

In our opinion, CD fractionalizations not only benefit our understanding of many property mechanisms and structure−property relationships but also reveal that CDs obtained in one pot lack uniformity, which is a major concern in their actual applications. Moreover, it has not been much reported what CD fractions were applied to, which might be related to the low yield.

■ CARBON DOTS AS BUILDING BLOCKS

Now that CDs can derive from carbon nanotubes,[7] can we utilize CDs to assemble carbon nanotubes? In fact, CDs are excellent building blocks for the assembly of many large one-, two-, and three-dimensional carbon-based nanomaterials with either physical or chemical strategies. The physical strategy mainly focuses on calcination, while the chemical strategy primarily indicates covalent conjugation.[62,63] In addition, self-assembly of CDs to form supra-CDs can be included into either strategy, which depends on whether there are covalent bonds formed.[63]

As early as 2012, Cheng et al. have succeeded in transforming 3−5 nm CDs into carbon nanotubes (CNTs; 200−300 nm in diameter) by electrophoresis deposition of CDs in a nanoporous anodic aluminum oxide template.[64] They found the as-prepared CNTs displayed features similar to those of many traditional CNTs, such as a hollow and tubular morphology. Also, they observed individual CDs interconnected with each other with a gap of 1 nm. The size and morphology of the resulting CNTs heavily relied on the used templates. Most importantly, X-ray photoelectron spectroscopy (XPS) was applied and demonstrated that both CDs and

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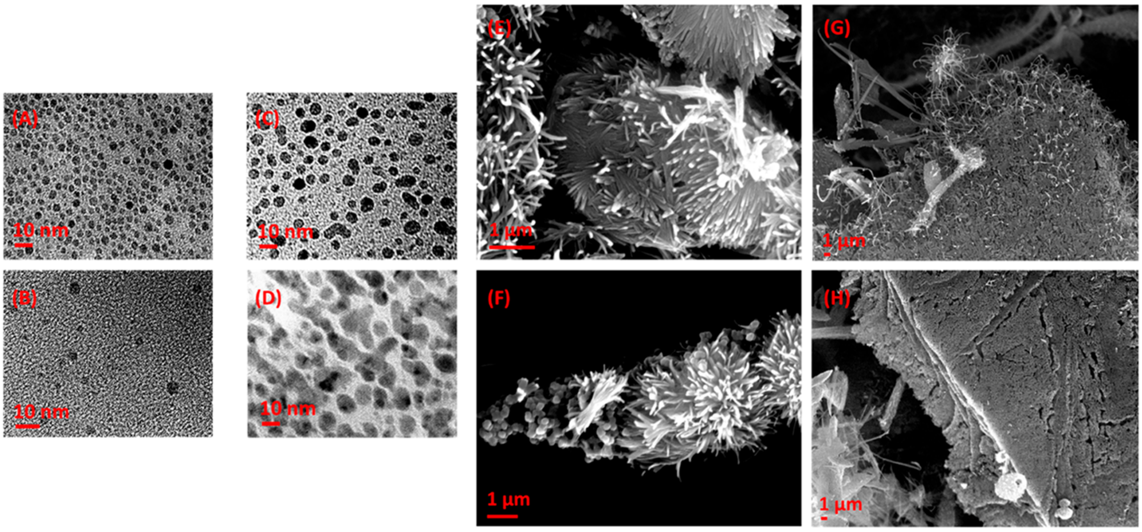

Figure 2. Morphology of CDs and diverse CD-derived structures formed via covalent conjugations.[62] Transmission electron microscopy (TEM) images of B-CDs (A), G-CDs (B), B−G CDs (5:3) (C), and B−G CDs (5:30) (D). SEM images of B−G CDs (5:100) (E, F) and B−G CDs (5:300) (G, H). Reprinted with permission from ref 62. Copyright 2020 Elsevier.

the derived CNTs had hydroxyl and carbonyl surface functional groups and a declined O/C ratio from CDs to CNTs revealed a reduction of O-containing functional groups in the formation of CNTs. Subsequently, the aforementioned different types of CDs were successively applied to synthesize CNTs and other two- and three-dimensional nanomaterials such as graphene-based nanosheets (GNSs) and porous carbon frameworks (PCFs), respectively. According to a few early studies,[65−67] CD-derived GNSs were mostly generated via annealing at high temperatures above 200 °C, and the formation usually proceeded from carbon chunks (300−400 °C), to multilayered sheets (400−700 °C), to GNSs with graphene morphology but lacking in the typical hexagonal lattice fringes of graphene (700−900 °C). Thus, it is clear that such a transformation from CDs to 2D carbon nanomaterials depends on the temperature. To catalyze this process, the addition of metal ions was very common.[68,69] Similarly, transformation from CDs to PCFs depends on all the aforementioned reaction conditions including the calcination temperature, catalyst, and template.[70−72] Most interestingly, to form PCFs, the calcination temperature usually ranges between 700 and 900 °C, which, however, coincides with the temperature to form 2D GNSs. This coincidence demonstrates that high-temperature treatments can give rise to both 2D GNSs and 3D PCFs, which are significantly affected by the use of templates such as supramolecular gels and magnesium hydroxide.[70,71] However, without any templates, CDs will be preferentially transformed into 2D GNSs.[71] Thus, templates are very important in the control of the morphology of the CD-derived structures.

Except for physical treatments, abundant surface functional groups enable CDs to be conjugated to a variety of ligands via covalent bonds.[46] Our group was the earliest to report the assembly of diverse large carbon-based nanostructures using CDs as Lego-like building blocks.[62,73] In one of our studies,[62] a direct covalent conjugation was initiated between two different CD species, namely black CDs (B-CDs) and gel-like CDs (G-CDs), whose morphologies are shown in Figure 2A,B, via EDC/NHS mediated amine coupling. Between the two CD species, B-CDs have abundant carboxyl surface groups, while G-CDs have sufficient primary amine surface functional groups. By investigation of the covalent conjugations between different CDs, it was found that (1) a two-step purification was inevitable; (2) the derived nanostructure inherited functionalities from both CDs; (3) changes occurred to thermostability, aqueous stability, PL emission, and morphology in comparison to CDs; (4) in terms of morphology, the conjugated complex (B−G CDs) obtained with a mass ratio of 5:3 (B-CDs:G-CDs) interestingly showed a figure-eight shape in Figure 2C with a width and length of 3 and 6 nm, respectively; (5) with more CDs participating in the conjugation, many well-studied nanostructures including nanodiamonds, nanofibers, nanotubes, nanowires, nanosheets, and porous carbon frameworks were obtained as demonstrated in Figure 2D−H; (6) most importantly, both carboxyl and primary amine functional groups had a minimum surface content to initiate the conjugation and self-conjugation; and (7) different conjugated nanostructures inherited properties from both parent CDs and demonstrated some strengthened ones.

Moreover, although CD self-assembly can be categorized into either strategy, it is more described as a physical strategy. Also, it often spontaneously occurs in the media where CDs cannot dissolve and tend to deposit on each other, which provides an opportunity for their interconnections.[65] However, the formed supra-CDs are not permanently stable due to the weak interparticular interactions.[63,65]

■ STRUCTURES OF CARBON DOTS

The structure of CDs is a frequently mentioned subject, but a deep investigation is often lacking. CDs are often described to possess a shell−core structure,[35] and the shell is typically comprised of diverse surface functional groups,[74] but what about the core? A good understanding of the CD core structure is significant, but it seems that there are not many studies solely dedicated to its investigation. And the reasons may include the following: (1) different core structures result from different precursors and reaction conditions; (2) different polymerization and carbonization degrees because of rapid and harsh reaction conditions can lead to different structures of

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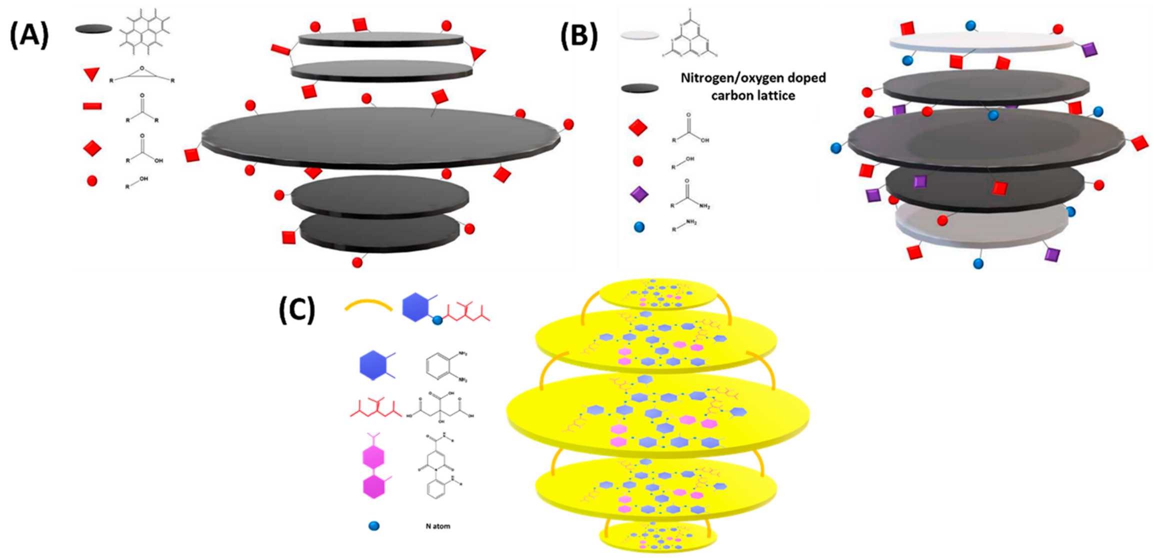

Figure 3. Graphical representative of three CD structural models,[34,75] based on various physicochemical property characterizations of B-CDs (A), CNDs (B), and Y-CDs (C). Reprinted with permission from ref 34. Copyright 2021 Elsevier. Reprinted from ref 75. Copyright 2021 American Chemical Society.

CDs in one reaction; (3) there is no clear boundary between the core and the shell; (4) current characterization techniques cannot distinguish the core and the shell; (5) one may doubt whether the CD has a core. Nonetheless, it is of great benefit to learn the structures of CDs including both the shell and the core, and this information can help promote the structure−property relationship studies of CDs and numerous applications. As one of the most promising NPs, this is an essential step in the future development of CDs. In addition, with the rapid development of machine learning, various experimental data of the structures of CDs can be collected and converted to a computer language, which can largely boost studies on the properties of CDs, structure−property relationships, and their interactions with diverse compounds by computational modeling. Also, with the help of machine learning, in the near future, many uniform CDs of interest can be developed with control such as gold NPs.

Meanwhile, studies on CD core structure have been actively carried out in our group. In 2021, three different CD species, namely black CDs (B-CDs), carbon nitride dots (CNDs), and yellow CDs (Y-CDs), developed in our group, were systematically characterized and rigorously analyzed for their structures.[34] B-CDs and Y-CDs were named after their physical appearances. Raman and electron paramagnetic resonance spectroscopies and X-ray diffraction analysis showed amorphous cores for B-CDs and CNDs but a crystalline core structure for Y-CDs. Combination of these results with FTIR and X-ray photoelectron spectroscopies, mass spectrometry, TGA, and atomic force and transmission electron microscopies presented three well-defined structural models as illustrated in Figure 3 with a distribution of structures in virtual samples. These structural models have laid foundations for a recent molecular dynamic simulation study[14] on the interactions between CNDs and microtubule-associated protein tau, whose aggregation is a hallmark of Alzheimer's disease (AD). In addition, these CD structural models are currently applied to study a CO_2 uptake hypothesis for an enhanced photosynthesis with Y-CDs previously reported by our group.[75] Above all, these structural models allow for a deep investigation of the interactions between B-CDs, CNDs, and Y-CDs, and the surroundings to understand their unique properties and potential applications. Significantly, with various structure−property relationships well utilized, these properties and applications can be optimized.

■ CARBON DOTS IN PHOTOCHEMISTRY

Photoluminescence of Carbon Dots. CDs possess excellent PL and high photostability that are ideal for their applications in light-emitting diodes (LEDs),[76,77] additive manufacturing,[78] sensing,[11] and bioimaging.[79] A precise control of the PL emission is a main research focus,[80] and for specific purposes such as to avoid the autofluorescence interference, the PL of CDs can be tuned and the techniques will be introduced in detail in combination with the mechanism.[81] Up to now, the mechanism of CDs' PL is actively discussed among the surface, molecule, and core state theories, cross-link-enhanced emission, and quantum confinement effects,[25] considering the structure−property relationships revealed by modulating various parameters during CDs' syntheses and postsynthesis surface modifications including precursors, synthesis methods, and dopants.[82]

As a predominant mechanism hypothesis for the PL of CDs, surface states determine the optical and electrical properties and energy level of CDs.[83] There are two main routes to change the surface states of CDs, namely (1) modifications of the surface configuration in functional groups, defects, and edge states and (2) heteroatom doping by, for instance, nitrogen, oxygen, boron, sulfur, fluorine, and phosphorus.[84−90] By changing the surface configuration of CDs, the electron energy levels of CDs are altered. For instance, Rogach's group obtained CDs with different sizes of π-conjugated domains, resulting in different emissions from blue to red.[91] Xiong's group synthesized CDs with similar particle sizes and graphitic cores but different oxidation degrees on the surfaces. The PL results showed red shifts that resulted from different surface states.[92] Additionally, nonphotoluminescent CDs were converted into highly photoluminescent CDs by a simple surface passivation.[10] More studies demonstrate that modifying the

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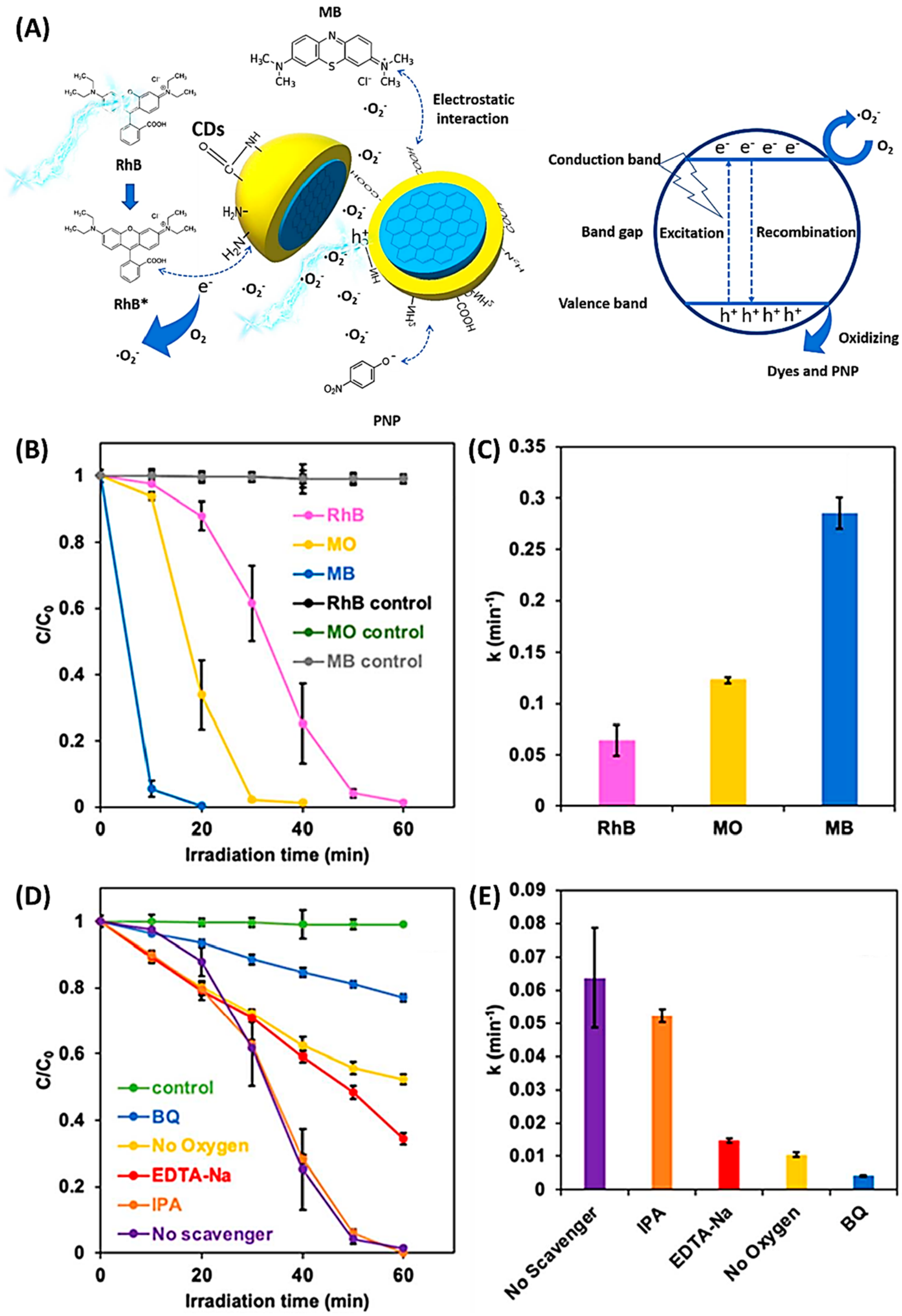

Figure 4. (A) Schematic diagram of the interaction between CDs and dyes in photocatalytic dye degradation.[54] (B) Photocatalytic degradation with G-CDs as the photocatalyst[33] and (C) pseudo-first-order rate constants of different dyes, namely rhodamine B (RhB), methyl orange (MO), and methylene blue (MB). (D) Photocatalytic degradation with G-CDs as the photocatalyst and (e) pseudo-first-order rate constants of RhB degradation in the presence of isopropyl alcohol (IPA), benzoquinone, EDTA-Na, and no scavenger. Conditions: initial dye concentration, 10 mg L^{-1}; photocatalyst weight, 12 mg; light power, 310 W; pH, neutral; and temperature, 20 °C. Controls refer to photodegradation of dyes in the absence of G-CDs. All experiments were conducted at least three times each. Reprinted with permission from ref 33. Copyright 2021 Elsevier. Reprinted with permission from ref 54. Copyright 2019 Elsevier.

surface states of CDs by varying their surface functional groups can effectively modulate the PL.[85,93,94] This has been utilized as a measure to determine whether a conjugation between CDs and a drug/protein/nucleic acid is successful.[46] Further, heteroatom doping is another commonly used surface state modulation technique. For instance, nitrogen doping results in a high radiative recombination yield by changing the electron status and promoting electron transfer, which leads to a high fluorescence QY and similar excitation dependencies.[86] Thus, both the surface configuration modification and heteroatom doping can significantly alter the electronic structures and energy levels of CDs, which is directly reflected by their PL behavior changes. Nonetheless, now that the surface state theory is a mainstream hypothesis for CDs' PL mechanism, it is essential to determine the energy levels, which in turn can provide strong evidence to support this mechanism hypothesis.

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In addition to the surface state theory, there exist other hypotheses regarding the PL mechanism of CDs. For instance, the quantum confinement effect is a well-accepted mechanism for the PL of quantum dots when the particle sizes are too small to be comparable to the wavelength of the electron. According to the effect, as the size of sp^2 domain increases, the band gap between the conduction and valence bands is reduced while the PL emission wavelength increases.[83,95] Theoretically speaking, the quantum confinement effect applies to CQDs and GQDs that possess graphene layers.[96] Lee's group prepared CQDs with four different particle sizes by electrolyzing ethanol under alkaline conditions. It turned out that CQDs with different particle sizes (1.2, 1.5−3.0, and 3.8 nm) exhibited PL emission in the UV, visible, and near-infrared regions, respectively.[97] However, Sun's group observed the PL of CDs synthesized with citric acid and urea depended on the extent of graphitization instead of particle size.[98] Furthermore, addition of specific molecular chromophores may lead to the change in the molecular state of CDs due to the n−π* and π−π* transitions of electron transfer.[12] However, although fluorophores generally have high fluorescence QYs, they suffer low PL stability.[81] For example, Choudhury's group reported a pH-dependent PL arising from solvatochromism ascribed to the surface and molecular states of CDs.[99] Duan et al. exploited multinuclear solid-state nuclear magnetic resonance (NMR) spectroscopy and determined a high concentration (18 ± 2 wt %) of a molecular fluorophore, namely 5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*a*]pyridine-7-carboxylic acid (IPCA) or its derivatives, in CDs synthesized with citric acid and 1,2-ethylenediamine by microwave-assisted reactions.[100] Later, Yao et al. also discovered a blue fluorophore, 5-oxopyrrolidine-3-carboxylic acid, in CDs synthesized from citric acid and urea.[101] These nontraditional fluorophores provide both an additional challenge to the community in seeking the PL mechanism of CDs and an opportunity for a greater range of CD design schemes and applications. Core state was first proposed by Giannelis and co-workers in the development of CDs from citric acid and ethanolamine.[102] Ortega-Liebana et al. later discussed that the PL of citric acid derived CDs mainly originates from the molecular states rather than the core states.[103] The cross-link-enhanced emission effect generates stable and compact aggregates of fluorophores in CDs. The cross-linked domains of fluorophores can significantly enhance the overlap of electron clouds, contributing to the PL of CDs.[104] However, despite the diverse PL mechanism hypotheses, it is difficult to validate the PL mechanism for any CDs if the structure is unknown. Also, similar to the structural models, the PL mechanism is likely to vary among different CD species. Most importantly, there might be multiple mechanisms contributing to the PL of any specific CDs.[83] It is worth noting that bioimaging is not a focus in this Perspective but our wide applications in bioimaging can be found elsewhere.[11]

Furthermore, the PL of CDs includes fluorescence and phosphorescence. In a comparison between fluorescence and phosphorescence, fluorescence is a fast process[105] while phosphorescent emissions remain longer and will not immediately cease after the removal of radiation sources.[106] After CDs absorb high-energy photons, electrons in CDs are excited from the ground state to an excited singlet state and then to a triplet state via an intersystem crossing. Then, radiative transitions of the electrons from the triplet state back to the ground state occur slowly and emit phosphorescence.[107] Recently, Lin's group successfully prepared CDs with an ultralong room-temperature phosphorescence (RTP) using 1,2-ethylenediamine and phosphoric acid as precursors, and the phosphorescence lasted for 10 s with a lifetime of 1.39 s.[108] Feng's group developed fluorine and nitrogen codoped CDs with a pH-responsive green RTP that originated from the energy difference between the singlet and triplet states during n−π* electron transitions in C—N/C═N bonds.[109] In order to obtain room-temperature-phosphorescent CDs, CDs can be doped with transition metals or embedded in certain matrixes to enhance the intersystem crossing process while producing more triplet excitons[107] and stabilizing the triplet excitations,[30] respectively. For instance, Lu's group applied layered double hydroxides embedding zinc as an inorganic matrix to optimize the intersystem crossing process to enhance the RTP of CDs.[110] As a room-temperature metal-free phosphorescent nanomaterial, phosphorescent CDs are environmentally friendly with a great application potential.[111]

A Promising Photocatalyst Material. Photocatalysis is an important topic in the photochemistry of CDs. CDs are promising photocatalyst materials considering their good light harvesting abilities, the aforementioned optical properties, and rich photoexcited excitons (electrons and holes) on the surface. However, in early studies, the photocatalytic capacity of CDs alone was negligible, though CDs were shown to enhance the photocatalytic performances of many well-established photocatalyst materials such as TiO_2, ZnS, and graphitic carbon nitride (g-C_3N_4).[112] To be a qualified photocatalyst, the material has to (1) meet the appropriate valence−conduction band gap for utilization of more sunlight, (2) have stability, and (3) have slow recombination of excitons.

It was not until 2019 that a significant turning point occurred when an aforementioned CD species was separated via SEC into three fractions with different particle sizes and the fraction with the smallest particle size displayed the best photocatalytic capacity among all the fractions.[54] The photocatalytic capacity was evaluated by measuring the pseudo-first-order reaction rate constants in a photocatalytic degradation experiment with dyes (rhodamine B and methylene blue) and a model environmental pollutant (*p*-nitrophenol) that were 1.3 × 10^{-2}, 3.6 × 10^{-2}, and 6.17 × 10^{-3} min^{-1}, respectively. Uses of sacrificial scavengers and argon protection demonstrated that they were mainly attributed to the oxidation by the holes and superoxide radical anions (Figure 4A). The best photocatalytic performance of the fraction with the smallest particle size was associated with the lowest valence−conduction band gap energy (2.04 eV) that resulted from the introduction of more energy levels by oxygen doping than the other two fractions. Thus, it was concluded that the photocatalytic effect of CDs was related to their particle sizes and structures. However, without knowing the energy levels of both the valence and conduction bands, although the fraction with the smallest particle size was observed to be capable of utilizing visible light in this photocatalytic degradation study, the viable portion in the full sunlight spectrum was unknown.

Subsequently, a recent study introduced a next-generation high-performance photocatalyst material that was a CD organogel (G-CD) with a narrow band gap energy of 2.94 eV.[33] It exhibited a photocatalytic capacity better than most known CD photocatalysts and comparable to that of the well-known nonmetal photocatalyst material, namely g-C_3N_4, as it was able to completely degrade all the model pollutants in short time scales (Figure 4B,C). Moreover, when an exfoliated g-C_3N_4 was incorporated into the G-CDs, it was found that the degradation rate constant was improved by 1.4 times, which was attributed to a synergy between g-C_3N_4 and the G-CDs. Nonetheless, without knowing the energy levels of both the valence and conduction bands of the G-CDs, the synergy mechanism was unknown. Radical trap experiments revealed that superoxide radical anions and holes were the dominant species generated in the presence of G-CDs, while in the presence of both g-C_3N_4 and G-CDs superoxide radical anions and hydroxyl radicals were the main reactive oxygen species (ROS) (Figure 4D,E). Additionally, the good photocatalytic stability and low cytotoxicity of G-CDs as well as of the composite of G-CDs and g-C_3N_4 were demonstrated by multiple cycles of degradation and a sea urchin *in vivo* model, respectively.

These two studies demonstrated that (1) particle size and structure play important roles in the photocatalytic performance of CDs; (2) the present development of CDs as photocatalyst materials is mainly limited by high valence—conduction band gap energy and a lack of accurate information on the valence band, conduction band, and band gap energy; (3) G-CD is an environmentally friendly, high-performance photocatalyst material comparable to g-C_3N_4; and (4) nonetheless, it was observed that the photocatalytic degradations of some model pollutants were slow. CDs should be applied to degrade microplastics and their monomers.

Photosynthesis Enhanced by Carbon Dots. In addition to photocatalysis, the light harvesting and conversion abilities enable CDs to be applied in agriculture to enhance the photosynthetic efficiency. As far as we are concerned, due to many limitations, plants usually exhibit photosynthetic capacities lower than the theoretical values.[75] Plant nanobionics have applied diverse NPs to living plants, which improved certain plant functions.[113,114] Also, the aforementioned Y-CDs were found to increase the photosynthetic efficiency of maize.[75] Y-CDs were applied to the plants foliarly or by adding to the growth solution, and it turned out that the photosynthetic parameters' values were generally higher with foliar treatments than with the growth solution treatments. Moreover, Y-CDs raised photosynthetic pigments while they reduced total phenolic content and total antioxidant activity, which depended on the manner of Y-CD application. As to the mechanism of how Y-CDs led to an enhanced photosynthesis, two hypotheses are given: (1) CDs increased CO_2 uptake due to viable interactions between the surface functional groups of CDs, especially amine and hydroxyl groups, and CO_2; (2) as mentioned previously, CDs in general possess good light harvesting abilities, so uses of CDs could capture more photons to be utilized by various photosynthetic activities. Nonetheless, the fluorescence emission spectra of Y-CDs showed an excitation-independent PL with maximum excitation and emission wavelengths at 400 and 562 nm, respectively. Considering the PL emission wavelength (562 nm) cannot be absorbed by pigments including chlorophyll *a*, chlorophyll *b*, and β-carotene, the light conversion ability of Y-CDs is less significant than the light harvesting ability for photosynthesis enhancement.

■ CARBON DOTS IN ELECTROCHEMISTRY

Electrochemical Properties of Carbon Dots. CDs possess many excellent electrochemical properties such as electrical conductivity, stability, structural defects, compatibility with different conductive materials, and tunability.[115,116] Also, CDs can provide excitons, namely electrons and holes. They can be precursors for the fabrication of conductive materials with unique properties and can be integrated into electrochemical devices.[117] Also, their surface functional groups can function as binding sites while being able to improve charge transfer.[116,118] Additionally, the electrochemical properties of CDs are closely associated with the structure. CDs with many defects tend to generate electron—hole asymmetry, affecting the local electronic state and leading to a high reactivity.[119] It was also reported that the defects of CDs can lower the potential barrier, offer ion channels enhancing the electrolyte diffusion, and increase the charge storage.[120] The surface functional groups of CDs can also boost their electrochemical performances by providing additional active sites for electrochemical reactions.[121] Furthermore, GQDs displayed high electrical conductivity owing to their π-conjugated structures, which is an essential characteristic of electrode materials.[122] Other structural features such as the surface functional groups, dopants, and interfaces can also greatly affect the electrical conductivity of CDs. Surface modifications have been widely applied to improve the electrochemical performances of CDs, and heteroatom doping is one of the most effective strategies.[123] The doped heteroatoms can affect the charge distribution and result in the change of local electronic structure, which improves the activity of the active sites.[123] Moreover, hybridization of CDs with other nanomaterials can lead to a synergistic effect to enhance the electrochemical performances of CDs. For example, N-doped GQDs hybridized with Cu nanorods showed a strong charge transfer with an enhanced catalytic performance due to the change of electron and charge states of the active sites.[119] Nonetheless, in order to apply CDs to the actual fabrication of solar cells or batteries, some major hurdles include the following: (1) many CDs do not possess crystalline structures; (2) many CDs cannot dissolve in chlorobenzene, which, however, is necessary for the assembly of solar cells.

Thermoelectric Properties of Carbon Dots. The TE effects indicate the phenomena by which either a temperature difference generates an electric potential or an electric current leads to a temperature difference. They can be specifically classified as the Seebeck effect (voltage generation from a temperature difference), the Peltier effect (heat transfer with an electric current), and the Thomson effect (reversible heating or cooling in a conductor in the presence of both an electric current and a temperature difference). Currently, the biggest challenge that limits the development and applications of TE materials is the low conversion efficiency (<10%).[43] To enhance the TE efficiency, the electrical conductivity and Seebeck coefficient of a TE material have to be enhanced while the thermal conductivity has to be reduced.[43] These properties are coupled to each other, but in nanoscale they can be decoupled by manipulation of matter at the atomic level.[43] Thus, nanoengineering is considered as a remedy for the low conversion efficiency of TE materials. Nonetheless, the current nanomanipulation techniques focus solely on thermal conductivity reduction by scattering heat carrying phonons with nanoscale artifacts.[43] Last but not least, given that most TE materials of interest are metal based such as bismuth telluride (Bi_2Te_3), they are cost-ineffective and may cause pollution. Thus, low-cost materials with good TE properties and biocompatibility are the most desirable.

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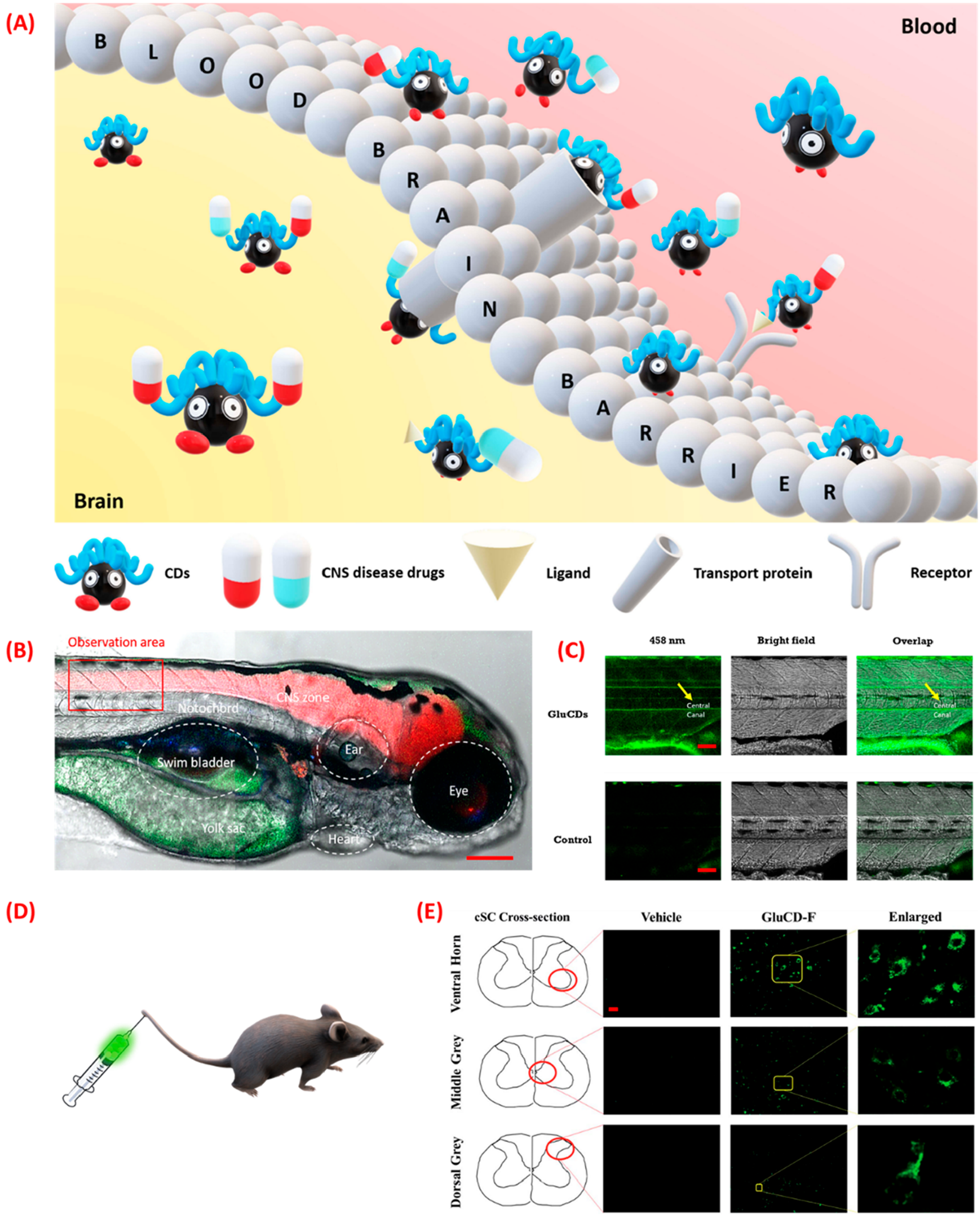

Figure 5. (A) Graphical representation of the BBB and drug delivery across the BBB with CDs as nanocarriers.[124] (B) Confocal image of a transgenic zebrafish showing the heart, CNS, and the observation area (central canal of spinal cord) after the intravascular injection of glucose-derived CDs conjugated to fluorescein (GluCD-F).[61] Scale bar: 142 μm. (C) Accumulation of GluCDs-F in the CNS of zebrafish.[126] The yellow arrows indicate the central canal of spinal cord. Scale bar: 61 μm. (D) Graphical illustration of a rat intravenous administration of GluCD-F. (E) GluCD-F was observed in different regions of rat CNS.[126] Images show GluCD-F localization in the ventral horn (top), middle gray matter (middle), and dorsal horn (bottom) of cervical spinal cord. The corresponding cervical spinal cord cross-section camera obscura schematics showing the area of the image taken are displayed in the left column. Scale bar: 50 mm. Reprinted with permission from ref 61. Copyright 2019 Elsevier. Reprinted with permission from ref 124. Copyright 2021 Dove Medical Press. Reprinted with permission from ref 126. Copyright 2021 Royal Society of Chemistry.

Our group was one of the first to investigate and report the TE properties of CDs. To be specific, the aforementioned G-CDs were observed to improve the TE properties of both Bi_2Te_3 and Cu_2Se TE systems.[43,44] In detail, it was observed

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that doping with 1% G-CDs exhibited a 6% higher TE efficiency than that of pure Bi_2Te_3 at room temperature. The enhancement mainly originated from a 16% enhancement in the Seebeck coefficient and a 57% decrease in thermal diffusivity. Unlike doping with larger-sized carbon black, a quantum enhancement effect observed in doping with nanoscale CDs significantly enhanced the Seebeck coefficient of Bi_2Te_3 while it decreased thermal diffusivity due to phonon scattering. Future work will be focused on determination of the figure of merit and characterizations of novel materials doped with different amounts of CDs. In addition, a hybrid system containing Cu_2Se and G-CDs showed a superior TE figure of merit compared to undoped Cu_2Se with the maximum figure of merit of 2.1 at 880 K at a CD dopant ratio of 2 wt %. To the best of our knowledge, this is the highest figure of merit at this temperature achieved for Cu_2Se and its composites in the literature. The structural analysis suggested a high level of purity that significantly contributed to the high figure of merit achieved. In addition, other factors that accounted for this achievement included the synergetic presence of quasi-spherical CD NPs, intensive grain boundaries, and a high density of sintered Cu_2Se matrix that amplified phonon scattering and electrical conductivity.

■ CARBON DOTS IN NANOMEDICINE

CDs are small, photoluminescent, biocompatible, and non-toxic, and they possess high surface-area-to-volume ratios and rich surface functional groups such as carboxyl, amine, and hydroxyl groups that are essential for surface modifications by drug compounds, proteins, and nucleic acids. Thus, CDs are often utilized as nanocarriers.[124] Significantly, targeted therapies with CDs as nanocarriers are promising. However, conjugation with targeting ligands such as antibodies may result in an increase of particle size and a steric effect that hinders drug loading, so CDs with intrinsic targeting capabilities are desirable.

Carbon Dots across the Blood−Brain Barrier. Due to the presence of the blood−brain barrier (BBB), brain is one of the most unreachable target locations. Owing to the protection mechanism of the BBB, most macromolecules, drugs, pathogens, and unwanted ions cannot reach the brain because of high molecular weights, hydrophilicity, large particle sizes, and high surface charges, respectively.[125] In order to effectively deliver drugs or genes for the treatments of various brain diseases and disorders, the drugs and genes are often linked to a carrier to promote the BBB penetration. Under such a circumstance, the BBB penetration abilities of different CDs are being evaluated in our group with *in vivo* models such as zebrafish and rats (Figure 5).[47,126] Between them, the zebrafish model was more often applied due to the following advantages: (1) It is more cost-effective to keep zebrafish than mouse colonies.[127] (2) Adult zebrafish breed approximately every 10 days to produce 50−300 fertilized eggs at a time, while mice generally produce about 50 pups in their whole lifetime.[128] Thus, zebrafish are more helpful in experimental replication. (3) Zebrafish embryos and larvae are transparent, which allows for real-time observations of fluorescently labeled activities inside zebrafish.[62,129] On the contrary, mouse embryos are not transparent and they naturally develop inside the mother, so currently, it is impossible to observe live embryo development or any fluorescently labeled activities in the body. Nonetheless, uses of zebrafish as an *in vivo* model have received many doubts and concerns, and a key question is whether the BBB of zebrafish is qualified to mimic human's. Although from the perspective of the BBB anatomy, the answer is positive, different results may be obtained between *in vivo* studies and clinical trials in human given the differences in the whole central nervous system between human and different animal models including zebrafish, rodents, and other mammalian species.

Carbon Dots Targeting Different Alzheimer's Disease Pathogeneses. Alzheimer's disease (AD) is an irreversible, progressive, and untreatable brain disorder.[128] Alzheimer's Association claims that it is the sixth leading cause of death in the United States. Each year, many promising drugs are developed but fail to cross the BBB. Eventually, they fail clinical trials despite a long wait for their research and development.[130] What is worse, many chemotherapies only target one or two mainstream pathogeneses such as acetylcholinesterase (AChE) activity (for example, donepezil, rivastigmine, and galantamine), β-amyloid (Aβ) deposit and aggregation (for example, aducanumab), abnormal hyper-phosphorylation and aggregation of microtubule-associated protein tau (MAPT), neurotoxic accumulations of the ROS, and genetic heritability. However, to the best of our knowledge, AD is multifactorial. Moreover, according to a recent study,[131] damages of the BBB precipitated dementia onset and some mainstream pathogeneses may be the effects instead of the causes of AD. Thus, in order to treat AD effectively, it is of great significance to discern the pathogeneses and develop innovative strategies to simultaneously target all of them. As a versatile nanomaterial, CDs are promising to help accomplish this task.

They are good nanodrugs for inhibiting the Aβ pathology given the fact that they are able to inhibit the production of amyloid precursor protein (APP), β-secretase activity, secretion, and aggregation of Aβ.[128,132] It is known that Aβ fibrils are formed with Aβ monomers generated via APP division by β and γ secretases and then form clumps depositing outside of neurons in dense formations as senile plaques.[133,134] Although the mechanism of how CDs inhibit APP generation is unclear, the Aβ fibrillation inhibition by CDs was partially discerned. To be specific, Aβ monomers can bind to CDs with either a hydrophilic or hydrophobic surface though they have more contact with a hydrophilic surface than with a hydrophobic surface. Most residues can interact with a hydrophilic surface through the backbone, whereas a few residues such as isoleucine, leucine, and phenylalanine have contact with a hydrophobic surface mainly through the side chains.[132] As a result, Aβ monomers form more extended structures on the hydrophilic surface while the structures on the hydrophobic surface are more compact. Additionally, the structural flexibility of Aβ monomers was also higher on the hydrophilic surface and previous experimental and computational studies[135,136] suggested that increased flexibility could inhibit fibril formation. Thus, the extended structure and flexibility of Aβ monomers induced by hydrophilic CDs are the possible mechanisms for Aβ fibrillation inhibition.

In addition, with the Aβ pathology becoming less convincing, tau pathology becomes the next therapeutic target. MAPT is a naturally disordered protein that contributes to the assembly and stability maintenance of microtubules. However, under abnormal conditions, MAPT will undergo misfolding and aggregation, and MAPT aggregates can further lead to the aggregation of normal soluble tau proteins in recipient cells, which results in the propagation of tau pathology in a prion-

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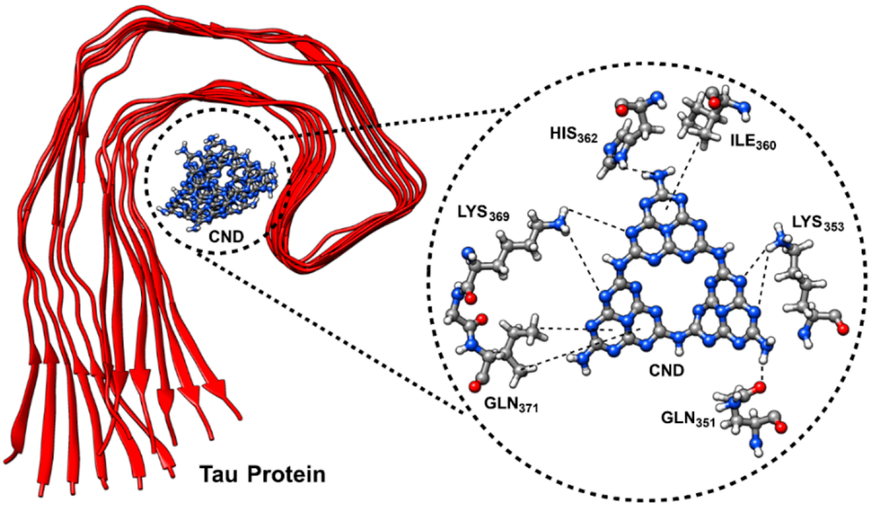

Figure 6. MD optimized structure of tau protein−CND complex,[14] with the nearest interacting residues shown on the right. Reprinted with permission from ref 14. Copyright 2022 Elsevier.

like manner.[137] Our group recently found the aforementioned CNDs could inhibit MAPT aggregation and ROS without causing any toxicity.[14] With CNDs fractionalized into five fractions, the MAPT aggregation inhibition was observed with relatively hydrophobic fractions. Molecular dynamics (MD) simulations then demonstrated that, inside the hydrophobic pocket of tau protein, each triple-heptazine sheet was able to interact with one peptide considering the same distance (3.5−4.5 Å) between each sheet and each peptide (Figure 6). For instance, the positively charged residues, Lys353 and Lys369, interacted with the nitrogen atoms in the heptazine rings via hydrogen bonds, which also applied to the neutral residues, Gln351 and His362, and the terminal amine groups on the sheet. On the other hand, the hydrophobic residues, Ile360 and Ile371, interacted with each sheet through weaker CH−π interactions. The computational study results matched our experimental observation that relatively hydrophobic CND fractions were more effective in tau aggregation inhibition than the relatively hydrophilic counterparts. Nonetheless, this study aroused two questions: (1) Why did CNDs before fractionalization show a higher inhibition effect? (2) Why did CNDs deactivate the ROS? For the first question, a synergistic effect was proposed. However, to answer the second question, we may acquire some hints from a photocatalysis study of CNDs.

Furthermore, CDs can be also applied as drug nanocarriers considering all the aforementioned properties and abilities to penetrate the BBB, cells, and nuclei without damaging their integrities. Also, gene delivery using CDs as nonviral vectors began recently. Based on reviews of twin and family studies, the AD genetic heritability ranges from 49 to 79%.[138] The best known genetic risk factor is the $\varepsilon 4$ allele of apolipoprotein E (APOE).[139,140] Of people with AD, 40−80% possess at least one APOEε4 allele.[140] Thus, one may wonder if CDs could carry a APOEε4 allele inhibitor (a drug or siRNA) to silence or modify the expression of APOEε4 allele.

Considering all the aforementioned inhibition effects of CDs on different mainstream AD pathogeneses, CDs, especially amphiphilic CDs, are very promising in the treatment of AD. Compared to the regular drug development process that usually requires years of endeavors, once CDs prove to be effective on all the mainstream pathogeneses, their development and applications will significantly compensate for the wait.

Magnetic Resonance Imaging with Carbon Dot Based Contrast Agents. Magnetic resonance imaging (MRI) is a nonintrusive medical imaging technique which applies strong magnetic fields and radio waves to the atomic nuclei in the body that absorb radio frequency energy resulting in spin polarization and inducing radio frequency signals.[141] Contrast agents are substances that can improve the signals of MRI by shortening the longitudinal (T_1) and transverse (T_2) relaxation times.[142] Two major types of contrast agents include paramagnetic lanthanide ion complexes and transition metal manganese that can shorten T_1 and the superparamagnetic materials that are able to shorten T_2 by reducing the signals from the negative contrast agents.[143] Paramagnetic ion complexes incorporating CDs have been reported as good nanoscale contrast agents for MRI. They enhanced T_1 contrast, and their hybridization with iron oxide NPs improved T_2 contrast.[144−146] Yi's group reported that gadolinium (Gd)-doped CDs prepared through a one-pot pyrolysis process showed a high MRI response with a shortened longitudinal relaxation rate.[147] Atomic Gd is toxic but is more tolerated in MRI due to the surrounding chemical clathrate.[148] Nonetheless, Gd-based MRI contrast agents have many side effects on cardiovascular, gastrointestinal, nervous, and respiratory systems; skin; and special senses; and the effects of Gd deposition in the brain are still unknown.[148] Gu's group prepared a type of green-emitting manganese-doped CDs for multimodal fluorescence/MR imaging of brain glioma.[149] Zhou's group hybridized magnetic Fe_3O_4 NPs with CDs via a one-pot solvothermal method.[150] The hybrid showed an excellent magnetic response from Fe_3O_4 NPs and also exhibited the PL of the CDs. The hybrid system was further loaded with doxorubicin and studied for fluorescence/MR imaging and photothermal therapy/chemotherapy. Above all, considering the potential leak of heavy metals in the hybrid systems, it is always a must to systematically investigate the side effects of novel MRI contrast agents.

Bone-Specific Targeting. Except for brain targeting, an aforementioned CD species, B-CDs, was observed to

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specifically target bones.[151] In order to deeply investigate this bone-specific targeting ability, B-CD was compared with two more CD species and its surface modified counterparts using a zebrafish model.[152] After they were independently administered in zebrafish larvae, it turned out that the surface modified B-CDs could still target bones and fluoresced. In contrast, the CDs prepared by other approaches could not achieve the same effect. Two hypotheses were proposed: (1) B-CD's fluorescence was enhanced by the bone microenvironment consisting of large amounts of calcium in the form of hydroxyapatite[153] that might interact with the negatively charged B-CDs. (2) During the embryogenesis, cartilage mineralization gives rise to most of the vertebrate bones,[154] and cartilage contains large amounts of chondroitin sulfate that could potentially trap the B-CDs as the tissues mineralize. However, this bone-binding-induced fluorescence eventually proved not to be stimulated by calcium, hydroxyapatite, or chondroitin sulfate. While the mechanism of B-CDs binding to bones remains unknown, it is clear that this bone-specific targeting ability will not be affected by chemical modifications, which has been confirmed by a study on direct conjugations between the B-CDs and the aforementioned G-CDs. This study suggested that conjugates of B-CDs and G-CDs inherited unique properties from both predecessors, and the retention of the bone-specific targeting ability is important for developing the B-CDs as a bone-specific drug delivery platform that can potentially benefit the treatment of skeletal diseases such as osteoporosis and help alleviate the severe side effects of most of the current pharmaceutical agents. This prospect became more feasible following a continued study[48] where the B-CDs were observed to bind to the areas where adult bones grew, which did not interfere with the biological processes of homeostatic turnover, repair, and regeneration. This study further demonstrated the feasibility to apply the B-CDs as theragnostic agents for skeletal diseases. In particular, current osteoporosis treatments heavily rely on early diagnosis to mitigate further bone erosion, but limited treatments are available to restore the lost bone mass.

Combating Viral Diseases with Carbon Dots. The life cycle of a virus in the host body can be generally divided into three stages: (1) target cell entry, (2) viral replication and assembly, and (3) release.[155] Viral entry starts from the virus attachment to the host cells.[156] Then, viruses can inject their genetic materials into the host cells, or the viruses can penetrate host cell membranes via endocytosis.[157] Given that viral replication can only take place inside the host cells, inhibition of viral entry is an effective strategy to prevent viral infection. Some CDs have been demonstrated to inhibit the viral entry, which was associated with surface chemical composition, structure, size, and shape.[158] For instance, Fahmi et al. reported that CDs derived from citric acid and modified by boronic acid can act as a viral entry inhibitor to prevent the HIV infection.[159] Since boronic acid was found to act on glycopeptides and glycoproteins to interact with HIV,[159] the boronic acid modified CDs were observed to bind gp120, a type of glycoprotein expressed on the HIV envelope and responsible for virus attachment to the host cells, via hydrogen and covalent bonding,[160] which hindered the interaction between HIV and T cells. In addition, due to the binding of CDs to viruses, benzoxazine-derived CDs were lately reported as a broad-spectrum antiviral agent to block the viral entry against a few life-threatening viruses including the Japanese encephalitis, Zika, and dengue viruses; adenoviruses; and porcine parvovirus.[161] CDs can also bind cell membranes to block the viral entry. Barras et al. reported that boronic acid modified CDs were demonstrated against the infection of herpes simplex virus type 1 by interacting with the host cell membranes with a higher antiviral capacity than that of many other NP-based inhibitors.[162] CDs can be also combined with antiviral drugs. Aung et al. synthesized CDs with boronic acid and graphene-like structures that showed a superior performance in the inhibition of HIV's cell entry, which was enhanced by combining them with durival, a multicomponent drug used to interfere with the function of reverse transcriptase.[160]

Once the viral genomes enter the host cells, viral genome's reverse transcription, DNA replication, gene transcription, and mRNA translation commence one another. During this process, a number of viruses are assembled. In addition to interfering with viral entry, CDs are also able to inhibit viral replication and assembly. For example, lately, some antiviral compounds were used as precursors to synthesize CDs. Tong et al. applied glycyrrhizic acid, a traditional Chinese herbal medicine with antiviral activities, as the precursor to synthesize CDs (Gly-CQDs) that inhibited the viral proliferation by approximately 5 orders of magnitude.[163] On the basis of both TEM and FTIR results, the Gly-CQDs were found to inherit most of the functional groups from glycyrrhizic acid and have a large surface area that facilitated their binding with viruses. Lin et al. reported a type of curcumin-derived CQDs (Cur-CQDs) against enterovirus.[164] Some curcumin molecules were preserved on the surface of Cur-CQDs. Compared with curcumin, Cur-CQDs displayed a lower cytotoxicity and an enhanced antiviral activity. All the infected mice without Cur-CQD treatment died within 12 days. In contrast, over 95% of infected mice with Cur-CQD treatment survived for over 1 month. The immunological analysis demonstrated that Cur-CQDs inhibited viral infection by interfering with both viral entry and replication. The superior antiviral activity of Cur-CQDs over curcumin might be due to the change of chemical structure and the increase of active groups such as guaiacol, anisole, and 1-hexatrienium on the surface of Cur-CQDs together with good hydrophilicity and high density of antivirally active moieties.

CDs have also shown a great capacity to combat COVID-19. In a recent study, Alizadeh and Khodavandi claimed that there is a positive relationship between the efficacy of nanomaterials and coronaviruses, and the particle size of nanomaterials had little effect on the antiviral capacity while the shape had a great impact on it.[165] Specifically speaking, spherical NPs showed an antiviral capacity about 39% higher than other morphologies in the studies of the Middle East respiratory syndrome related coronavirus (MERS-CoV). Owing to a spherical shape, CDs are expected to exhibit positive effects against coronaviruses. Additionally, Łoczechin et al. reported CDs prepared with citric acid and 1,2-ethylenediamine led to the inactivation of human coronavirus 229E with an estimated EC50 of $52 \pm 8\ \mu g\ mL^{-1}$ after being coupled with different boronic acid containing compounds.[166] On the contrary, addition of mannose resulted in a loss of inhibition. These could be ascribed to the boronic acid on the CDs that can interact with glycan units on the surface of viruses and form tetravalent complexes, leading to the inactivation of viruses. Furthermore, CD-based vaccine delivery platform and adjuvant strategies have gained much attention. Li et al. developed a CD-based intranasal vaccine delivery platform to induce a specific immune response.[167] The CDs were synthesized from chitosan

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and branched polyethylenimine and attached by negatively charged antigen via an electrostatic interaction. The internalization of antigen/CDs composite by dendritic cells was observed under a confocal laser scanning microscope, while in the control group where CDs were not present no antigen was internalized at 2 and 6 h. Moreover, CD-based vaccine formulations were observed to be retained at the mucosal sites for a long time with a stronger antigen transportation. Compared with antigen alone, mice that were vaccinated with antigen/CDs composite showed antigen-specific immune responses and induced more memory T cells. Such a high immune boosting ability might be due to the permeation enhancement effect that promoted the antigen transport. Above all, the research on antiviral CDs is still in its infancy, and their antiviral activities at multiple points in the life cycle of the virus remain to be explored.

Gene Therapy with Carbon Dots as Nonviral Vectors. Extensive literature studies demonstrate that the CDs applied to gene delivery normally contain abundant amine groups resulting in CDs with positive surface charges, which promotes their binding to negatively charged nucleic acids by electrostatic interactions.[168] To prepare positively charged CDs, polyethylenimine (PEI), polyethylene glycol (PEG), polyethylene diamine (PAMAM), chitosan, and poly-L-lysine are frequently used as precursors or grafted on the surface of CDs.[169] Among them, PEI as a commercial transfection reagent is popular in the development of cationic CDs and gene delivery applications. For instance, Li et al. synthesized a type of orange-emission CDs using 1,2,4-triaminobenzene and PEI as precursors.[170] It was found that an siRNA that targeted hepatoma-derived growth factor (HDGF) could be adsorbed and delivered by such CDs, silencing HDGF expression of glioblastoma cells at a CD concentration of 250 μg/mL. In addition, Yang et al. prepared positively charged CDs from folic acid and PEI to achieve targeted delivery of genes to cancer cells.[171] In their study, the transfection of plasmid DNA showed that these CDs displayed 24.53% positive EGFP (green fluorescent protein) cells in 293T cells and 42.63% positive EGFP cells in HeLa cells. Although these types of CDs had abilities to deliver genes into cells, higher transfection efficiency was expected. Therefore, Hashemzadeh et al. investigated the transfection efficiency of arginine-conjugated PEI-based CDs (CD-$PEI_{1.8K}$-Arg) and observed that the transfection of CD-$PEI_{1.8K}$-Arg was around 60% when the mass ratio of CD-$PEI_{1.8K}$-Arg to plasmid was 160:1.[172] However, this transfection efficiency was still lower than that of PEI at the same mass ratio. Fluorine doping is a strategy to improve the transfection capacity of CDs, which has been confirmed by Yu, Dong, and co-workers.[173,174] Zuo et al. reported that tetrafluoroterephthalic acid derived PEI-CDs exhibited a higher transfection capacity than PEI.[174] Nonetheless, together with a good transfection efficiency, PEI also has high cytotoxicity that is disadvantageous for gene delivery and the formation of CDs from PEI barely reduces the toxicity of PEI while the development of CDs with low toxicity is of great significance. However, studies that address both cytotoxicity and transfection ability of CDs are limited. Moreover, currently, nucleic acid loading on CDs is mostly via electrostatic force that is not as stable as covalent bonds. Thus, for a stable loading, more attention should be given to other loading approaches such as phosphoramidation reactions, which will largely expand the applicable CD species.

CARBON DOTS IN SURFACE CHEMISTRY: LANGMUIR MONOLAYER OF CARBON DOTS

The Langmuir monolayer is an important constituent of surface chemistry. Its use first discerned lipid bilayers of the cell membrane.[175] Subsequently, the Langmuir monolayer was widely used to measure molecular dimensions.[175] Most importantly, it can mimic the cell membrane for studies on the impacts of diverse proteins, pharmaceuticals, and toxins.[175,176] Nonetheless, in order to form a Langmuir monolayer, molecules have to be insoluble in water, which largely limits its applicability with a number of hydrophilic molecules and NPs including most CDs. Thus, to date, few studies have been successfully conducted and reported on the Langmuir monolayer of CDs. Among the few present studies, our group first reported the formation of stable Langmuir monolayers with characteristic phase changes with amphiphilic CDs derived from different saccharides including lactose, glucose, and galactose, which was confirmed by surface pressure−area, surface potential isotherms, and compression−decompression studies.[52] Most interestingly, different from the lactose-derived CD (LacCD) aqueous dispersion, the LacCD monolayer exhibited an excitation-independent PL that was likely to be caused by a uniform orientation of LacCD NPs in a rigid, close-packed Langmuir monolayer. The uniform orientation of LacCD NPs in a Langmuir monolayer occurred simultaneously with the hydrophilic and hydrophobic surface functional groups oriented toward water and air, respectively, at the air−subphase interface. Also, once the conformation of surface functional groups was changed and the LacCD NPs were closely packed, they could generate new electronic states between the ground and excited states similarly to the aggregation-induced emission,[177] which was supported by a red shift in the maximum excitation and emission wavelengths of the LacCD monolayer in comparison to the LacCD aqueous dispersion. In addition, although it was not discussed, CD fractionalization was another plausible mechanism. It was likely that the amphiphilic CD fractions with a unique PL behavior formed a Langmuir monolayer while the hydrophilic CD fractions were dissolved in water. Above all, this study revealed many different physicochemical properties between the solution/dispersion and the Langmuir monolayer of CDs. However, to discern the mechanism that leads to the differences, further studies are required.

CONCLUSION

Since the discovery of CDs, much attention has been given to their versatile syntheses and applications due to many excellent properties. In contrast, many conclusions on the structure, property mechanisms, and various structure−property−activity relationships remain hypothetical. In this Perspective, we provide updated progress on and personal perspectives of these issues mostly based on our research outcomes in combination with a few literature studies. Most interestingly, a variety of structure−property−activity relationships are often attained via CD fractionalization and CD fractionalization indicates that CDs are heterogeneous in one pot. In turn, a good understanding of these relationships can help control the development of diverse large zero-, one-, two-, and three-dimensional carbon-based materials with desired properties with CDs as building blocks. In addition, three CD models were designed based on extensive structural characterizations, which demonstrates that CDs prepared by different approaches

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are unique. Furthermore, a few well-studied properties and applications including CDs in PL, photocatalysis, photosynthesis, electrochemical properties, BBB penetration, AD, MRI, antiviral activities, and gene delivery are summarized. Our perspectives on the PL mechanism, future photocatalytic activities, photosynthesis enhancement mechanism, structure–property relationships in electrochemical properties of CDs, doubt of appropriateness of the BBB model, AD pathogeneses and a lack of comprehensive *in vivo* models, MRI contrast agent leak, infancy of CDs in antiviral studies, and limitations in CDs as nonviral vectors for gene delivery are presented in hopes of improving the current accomplishments. Moreover, some novel properties and applications such as TE properties, bone-specific targeting, and Langmuir monolayers are mostly observed in the CDs developed by our group, which suggests their uniqueness but also opens up new horizons of research.

Our future outlooks include the development of CDs with red/NIR-emitting PL, chirality, controlled synthesis, clear structure, energy levels, and metabolisms *in vitro* and *in vivo*. In particular, regarding the metabolism study of CDs *in vitro* and *in vivo*, it is essential to study their interactions with various enzymes and our genetic materials, which are largely lacking compared to the other aforementioned studies though CDs have been applied as nonviral vectors for gene delivery. The essence can be ascribed to the following facts. First of all, owing to the PL and high fluorescence QYs, CDs were observed to localize in cell nuclei and mitochondria,[45,178] where our genetic materials exist. In addition, CDs possess small particle sizes that are comparable to that of a nucleotide unit (0.33 nm),[179] abundant surface functional groups that offer the possibilities to interact with enzymes/nucleic acids by hydrogen bonds, and surface charges, especially positive charges, that benefit the nucleic acid adsorption to CDs via electrostatic interactions. Furthermore, considering the widespread presence of CDs in nature, studies of the interactions between CDs and our genetic materials can significantly promote our understanding of how the surroundings influence biological development and evolution. In the end, from our perspective, observations of how CDs affect living organisms including toxicity and behavior are encouraging but a deep investigation into the interactions between CDs and enzymes/nucleic acids will shed light on the mechanisms behind them, which indicates another important yet less studied research path to pursue in the long run.

■ AUTHOR INFORMATION

Corresponding Author

Roger M. Leblanc − *Department of Chemistry, University of Miami, Coral Gables, Florida 33146, United States;* orcid.org/0000-0001-8836-8042; Phone: (305) 284-2194; Email: rml@miami.edu

Authors

Yiqun Zhou − *Department of Chemistry, University of Miami, Coral Gables, Florida 33146, United States; C-Dots LLC, Miami, Florida 33136, United States; Department of Biological Sciences, Florida International University, Miami, Florida 33199, United States;* orcid.org/0000-0002-6594-9925

Wei Zhang − *Department of Chemistry, University of Miami, Coral Gables, Florida 33146, United States*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.jpcb.2c06856

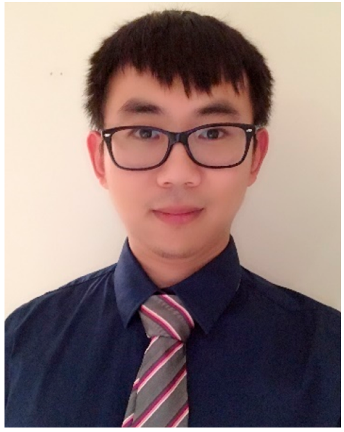
Author Contributions

[‖]Y.Z. and W.Z.: These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

Biographies



Yiqun Zhou is the R&D Director of C-Dots, LLC. He received his B.S. (2014) in chemistry from Shaanxi University of Science and Technology, and he completed his Ph.D. in chemistry in Prof. Leblanc's group at the University of Miami in the spring semester of 2019. Then, he became a postdoctoral associate in Prof. Leblanc's group at the University of Miami. During his Ph.D. and postdoctoral periods, he focused on the development of carbon dots including their diverse preparations, separation, characterizations, and applications. His current research interests include nanomaterials, 3D printing, photocatalysis, photosynthesis, thermoelectricity, nanofuels, bioimaging, immunotherapy, gene therapy, PCR, chemotherapy, and targeted drug delivery for the treatment of Alzheimer's disease, glioblastoma, neuroblastoma, and bone diseases involving the design of innovative nanosystems, advanced characterization techniques, multiple *in vitro* and *in vivo* models (zebrafish and mice), and complex data analyses.

Wei Zhang is a Ph.D. student in Prof. Leblanc's group at the University of Miami. She received her B.Eng. and M.Eng. in chemical engineering technology at Liaocheng University and Dalian Polytechnic University, respectively. She started her Ph.D. program at the University of Miami in August 2019. Her research started in May 2020 on the preparation, purification, and characterization of carbon dots. Her applications of carbon dots are oriented toward the treatment of Alzheimer's disease by inhibiting tau pathogenesis.

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Roger M. Leblanc received his B.S. in chemistry in 1964 from Universite Laval, Canada, and his Ph.D. in physical chemistry in 1968 from the same university. From 1968 to 1970, he was a postdoctoral fellow in the laboratory of Prof. George Porter, FRS, in the Davy Faraday Research Laboratory at the Royal Institution of Great Britain. He was a professor from 1970 to 1993 in the Department of Chemistry and Biology at Universite du Quebec a Trois Rivieres, Canada. During this period, he was chair from 1971 to 1975 in the same department and director from 1981 to 1991 at the Photobiophysics Research Centre. In 1994, he moved to the University of Miami, where he has been a professor in the Department of Chemistry up to the present time. At the University of Miami, he was chair of the Department of Chemistry from 1994 to 2002 and he was appointed as chair from 2013 to 2021. He was also one of the three editors of *Colloids and Surfaces B: Biointerfaces* from 1998 to 2013. During his early career as a scientist, his research interest was photosynthesis and photoconductivity using surface chemistry and spectroscopy. His current research interests include the following: (1) applying surface chemistry combined with spectroscopy and microscopy to investigate properties of nanomaterials (mainly carbon dots); (2) fibrillation processes of amyloidogenic proteins (β-amyloid, tau); (3) targeted drug delivery; (4) designing and developing biosensors with high sensitivity and selectivity for disease diagnoses. He has published more than 550 scientific articles in peer-reviewed journals. As a professor, he has supervised more than 100 M.S. and Ph.D. students.

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