

**Abstract:** Carbon-based and carbonaceous nanocolloids attracted significant attention of researchers during the last decade because of their outstanding properties, including green and facile synthesis methods, water solubility, tunable photoluminescence, easy surface modification, and high biocompatibility. Among the latest development in carbon-based nanostructures are chiral nanocarbons exemplified by particles commonly referred to as the chiral carbon dots (CDots). They are known for potential applications in sensing, catalysis, imaging, and nanomedicine. However, the current methods of CDots synthesis show a wide range of often contradictory chemical/optical properties and structural information, that required a dedicated systematic study and careful mechanistic evaluation. Here, we investigate and optimize chiroptical activity and photoluminescence of *L*- and *D*-

CDots obtained by hydrothermal treatment of *L*- and *D*-cysteine, respectively. Nuclear magnetic resonance (NMR) spectroscopy demonstrates that they are formed via gradual condensation reactions of the starting amino acid leading to particles with a wide spectrum of functional groups including aromatic cycles. We found that the chiroptical activity of CDots has an inverse correlation with the synthesis duration and temperature, while the photoluminescence intensity has a direct one, which is associated with increase of degree of carbonization. Also, our studies show that the hydrothermal synthesis of cysteine in the presence of boric acid leads to the formation of CDots rather than boron nitride nanoparticles as was previously proposed in several reports. These results can be used to design chiral carbon-based nanoparticles with optimal chemical, chiroptical, and photoluminescent

## Optimization of Hydrothermal Synthesis of Chiral Carbon Dots

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### Introduction

Chiral inorganic nanostructures have stronger chiroptical activity compared to that of similarly sized organic objects because of their high electrical polarizability and magnetic susceptibility.<sup>1,2</sup> Exceptional optical, chemical, and physical properties of chiral nanostructures coupled with their protein-mimetic biological activity,<sup>1</sup> allow exploration of multiple fundamental questions such as the origin of homochirality on Earth and multiscale chirality transfer.<sup>2</sup> Chiral nanomaterials are also promising for chiral sensing, separation, bioimaging, enantioselective recognition, and chiral catalysis.<sup>1,3,4</sup> Among all chiral inorganic nanostructures, those based on noble metals (e.g., gold, silver) and II-VI semiconductors (e.g., CdTe, CdSe) nanoparticles (NPs) are the most studied ones.<sup>5</sup> However, their use for biomedical needs is limited by their high cost and toxicity. Carbon-based nanomaterials with mirror asymmetry, including carbon nanotubes,<sup>6</sup> graphene,<sup>7</sup> and nanodiamonds<sup>8</sup> can potentially address these problems. Among them are carbonaceous chiral particles often referred to as carbon dots (CDots) that have gained

significant attention during the last decade because they offer a hard-to-find combination of multiple properties: biocompatibility, biodegradability, low toxicity, high colloidal stability, high photostability, bright photoluminescence, spectral tunability, and facile chemical functionalization.<sup>9</sup> While their chemical structure contains a lot of unknowns exemplified by the uncertainty about the chemical nature and scale of chiral geometries they possess, these properties allowed CDots to be used in sensors, bioimaging, drug delivery, catalysis, photovoltaics, and optoelectronics.<sup>10-14</sup>

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The extensive studies of nanocarbons for biomedical applications stimulated early works on their chirality.<sup>15</sup> For example, covalent attachment of *L*- or *D*-Cys moieties to the edges of graphene NPs leads to their helical buckling due to chiral interactions at the "crowded" edges.<sup>7</sup> Exposure of human liver hepatocellular carcinoma cells (HepG2) to *L*-/*D*-Cys-stabilized graphene NPs reveals their general biocompatibility and a noticeable difference in the toxicity of the stereoisomers. Molecular dynamics simulations demonstrated that *D*-Cys-stabilized graphene NPs have a stronger tendency to accumulate within the cellular membrane than *L*-Cys-stabilized graphene NPs. It was also found that CDots prepared from *D*-enantiomers of Cys and citric acid facilitate the growth and photosynthesis of plants more than those from *L*-enantiomers.<sup>16</sup> Also, human bladder cancer cells treated with *L*-Cys-derived CDots showed up-regulated glycolysis, while *D*-Cys-derived CDots had no similar effect.<sup>17</sup> *L*-lysine-based CDots dramatically remodeled amyloid beta-42 (A $\beta$ 42) secondary structure and fibril morphologies, as well as inhibited A $\beta$ 42 cytotoxicity.<sup>18</sup> CDots based on *L*- or *D*-glutamic acid reduced the production of blood glucose with *D*-CDots having a higher inhibitory efficiency than *L*-CDots.<sup>19</sup> Cys-based CDots can also act as chiral templates to induce porphyrins to form chiral supramolecular assemblies.<sup>20</sup> However, chirality of nanoscale carbons remains underutilized, poorly understood, and hardly optimized, especially in conjunction with other properties, such as fluorescence, despite both of them being central for biomedical applications. The implicit assumption is that these two properties can be independently maximized, which is not necessarily true. Eco-friendly and low-cost hydrothermal synthesis is the most widely used method for the preparation of CDots.<sup>15</sup> It also allows one to utilize a broad pool of starting materials (e.g., saccharides, amines, organic acids, and their derivatives, etc.).<sup>14,21,22</sup> Chiral organic precursors are typically dissolved in a solvent and then heated in a Teflon-lined autoclave above the carbonization threshold. There are several separate reports on the influence of hydrothermal synthesis conditions (e.g., temperature, synthesis duration, polarity of the solvent) on chiroptical and photoluminescent properties of CDots.<sup>17,23–25</sup> However, to the best of our knowledge, there are no studies on the correlation between these optical properties and their dependencies on synthesis duration and temperature. These studies are required to develop CDots with optimal chiroptical and photoluminescence resonances. The doping of CDots has been proven to increase their PL QY, which could be used to attain the combination of chirality and high PL simultaneously. The addition of boron (an electron acceptor) or nitrogen (an electron donor) into the chemical structure of nanocarbons could be accomplished by adding boric acid and nitrogen-containing organic molecules to the reaction mixture for hydrothermal reaction.<sup>26,27</sup> Nitrogen and boron-doped CDots were reported for the hydrothermal process in the presence of citric acid, borax, and *p*-phenylenediamine,<sup>28</sup> which appeared to us quite an unusual finding considering low temperature of the synthesis. Hydrothermal method was also used for the fabrication of boron-doped CDots using ascorbic acid and boric acid as the precursors.<sup>29</sup> Boron-doped CDots were reported to have strong fluorescence in the blue region upon UV excitation and an increase in the non-linear optical properties when compared to undoped CDots.<sup>26</sup> However, some studies reported that there is no significant boron-doping observed in the CDots even after over 6 h in the reaction chamber, because the reaction conditions did not provide enough energy to incorporate the boron into the molecular structure of CDots.<sup>30</sup> Furthermore, several studies claimed the formation of boron nitride NPs in a hydrothermal

reaction using amino acid as a nitrogen source.<sup>31,32</sup> Interestingly, the color of the produced dispersions and their optical properties were similar to those characterized as CDots and made from different amino acid hydrothermal reactions. These discrepancies between prior reports for chiral and other CDots make it essential to understand the chemistry of the products, especially for biomedical applications.

Here, we report the effect of hydrothermal synthesis duration and temperature on both chiroptical and photoluminescent properties of CDots derived from *L*- and *D*-Cys that will be abbreviated as *L*- and *D*-CDots, respectively. We demonstrate that the NPs produced in the hydrothermal synthesis at 150°C have complex chemical structure due to the gradual dehydrogenation reactions leading to the formation of multiple functional groups. The degree of carbonization and content of aromatic groups increases with duration of the synthesis. The change in chemical structure leads to a decrease in chiroptical activity of CDots and an increase in their photoluminescence quantum yield (PL QY). The same trend occurs when the synthesis temperature increases for a fixed duration of the synthesis (4 h). We also demonstrated that the same reaction in the presence of boric acid (BA) leads to the formation of NPs whose properties are very similar to CDots rather than boron nitride NPs, as several published papers report.<sup>31,32</sup>

## Materials and Methods

### Materials

*L*-cysteine (*L*-Cys), *D*-cysteine (*D*-Cys), boric acid (BA), NaOH, and Rhodamine 6G were purchased from Sigma-Aldrich. All the chemicals were analytical grade and used without further treatment. The 0.22- $\mu$ m filter membranes were purchased from Sigma-Aldrich. Dialysis membranes with molecular weight cut-off 1 kDa were obtained from Fisher Scientific. All solutions were prepared using ultrapure water (18.2 M $\Omega$ -cm) from a Milli-Q automatic ultrapure water system.

### Hydrothermal synthesis of *L*- and *D*-Cys CDots

*L*-/*D*-Cys-derived CDots were synthesized by a one-step hydrothermal method. Briefly, 0.1 g of *L*- or *D*-Cys was sufficiently dissolved in 10 mL of water. Then, this solution was transferred to a 50 mL Teflon-sealed autoclave and heated at (i) 100/150/200/250°C for 4 h and (ii) 150°C for 1–20 h. If needed, the pH of the resulting solutions was adjusted to 7 using 0.1 M NaOH. Then, solutions were purified by passing through a 0.22- $\mu$ m filter membrane (see Supporting Information, Figure S1) and dialysing against deionized water in a 1 kDa dialysis bag for 24 h. The pH of the NP dispersion after dialysis was found to be neutral, or the same pH as Millipore water, which means that unreacted cysteine and ultra-small molecular aggregates were removed. Also, all the samples were of 10 mL of volume, while the dialysis tank was 500 mL, which was also stirred to make the system homogenous. Thus, decreasing the concentration of solutes in about 50 times ensures better purification. As a result of hydrothermal synthesis and a further two-step purification procedure, ~ 10 mg of product was produced per 10 mL of purified solution.

### Hydrothermal synthesis of cysteine in the presence of boric acid

The protocol is similar to that described above (Hydrothermal synthesis of *L*- and *D*-Cys CDots) except for the addition of 0.67 g of boric acid to the cysteine aqueous solution. The resultant mixture of cysteine (0.1 g) and boric acid (0.67 g) was carefully mixed and put into a 50 mL Teflon-sealed autoclave. The rest of the procedure is identical to the described above.

### Characterization

UV-Vis absorption and photoluminescent (PL) spectroscopy were carried out using a Cary 8454 UV-Vis spectrophotometer and FluoroMax-3 fluorescence spectrophotometer (Horiba), respectively. Photoluminescent quantum yields were measured using the comparison approach using Rhodamine 6G in ethanol (PL QY = 95%) as a standard. Transmission Electron Microscopy (TEM) was performed using a JEOL 3100R05 electron microscope operating at a beam voltage of 300 kV. X-ray photoelectron spectroscopy was performed using a Kratos Axis Ultra XPS. Fourier-transform infrared spectroscopy was carried out using JASCO (FT/IR-4100) Fourier-transform infrared spectrometer. Nuclear magnetic resonance spectroscopy was performed using Bruker Advance Neo 500 spectrometer. Circular dichroism (CD) spectroscopy was carried out using a J-815 CD spectrometer (JASCO, Japan) operating under a N<sub>2</sub> flow of 5-8 L/min. Typical scanning parameters were as follows: scanning speed 100 nm/min; data pitch 1 nm; bandwidth 1 nm, digital integration time, 2 s; one accumulation. The anisotropy factor (*g*-factor) was calculated according to the equation  $g = CD/(32,980 \cdot Abs)$ , where CD is the signal obtained from CD/DC channel (in mdeg) and Abs is the total absorbance. CD spectra were stopped at wavelengths where the HT voltage exceeded 400 V to avoid artifacts during acquisition.

### Results and Discussion

Hydrothermal carbonization of *L*- or *D*-Cys was carried out under different temperatures and reaction times (Figure 1). At all other conditions being equal, the resulting *L*-CDots and *D*-CDots were very similar in structure and optical properties. Therefore, this manuscript focuses mainly on the *L*-CDots while additional details about *D*-CDots are provided in Supporting Information.

The purification of as-synthesized samples is a vital step in the preparation of high-quality CDots because the excess of unreacted cysteine and small molecular species produced as byproducts could be responsible for the observed chemical and optical properties attributed to CDots. For example, recent <sup>1</sup>H nuclear magnetic resonance (<sup>1</sup>H-NMR) spectroscopy studies on CDots made from tryptophan and other precursors showed that fluorescent aromatic molecules are indeed forming.<sup>33</sup> We extensively dialysed our samples and tested dialysis bags with different pores sizes (1 kDa and 3.5 kDa). When the reaction was less than 4 h, as-synthesized samples had CD spectra similar to untreated cysteine with some shifts. After dialysis in a 3.5 kDa bag, these samples became chiroptically silent since they passed through the membrane and were found in the dialysis tank (Figure S2a). However, samples synthesized for over 4 h remained their CD signal both after 1 kDa and 3.5 kDa bags (Figure S2b and Figure S2c). Given the fact that all the small soluble molecules were removed by dialysis, the CD spectra observed for products of the reactions lasting over 4 h originate

from the particles (a detailed discussion on the chiroptical activity of CDots is provided below).

<sup>1</sup>H NMR spectra of purified CDot samples were collected for different durations of the hydrothermal reaction at 150°C. As the duration of synthesis increases from 2 h to 4 h and 20 h, the <sup>1</sup>H NMR spectra experience distinct broadening (Figure 2). Concomitantly, the new peaks in the spectral windows of 7.5-6.5 ppm and 4.9-1.0 ppm also emerge. The increase of the NMR intensity in these two regions indicates the formation of aromatic (Ar) groups and, in particular, peaks around 7 and 4 ppm indicate the formation of Ar-H and Ar-NH<sub>2</sub> functionalities. The formation of ether C-O-C cross-links as well as alcohol >C-OH groups are also likely. Based on these data, one can confidently conclude that CDots cannot be represented by a structural model assuming nearly perfect crystalline graphitic core at all reaction conditions which would contradict the NMR data (Figure 2). Instead, CDots should be described as complex, extensively cross-linked NPs that acquire a dense, partially crystalline core only after extensive carbonization.

### MORPHOLOGY AND STRUCTURE OF THE CHIRAL CARBON DOTS

The size distribution of CDots was calculated from the transmission electron microscopy (TEM) images by counting ~100 NPs. *L*-CDots synthesized at 150°C for 4 h and 20 h displayed an average size of 4.4 ± 0.5 nm and 5.3 ± 0.3 nm in diameter, respectively (Figure 3). Diameters of *D*-CDots synthesized at 150°C for 4 h and 20 h were similar to those of corresponding *L*-CDots: 4.3 ± 0.3 nm and 5.2 ± 0.6 nm, respectively (see Supporting Information, Figure S3). Thus, the longer duration of the hydrothermal synthesis results in a larger average diameter of CDots. In all cases discussed above, CDots were of uniform spherical morphology and fairly narrow size distribution. Notably, no NPs were detected when the synthesis duration was relatively short (< 4 h) at 150°C, meaning these conditions were not enough to form the dense carbon cores. Similarly, samples synthesized for 4 h at 100°C displayed distinctly high crystallinity but very faint contrast and it was challenging to assume the edge of these small particles/clusters to determine their sizes (see Supporting Information, Figure S4). Hydrothermal carbonization for 4 h at 250°C resulted in crystalline NPs with elongated geometry with long and short axes of ~13 nm and ~7 nm, respectively (see Supporting Information, Figure S5). Quite expectedly based on NMR data (Figure 2), hydrothermal carbonization of cysteine is very sensitive to the synthesis temperature and duration, and higher temperatures and longer synthesis durations lead to NPs formation. It was reported previously that depending on the amino acids used as the precursors for hydrothermal synthesis of CDots, the sizes of resulting CDots can decrease or increase with increasing the temperature of the synthesis.<sup>22</sup> The different variation trends of the diameters of CDots were explained with the different chemical structures of their precursors and their molecular weight.

X-ray photoelectron spectroscopy (XPS) of CDots was compared to that of Cys (Figure 4a-c). From the XPS spectra of CDots synthesized for 4 h at 150°C (Figure 4b), the C 1s peak consisted of peaks attributed to 284.80, 286.10, 287.44, and 289.97 eV peaks that corresponded to C-C, C-O, O-C=O, and O-C=O bonds, respectively,<sup>22,34</sup> which agree very well with the conclusions from H-NMR study. The intensity and integrated area of the C-C bond peak increased with the increasing synthesis duration from 4 h to 20 h (Figure 4b, c), indicating the increasing dominance of C-C bonds and a greater degree of carbonization.

FTIR spectrum of Cys also changes after hydrothermal synthesis reaction (Figure 4d). The FTIR spectra of *L*-/*D*-CDots agreed with previously published data on chiral carbon-based NPs.<sup>20,25,35</sup> Using FTIR, it was determined that the peak at about 1195 cm<sup>-1</sup> includes sulfur, a C-S bond, and a C-O bond representing the cysteine chain.<sup>23</sup> As the CDots form, there is a peak at 1100 cm<sup>-1</sup> that is C-C-C bending with medium intensity.<sup>36</sup> The peak at 3000 cm<sup>-1</sup> corresponds to C-H, while the peak at 3300 cm<sup>-1</sup> is either C-OH or C-NH vibration.<sup>17,23</sup> The peak at 1600 cm<sup>-1</sup> represents double bonds, specifically C=C and C=O.<sup>17,23</sup> Since the peak at about 3000 cm<sup>-1</sup> decreases with the reaction time, there are less C-H bonds in the structure. The FTIR results and XPS data both prove that as cysteine undergoes hydrothermal synthesis, C-H bonds are broken, the carbon-based skeleton of cysteine becomes stronger, and the amount of carbon increases as carbon dots emerge. We hypothesize that cysteine becomes more rigid as its skeletal bonds become more prevalent and the C-H bonds and functional groups decrease in intensity. The surface of CDots is passivated with carboxyl groups.<sup>17</sup>

#### OPTICAL PROPERTIES OF CYSTEINE-BASED CARBON DOTS

To study the influence of hydrothermal synthesis duration and temperature on the optical properties of CDots, their UV-Vis absorption (Figure 5) and PL emission spectra were recorded (Figure 6). Varying synthesis conditions, CDots samples have slightly different profiles of absorption spectra but all of them were located in 200 – 400 nm spectral region. Optical transitions in the 200–300 nm spectral range correspond to  $\pi$ - $\pi^*$  transitions in sp<sup>2</sup>-hybridized carbon domains, while 300–400 nm range is attributed to n- $\pi^*$  transitions.<sup>37</sup> As can be seen, there are no specific trends in CDots absorption spectra as the duration/temperature of their synthesis increase.

Analysis of photoluminescent properties of CDots shown that the shape and peak position of PL band (430 nm) remains the same as the duration/temperature of CDots synthesize increase. Under the excitation of the samples with 350 nm light, the position of the maximum PL intensity was at ~ 430 nm. Notably, the PL band maximum wavelength of CDots synthesized for 4 h and 20 h at 150°C experiences the redshift as the excitation wavelength increase from 260 nm to 400 nm (see Supporting Information, Figure S6), which indicated the presence of lower energy states in accordance with the reported literature.<sup>38</sup> Also, both the increase of (1) synthesis duration at a fixed temperature and (2) synthesis temperature at a fixed time lead to the increase in the PL QY of CDots (Figure 6a and 6b, inserts). However, the trends of the PL QY increase are different. In the first case, PL QY was increasing faster but reached the saturation of ~ 5% after 12 h of synthesis. In the second case, the synthesis temperature increase from 100°C to 250°C followed by the PL QY rapid increase which also allowed to reach higher PL QY values with ~ 11% efficiency. In both cases, the PL QY increase could be associated with the better crystallinity of CDots and removal of defects upon time/temperature increase, which also had been observed for other types of nanostructures.<sup>39</sup> And the difference between two conditions could be explained by the different dynamics of the crystal growth/crystallization, which occur faster at higher temperatures.

#### CHIROPTICAL PROPERTIES OF CYSTEINE-BASED CARBON DOTS

Besides CD spectra, for quantitative analysis of the optical activity of liquid solutions and dispersions, the dissymmetry factor (*g*-

factor) is used, which is defined as  $g = \Delta\epsilon/\epsilon = (\epsilon_L - \epsilon_R)/(\epsilon_L + \epsilon_R)$ , where  $\Delta\epsilon$  is molar CD,  $\epsilon$  is molar extinction, and  $\epsilon_L$  and  $\epsilon_R$  are the molar extinction coefficients for left- and right-handed circularly polarized light, respectively (see the Materials and Methods section for more details). The dissymmetry *g*-factor is independent of sample concentration and cell path length, which is important for the comparative studies of samples with variable concentrations.

The mirror-imaged CD (see Supporting Information, Figure S7) and *g*-factor (Figure 7) spectra of *L*- and *D*-CDots synthesized for 4 h at 150°C indicate the successful synthesis of CDots with chiroptical activity. The further increase in synthesis duration to 20 h led to the CDots that are chiroptically silent (Figure 7 and Figure S7, Supporting Information).

Analysis of the effect of synthesis duration and temperature on chiroptical activity of CDots allowed to establish that untreated Cys has the highest chiroptical activity and the hydrothermal reaction of Cys and its decomposition to CDots is accompanied by the *g*-factor spectra dramatic transformation at ~4 h of reaction (Figure 8). Prolonged synthesis duration and increased reaction temperature decreased *g*-factor value and caused the disappearance of chiroptical activity after 12 h of reaction (Figure 8). We believe that this phenomenon occurs due to the increased carbonization and the loss of atomic-scale chirality on the surface of CDots as the optical center of Cys decomposes in the course of the hydrothermal synthesis. Additionally, longer duration and higher temperatures facilitate “racemization” of CDots under harsh conditions.<sup>37</sup> Importantly, the PL QY trend is the opposite – PL QY (Figure 6) improves with both reaction parameters and increased crystallinity of CDots (Figure 3). The same trends were reported for semiconductor CdSe NPs.<sup>39</sup>

#### HYDROTHERMAL SYNTHESIS OF CYSTEINE IN THE PRESENCE OF BORIC ACID

The doping of CDots could be potentially used to increase their PL QY and chiroptical activity at the same time. Here, we attempted to synthesize chiral boron-doped CDots with cysteine and boric acid as precursors (see Materials and Methods). We found that both absorbance (Figure 9), PL (Figure 9), CD (Figure 10), and FTIR (Figure S8) spectra of samples prepared with and without boric acid are very similar to each other. This indicates that boric acid has little to no effect on the formation of CDots and the chiral boron nitride NPs are unlikely to form in this reaction pathway. Unlike previous reports,<sup>31,32</sup> our analysis concludes the exclusive formation of CDots. It is also critical to state that our experiments included controls of boric acid, *D*-Cys, and *L*-Cys, so that we could analyze and compare all aspects of the experiments.

#### Conclusion

We synthesized CDots by one-step hydrothermal method from Cys precursor and studied their chemical structure and optical properties. We demonstrated that the PL QY of CDots has a direct correlation with the synthesis duration and temperature, while *g*-factors have an inverse one. Also, we established that the similar hydrothermal reaction with thermal decomposition of amino acid in the presence of boric acid leads to the formation of NPs those optical properties similar to that of CDots rather than to boron nitride NPs. These findings will facilitate the synthesis of chiral carbon-based and other NPs with application-optimized chemical, chiroptical, and photoluminescent properties.

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## Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website. Supplementary characterization of CDots and materials obtained during the hydrothermal synthesis of amino acids in the presence of boric acid.

The data that support the findings of this study are available from the corresponding author upon request.

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Graphical Abstract

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