**ZnO-Associated Carbon Dot-Based Fluorescent Assay for Sensitive and Selective Dopamine Detection**

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**ABSTRACT:** This paper presents a simple and highly efficient method for dopamine detection using water-soluble carbon dot nanoparticles. The ZnO-associated carbon dots (CDZs) were synthesized using a green chemical strategy. An examination of the effects of biomolecules on the fluorescence of CDZs revealed selective dopamine-induced quenching. In a phosphate buffer (pH = 7.4) medium, a detection limit of 1.06 nM was obtained. This “turn off” phenomenon was attributed to the electronic interaction between CDZs and dopamine, during the oxidation of dopamine. At lower pH, however, the effects of dopamine on the fluorescence of CDZs were insignificant as the oxidation of dopamine was hindered when the proton concentration was increased. This method was found to be free from the interference of coexisting molecules, that is, ascorbic acid and uric acid. This sensing platform was applied successfully in biological fluids to confirm the practical significance of the designed sensor.

**INTRODUCTION**

Dopamine (DA) is a vital catecholamine neurotransmitter that acts within the brain and central nervous system. DA plays an important role over a wide range of physiological processes. An imbalance of DA in the systems would cause severe diseases, including schizophrenia,  
Parkinson’s disease, and depression. DA also affects the blood pressure, construction of heart muscles, and renal systems. The detection of DA is clinically very important. The DA metabolism follows two pathways: homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid pathways. The biological functions in the human body depend on the HVA concentration in the cerebrospinal fluid containing cellular information and biochemicals that are favorable for brain activation. This makes DA very important in neurosystems.

DA is a clinically crucial compound; its accurate detection has become a major topic of interest. Since the past, different techniques have been adopted to achieve the sensitive detection of DA, including electrochemical, fluorometric, colorimetric, voltametric, and chromatographic. Among them, the fluorometric detection of DA showed better results for its high signal to noise ratio, good reproducibility, low cost, and easy removal of the interference of coexisting biomolecules.

Fluorescent nanomaterials, namely, quantum dots (QDs), metal nanoclusters (MNCs), and carbon dots (CDs), are important fluorescent probes that can be used to detect DA. QDs (with cadmium and selenium) and MNCs (gold and silver nanoclusters) are often associated with synthetic complications and significant cytotoxicity. CDs have emerged as an efficient probe owing to their unique properties, including their small and well-defined sizes, biocompatibility, low cytotoxicity, water solubility, tunable photoluminescence, and good stability against photobleaching. Owing to their unique physico-chemical properties, CDs are often successfully utilized for chemical as well as biosensing, catalysis, electrocatalysis, optoelectronic devices, environmental applications, and biomedical applications. The facile electron acceptance/donation properties of CDs were used to design CD-based sensors. The sensing process takes place through different photophysical processes, including photoinduced electron transfer, intramolecular charge transfer, twisted intramolecular charge transfer, metal–ligand charge transfer, electronic energy transfer, and fluorescence resonance energy transfer. Generally, these processes involve intermolecular interactions between the sensor and analyte.

In recent days, CD–metal/metal hydroxide (CDM/CDMO) have gained significant importance in different fields of sensing, photocatalysis, and photovoltaics. The CDM/CDMO-based sensors have better efficiency than those of pure metal or metal oxide-based nanoparticles because of the introduction of properties, including the change in conductance, increasing surface reaction sites, high porosity, and contact potential at the junction of two components. Previous reports of CDMO hybrids encouraged the use of hybrid materials for different sensing. Some notable works include the CD–MnO2-based glutathione sensor designed by Wang et al., CD–Au nanocomposite-based cysteine detector by Deng et al., and CD–MnO2-based N-acetyl-l-cysteine sensor by Jana et al.
In this study, a fluorometric DA sensor utilizing CD, as a probe, was designed. Citric acid (CA) and tetraethylenepentamine (TEPA) are used as carbon and hetero atom (nitrogen atom) sources, respectively, for the synthesis of CDs. ZnO serves as a surface-passivating agent and provides stability to the CDs by preventing aggregation. ZnO attaches preferentially to the amine group on the CDs. The electronic interaction within ZnO and CDs influences radiative recombination in carbon tuning its opto-electronic properties. Upon excitation, the electrons at the valence band might be excited to the conduction band leaving holes in the valence band. The generated excited electrons can transfer to the carbon layer, tuning the inherent radiative recombination within the CD. On the other hand, the photoelectron, generated upon excitation in the ZnO moiety, could be used to interact with the external analyte present in the medium. In the present experiment, the intriguing fluorescence of ZnO-associated CDs (CDZs) was quenched in the presence of DA. The detection limit was as low as 1.06 nM. The selectivity of DA in the presence of other coexisting biomolecules can be attributed to the electronic involvement of as-synthesized CDZs into DA oxidation. The good compatibility of highly selective detection on DA in a biological fluid sample highlights the potential of the as-synthesized CDZs for DA detection in biomedical fields.

RESULTS AND DISCUSSION

Physical Characterization of CDZs. Figure 1A presents a transmission electron microscopy (TEM) image of the as-synthesized CDZs. The CDZ particles had a mean diameter of 1.65 nm. Close observations with high-resolution TEM (HRTEM) analysis showed crystallinity with lattice fringes of 0.23 and 0.19 nm that corresponded to the (100) plane of carbon and the (102) plane of ZnO, respectively (Figure 1B). The X-ray diffraction (XRD) pattern in Figure 1C showed only one broad peak at approximately 22° 2θ that corresponds to the graphitic carbon peak. Besides, a tiny peak at 72.9° was observed that can be attributed to the (004) plane of ZnO, DB card: 01-080-0075. Fourier transform infrared (FTIR) spectroscopy and X-ray photoelectron spectroscopy (XPS) were carried out to study the chemical composition and functional groups of the CDZ particles. As depicted by the FTIR spectrum in Figure 1D, the peaks at 3456, 2912, 1649, 1230, and 1037 cm⁻¹ corresponds to the stretching vibration of N–H, asymmetric stretching vibration of CH₂, stretching vibration of C≡C/C≡O, and stretching vibration of C=O, respectively. The attachment of ZnO with the ex situ prepared CD particles was examined through FTIR studies. In another set of experiments, the hydrothermal treatment of zine acetate dihydrate was performed in the absence of CDs (prepared via microwave treatment). Figure S1 shows a comparative FTIR for normal CD, ZnO, and CDZs. It was observed that for CDZs and ZnO a weak peak appeared at ~900 cm⁻¹ which corresponds to Zn–O stretching. This peak was absent for CD indicating association of ZnO with CD. The XPS spectrum in Figure 2 shows that the CDZs comprised carbon, nitrogen, oxygen, and zinc. The high resolution XPS spectra of C 1s could be resolved into four peaks with binding energies at 284.04, 284.97, 288.33, and 291.38 eV, corresponding to C–C, C–C, C–N, and C=O, respectively. The N 1s spectrum was fitted to two peaks at 399.36 and 401.15 eV, which were assigned to N–C and N–H bonds, respectively. Deconvolution of the O 1s peak gives three components at 530.66, 531.64, and 532.7 eV for O–Zn, HO–, and O–C bonds, respectively. Fitting of the Zn 2p spectrum provided two main bands at 1021.56 and 1044.65 eV, which were assigned to Zn 2p₃/₂ and Zn 2p₁/₂ of ZnO, respectively. The above analysis indicated that the as-synthesized CDZ particles might have functional groups, such as –NH₂, –COOH, and ZnO, that might be associated with the carbonized entity. The stability of CDZs was examined with respect to the emission intensity and emission peak over a period of 60 days (Figure S2). The results suggested the long-term stability and usability of CDZs.

Optical Characterization of CDZs. The UV–vis absorption spectrum revealed two distinct peaks at 266 and 362 nm, which were assigned to the π–π* transition of the aromatic C≡C bond and n–π* transition of the C≡O bond, respectively (Figure 3). The CDZ aqueous solution emitted strong blue light under a UV irradiation of 365 nm. While excited at 340 nm, CDZs showed very strong fluorescence with an emission maximum of 440 nm. The fluorescent quantum yield was calculated to be 25.96% (reference: quinine sulfate). The lifetime was calculated to be 12.46 ns from the fluorescence decay profile (Figure S3). The fluorescence excitation spectrum of the CDZ, with an emission maximum at 440 nm, exhibited a broad peak with a maximum at approximately 344 nm. When the excitation wavelength was increased from 320 to 600 nm in 20 nm increments, the spectra exhibited excitation wavelength-dependent behavior, along with a red shift of the emission peak with an increasing excitation wavelength (Figure S3). This tunable fluorescence of CDZ particles may arise from the different sizes or the existence of different emissive sites on the surfaces of the CDs. On the other hand, the precise mechanism of this excitation wavelength-dependent tunable emission of CDs requires further study. The emission of CDZs depends on the pH of the medium. Figure S4 shows a blue shift of the CDZ emission peak with increasing pH. Furthermore, the fluorescence spectra of CDZs were examined in the presence of NaCl solutions of different concentrations to check the...
stability of CDZs under high ionic strength. The results showed no significant alteration of the fluorescence nature of CDZs (Figure S5), suggesting that CDZs have excellent stability under high ionic strength conditions.

**Fluorescence Quenching of CDZs.** The effect of fluorescence response behavior of CDZs toward various biomolecules [ascorbic acid (AA), citric acid (CA), cysteine (Cys), dopamine (DA), fructose (Fru), glucose (Glu), sucrose (Suc), and uric acid (UA)] was investigated. As shown in Figure 4, almost no other molecules except for DA caused significant changes in the CDZ emission. This paves the way for selective DA detection. DA itself is fluorescent that shows emission at an excitation wavelength of 270 nm. The emission changed in the presence of CDZs. The simultaneous changes in the CDZ and DA emission, upon mixing, indicates electronic interactions between the moieties. CDZs are believed to interact with DA during oxidation to its quinone derivative. XPS of the CDZ−DA system revealed a shift in the C 1s and N 1s peaks (Figure S6). Deconvolution of the C 1s peak provided peaks at 284.5, 285.5, 287.9, and 288.9 eV, corresponding to $\text{C} = \text{C}$, $\text{C} − \text{C}$, $\text{C} − \text{O}/\text{C} − \text{N}$, and $\text{C} = \text{O}$ bonds, respectively. This may be due to the partial shift in the electron density during participation in DA oxidation. The $\text{C} = \text{O}$ bond became prominent possibly because of evolution of the keto group in the CDZ−DQ system. Similarly, the $\text{sp}^3/\text{sp}^2$ ratio increased in the system causing a shift of the $\text{C} = \text{C}$ and $\text{C} = \text{C}$ peaks toward a higher binding energy. For N 1s, the peak at 399.3 eV for N−C remained unaltered, but a new small peak at 398.1 eV was observed. This may correspond to $\equiv \text{N}−/−\text{NH}_2$ generated during the reaction process. On the other hand, the Zn 2p peak remained unaltered. Such behavior can be explained by the catalytic activity of the ZnO moiety during reduction. ZnO might have interacted with the $−\text{OH}$ group.

**Figure 2.** (A) Broad range XPS spectra of CDZs. Elemental analysis of elements of CDZs, (B) C 1s, (C) N 1s, (D) O 1s, and (E) Zn 2p. The sample was vacuum dried for analysis.

**Figure 3.** Spectral profile of CDZs. Black line: absorbance, peaks at 266 and 362 nm; red line: emission spectra at excitation wavelength of 340 nm; blue line: excitation spectra at an emission wavelength at 440 nm.

**Figure 4.** (A) Relative fluorescence intensity and (B) absorption spectra of CDZs in the presence of different biomolecules. Inset (A): fluorescence spectra of CDZs and CDZ−DA. $\lambda_{ex} = 340$ nm, [CDZ] = 0.005 g/mL, [biomolecule] = $12 \times 10^{-4}$ M, $I_0$ and $I$ denote the fluorescence intensity of CDZs in the absence and presence of biomolecules, respectively.
of DA, causing the activation of the group and facile electron transfer. Figure 4 shows that in absorption spectra the ∼266 nm peak of CDZs suffered an enhancement along with the red shift. The CDZ absorption peak at 362 nm remained almost unaltered. This phenomenon might be explained considering the absorption of AA,45 oxidized DA,46 and UA47 which became prominent along with CDZ absorption under present experimental conditions. The pH of the medium is a crucial factor for biosensing. Therefore, the effect of DA on the emission of CDZs was examined at different pH from 2 to 10 (Figure S). The fluorescence intensity of CDZs decreased gradually in the presence of DA at higher pH. DA-induced quenching was attributed to the engagement of CDZs in the oxidation of DA. As in alkaline media, DA could be oxidized rapidly to its quinone derivative,48 and the DA-induced fluorescence quenching of CDZs became more prominent. Nevertheless, the sensitivity of DA was examined in a phosphate-buffered saline (PBS) medium so that the sensor can be used in a biological environment.

**Determination of DA with CDZs as a Fluorescent Probe.** The selective quenching of CDZ fluorescence by DA was used for the quantitative detection of DA. This concentration dependence was examined in PBS (pH = 7.4). Figure 6 presents the DA concentration-dependent fluorescence of CDZs. The fluorescence of CDZs decreased with increasing DA concentration. The relative fluorescence intensity \( \frac{I_0}{I} = \text{fluorescence intensity of CDZs in the absence of DA, } I = \text{fluorescence intensity of CDZs in the presence of DA} \) at 440 nm as a function of the DA concentration, [DA], was calculated over the concentration range, 18 nM to 1.2 mM. The quenching mechanism of a fluorophore is described using a Stern–Volmer plot as follows

\[
\frac{I_0}{I} = 1 + K_{SV}[Q]
\]

where Q is the quencher and \( K_{SV} \) is the Stern–Volmer constant. The linearity of the plot depends on the quenching mechanism.49 From the plot, a linear relationship between the relative fluorescence intensity and [DA] was obtained over a concentration range of 180 nM to 15 \( \mu \)M (\( R^2 = 0.98 \)). The lower detection limit was calculated to be 1.06 nM (signal/noise = 3). This makes the CDZ a very sensitive probe for DA detection.

**Study on Interference during the Sensing Process.** Because CDZs are intended for use in the detection of DA, the interference study was done using other molecules that may coexist with DA in a cell. The effect of biomolecules (AA, CA, Cys, Fru, Glu, Suc, and UA) and some metal ions (Na+,K +, and Zn2+) on the emission of the CDZ–DA system was recorded. Figure 7 shows that at a 1:1 ratio of other moieties and DA, there is no significant change in the emission of the CDZ–DA system. The PBS medium was used for these experiments at room temperature. Compared to previous reports (Table S1), this prescribed method showed a significantly important detection limit of DA.

**Determination of DA in Spiked Biological Systems.** The as-designed sensing platform in the biological fluid, where DA, AA, and UA can coexist, was performed on human blood samples. The blood sample was collected from a healthy donor and centrifuged to remove the heavy particles. A dilution of 2000 gave significant % recovery (Table 1). The % recovery

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**Figure 5.** Relative fluorescence intensity of CDZs in the presence of DA at different pH. \( \lambda_{ex} = 340 \) nm, \( I_0 \) and \( I \) denote the fluorescence intensity of CDZs in the absence and presence of biomolecules, respectively.

**Figure 6.** (A) Variation of the fluorescence intensity of CDZs with different concentrations of DA, (B) relative fluorescence intensity of CDZs vs the concentration of DA (inset: linear dependence of the relative fluorescence intensity with the concentration of DA). \( \lambda_{ex} = 340 \) nm, \( I_0 \) and \( I \) denote the fluorescence intensity of CDZs in the absence and presence of biomolecules, respectively.

**Figure 7.** Fluorescence intensity of the CDZ–DA system in the presence of other moieties. \( \lambda_{ex} = 340 \) nm, [CDZ] = 0.005 g/mL, [DA/biomolecule/metal ion] = 12 \( \times \) \( 10^{-4} \) M.
and % RSD highlight the efficiency of the CDZ sensor (Table 2).

### Table 1. Influence of the Dilution Ratio on the Detection of Spiked DA in a Blood Sample

| dilution ratio of the blood serum sample | spiked DA concentration (μM) | measured DA concentration (μM) | recovery of DA (%) | RSD (%) |
|----------------------------------------|-----------------------------|-------------------------------|--------------------|--------|
| I                                      | 50                          | 53.3                          | 106.6              | 2.28   |
| II                                     | 100                         | 105.6                         | 106.3              | 1.57   |
| III                                    | 250                         | 266.8                         | 106.8              | 1.93   |

### Table 2. Determination of DA in a Blood Sample Using the Proposed Method

| sample | spiked DA concentration (μM) | measured DA concentration (μM) | recovery of DA (%) | RSD (%) |
|--------|-----------------------------|-------------------------------|--------------------|--------|
| I      | 50                          | 53.3                          | 106.6              | 2.28   |
| II     | 100                         | 105.6                         | 106.3              | 1.57   |
| III    | 250                         | 266.8                         | 106.8              | 1.93   |

A quick survey of DA sensing in cells was performed using HeLa cells. Illumination of the cells containing CDZ particles at 405 nm exhibited a blue emission from the cytoplasm area. The nucleus was not stained by DAPI; the emission was solely from the CDZ particles. When DA was introduced into the cells, the CDZ-induced emission in the cell was found to be less intense (Figure 8). Nevertheless, further experimentation with the dosage and cellular interaction mechanism will be needed.

### Interaction of CDZs with BioMolecules at Lower pH.

In a parallel experiment, while checking the effects of biomolecules on the fluorescence of CDZs at different medium pH, CA was found to quench the CDZ emission at lower pH (Figure 9), whereas DA did not show any effect. This “turn off” phenomenon may be because of the CA–CDZ interaction. Further investigation showed that at pH = 2, the CA-induced quenching predominated showing a linear relationship between the relative fluorescence intensity and the CA concentration over the range, 5 μM to 1 mM (Figure 10). This simple fluorometric CA sensing platform has significant potential because CA is an important ingredient for different food and soft drink beverages. Therefore, a fluorescent probe, that can be used for multisensing by tuning the medium pH, was synthesized.

### CONCLUSIONS

A ZnO-associated amine-functionalized CD was designed for the selective and sensitive detection of DA. The sensing performance of the as-synthesized CDZ was evaluated through a fluorescence “turn off” phenomenon. The quenching was attributed to the oxidation of DA in the presence of CD particles. The prescribed sensor achieved a nanomolar detection limit in the PBS medium. The applicability of the sensor was checked using a DA-spiked human blood sample with reasonable RSD values. The medium pH-dependent behavior of these CDZs provided a platform for DA as well as CA detection to a satisfactory level. The fluorometric DA sensor was free of UA and AA interference, suggesting that it will be useful in biomedical applications. The overall process is depicted in Scheme 1.

### EXPERIMENTAL SECTION

The detailed list of chemicals and characterizations have been documented in the Supporting Information.

#### Synthesis of ZnO-Associated CDs.

The hydrothermal treatment was employed for the synthesis of CDZs. The mixture of 500 μL, 0.01 M Zn(OAc)·2H2O and 500 μL, 0.01 g/10 mL CD was taken in a Teflon-lined autoclave reactor and kept at 180 °C for 6 h. The CDs were synthesized using microwave treatment of the solution containing 1 M 200 μL TEPA and 0.1 M 300 μL CA for 5 min at the highest power of a domestic microwave oven. A brown solid precipitate was found after the microwave treatment. This solid was readily soluble in water. This solution was taken for the hydrothermal treatment which produced a pale-yellow colored solution. The solution was centrifuged and dialyzed before storing at room temperature. This solution exhibited blue emission under UV irradiation.

The quantum yield of this blue emitting solution was calculated using the following equation,

$$\phi = \frac{Y_{\text{ref}} F_{\text{ref}}(A_{\text{ref}}/A_{\text{sl}})(\eta_{\text{ref}}/\eta_{\text{sl}})^2}{Y_{\text{sl}} F_{\text{sl}}(A_{\text{sl}}/A_{\text{ref}})(\eta_{\text{sl}}/\eta_{\text{ref}})}$$

(2)

where, \(Y\), \(I\), \(A\), and \(\eta\) denote the quantum yield, fluorescence, absorbance, and refractive index, respectively. The subscripts “sl” and “ref” refer to the sample (CDZ) and reference, quinine sulfate (prepared in 0.1 M H2SO4 solution), respectively.

#### Preparation of the Sensing Platform.

The sensing studies were performed in an aqueous medium at room temperature. The biomolecules were added individually to the as-prepared CDZ solution for fluorescence measurements at an excitation wavelength of 340 nm. The time-dependent study showed that an incubation time of 6 h provided best results. The DA concentration-dependent emissive behavior of CDZs was also studied under the same experimental conditions. The interference study was performed by mixing other biomolecules and cations at a 1:1 ratio. For the general study, PBS (pH = 7.4) was used. CA sensing was performed in an acidic solution (pH = 2.0) following the abovementioned process.

#### Real Sample Analysis.

The blood sample was collected from a healthy volunteer. The blood was centrifuged to remove the heavy particles and the centrifugate was collected for analysis. The centrifugate was diluted at various ratios. DA was spiked over the samples using a standard addition method. The PBS medium was used throughout the experiment.

#### Cell Culture and Fluorescence Imaging.

The cell-imaging studies were performed on HeLa cells. ~8 × 10^4 cells per well, seeded in 6-well plates were taken for the experiment.
Cells were cultured in Dulbecco’s modified Eagle medium at 37 °C in a humidified atmosphere containing 5% CO₂. For complete adherence of cells to the surface a time period of 24 h was needed. After that, the culture medium was replaced with 0.5 mL freshly synthesized CDZ solution (1 mg/mL) and was kept under incubation for 6 h. The cells were washed three times with PBS buffer (pH = 7.2) before recording the cell images to remove the excess CDZ, followed by fixation of cells with a 4% paraformaldehyde solution for 15 min. The system was washed twice using the PBS solution. The fixed

Figure 9. Fluorescence spectra of CDZs in the presence of biomolecules at different pH. (A) pH = 2.0, (B) pH = 4.0, (C) pH = 6.0, and (D) 10.0. \( \lambda_{ex} = 340 \text{ nm} \).

Figure 10. (A) Variation of the fluorescence intensity of CDZs with different concentrations of CA, (B) relative fluorescence intensity of CDZs vs the concentration of CA (inset: linear dependence of relative fluorescence intensity with the concentration of CA). \( \lambda_{ex} = 340 \text{ nm} \), \( I_0 \) and \( I \) denote the fluorescence intensity of CDZs in the absence and presence of biomolecules, respectively.

Scheme 1. Schematic Representation of the Sensing Platform
cells were then observed using a 405 nm laser excitation through a confocal fluorescence instrument.

**ASSOCIATED CONTENT**

**Supporting Information**
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b02637.

Experimental section, FTIR spectra of CDZs along with CD and ZnO, stability spectra of CDZs; emission spectra of CDA with different excitation wavelengths; pH-dependent fluorescence spectra of CDZs; comparative emission spectra of DA, CDZs, and CDZ–DA; and XPS spectra of CDZ–DA (PDF)

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**Notes**
The authors declare no competing financial interest.

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