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Biocompatible Ionic Liquid based on Curcumin as Fluorescence Probe for Detecting Benzoyl Peroxide without the Interference of H_2O_2

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ABSTRACT: Accurate estimating the level of benzoyl peroxide (BPO) is of considerable significance because of its threat to humanity and environment. Several research efforts have been devoted to the detection of BPO by fluorescent method with high sensitivity and selectivity. However, it remains challenging to eliminate the interference of H_2O_2 due to its similar property to BPO. In this work, the first demonstration of fluorescent and colorimetric probe for specific detection of BPO without the disturbance of H_2O_2 is achieved by curcumin-based ionic liquid (CIL) that possesses simple fabrication, good biocompatibility and low cost. The fluorescence quenches and emission peak blue-shifts once the probe selectively interacts with BPO, whereas the other possible interfering agents including H_2O_2 do not have this phenomenon. The probe CIL exhibits prominent sensitivity for BPO sensing and enables the detection limit at level as ultra-low as 10 nM. The local detection of BPO in practical samples is realized by visualized and portable device derived from CIL-based liquid atomizer.

INTRODUCTION

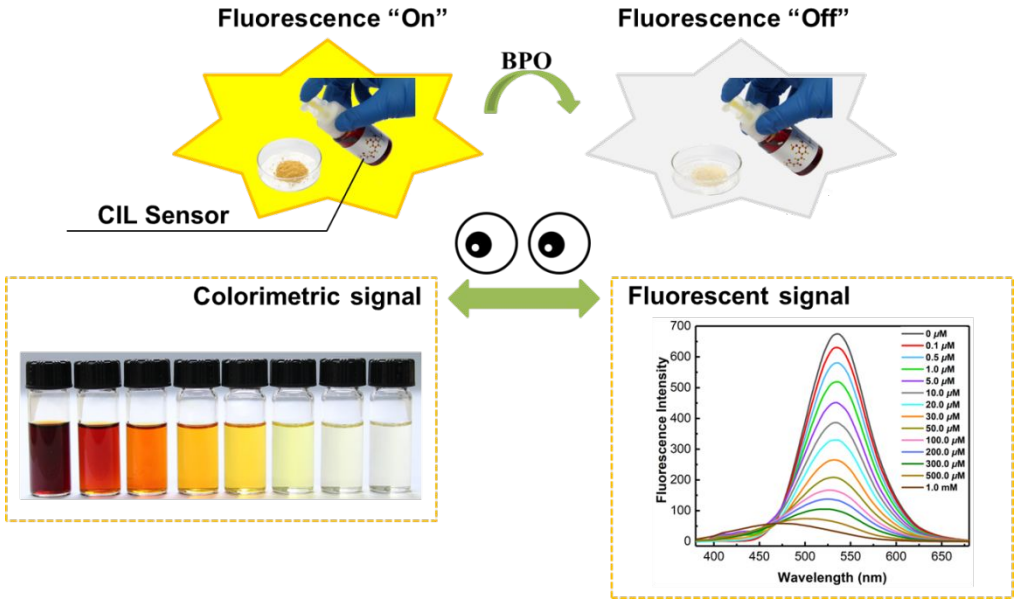
Benzoyl peroxide (BPO) is an extensive ingredient used in plastics, antimicrobial drugs, cosmetics, and a flour bleacher in food industry[1,2]. However, as a strong oxidizer, the widespread use of BPO is considered a potential threat to humanity and environment. BPO plays critical roles in mutagenicity of TA97 and TA1537 strains and it may be a tumour promoter that can induce skin cancer[3,4]. In addition, BPO is lipophilic, with a log P_{ow} of 3.43 at 25 °C[5]. According to data reported, the K_{oc} value of BPO is 1,800 in soil[5], which means that BPO is low mobility and tends to accumulate if it is released into the soil. BPO also shows high acute toxicity to aquatic organisms, such as EC_{50} of algae, invertebrate and fish is 0.07 mg/L, 2.91 mg/L and 0.24 mg/L, respectively[6]. BPO should therefore be considered a contaminant to environment. In European Union and China, BPO was prohibited as food additives in wheat flour[7,8]. Therefore, accurate monitoring BPO level is necessary to ensure human and environmental safety.

Current analytical methods used for the BPO detection including HPLC[9], spectrophotometry[10], chemiluminescence[11], electrochemistry[12], colorimetry[13,14] and fluorescent spectrometry[7]. Among them, fluorescent probes have attracted tremendous attention due to its convenience, sensitivity, and rapid response to BPO. Chen et al. first reported a fluorescent probe for the BPO detection. The probe was designed to incorporate an arylboronate group into resorufin matrix, which could be employed to monitor BPO through the deprotection of boronate[7]. In this context, several fluorescent probes have been reported for the detection of BPO in living cells based on this mechanism of deboronation[15,16]. However, H_2O_2, whose property is similar to BPO, is an extremely sensitive mediation with boronate and it causes the fluorescence response either[17,18]. It means that these probes based on arylboronate group were difficult to separate H_2O_2 from BPO during the detection[7]. Silver nanorods with transverse and longitudinal surface plasmon resonance have also been developed for the detection of trace BPO[19]. However, inconvenient color resolution, and poor selectivity limit their practical application. Thus, searching for a novel fluorescent probe with high sensitivity and selectivity to distinctly define BPO is still a challenge.

As environmental friendly "green solvents and functional materials", ionic liquids (ILs) are considered to be essential roles in various fields such as synthesis, electrochemistry, extraction and analysis due to their highly tunable properties[20-29]. Recently, more and more researches showed that ILs had great potential in sensors[30-33]. Hice et al. provided a means for rapidly capture and concentration of *Salmonella* by using magnetic ILs. The concentrate sufficient cells could be detected and a low detection limit was realized[30]. Che et al. reported an anion-functionalized IL with high fluorescent effect. They utilized the specific "chemical and physical" two-step interaction between the anion and SO_2 to design a fluorescent sensor with good quantification and excellent reversibility[31]. Be different from traditional sensors, IL-based sensors possess a unique advantage of negligible vapor pressure, which means the detection would not be influenced by concentration change from solvent evaporation. The adjustable characteristic of ILs makes it possible to meet specific requirements by combining various cations and anions. As a result, the sensors based on functional ILs can be designed to exhibit exceptional selectivity for targeted components[34].

Herein, we firstly designed a novel task specific ionic liquid derived from biomass curcumin. The ionic liquid ([N_{3333}][Cur],

CIL) was prepared by an acid-base neutralization reaction between curcumin and tetrapropylammonium hydroxide. Benefited by the eminent optical activity and biocompatibility of



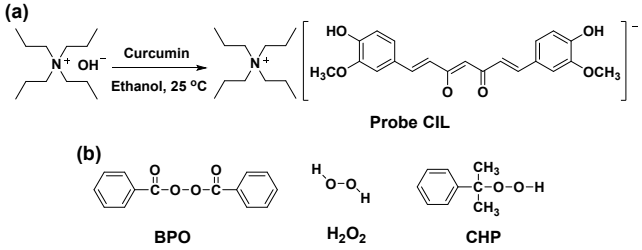
Scheme 1. Schematic Illustration for Specific Detection of BPO by the Colorimetric and Fluorescent Signals.

curcumin[35], the CIL probe can simultaneously provide colorimetric and fluorescent signals for BPO detection. Importantly, the CIL probe exhibited highly sensitivity and selectivity which had the identification to BPO from other interferences including H_2O_2 (Scheme 1).

EXPERIMENTAL SECTION

Materials. Curcumin, benzoyl peroxide, tetrapropylammonium hydroxide (TPAH) (25%) and cumene hydroperoxide (CHP) (60%) were purchased from J&K Scientific Ltd. (Beijing, China). Glucose, vitamin C, glycine, arginine, serine, $K_2S_2O_8$, $K_2Cr_2O_7$, $NaNO_3$, $MgSO_4$, $ZnCl_2$, KCl, NaCl, H_2O_2, ethanol were sourced from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). Benzoyl peroxide gel was purchased from Mingxin Pharmaceutical Co., Ltd. (Shanghai, China). Wheat flour was purchased from local supermarket. All chemicals and reagents of analytical grade were obtained commercially and used without further purification. Ultrapure water of 18 MΩ cm was used throughout the experiments.

Instruments and Characterization. Fourier transform infrared spectra (FT-IR) were recorded on a Bruker ALPHA infrared spectrometer in the range of 400−4000 cm^{-1} at the resolution of 2 cm^{-1} and 32 scans per time. NMR experiments were performed with a Bruker 400 MHz nuclear magnetic resonance spectrometer operating at 400 (^{1}H) and 100 (^{13}C) MHz, respectively, with DMSO-d_6 as the locking solvent. The elemental analysis (H, C, N) of the sample was determined using an Elementar Vario MICRO CUBE elemental analyzer. Rayleigh UV-1601 UV-vis spectrophotometer was employed



Scheme 2. (a) Design and synthesis of CIL probe. (b) Chemical structures of BPO, H_2O_2 and CHP used in the tests.

to measure UV-vis absorption spectra. Steady state fluorescence spectra were recorded by a Shimadzu RF-5301PC fluorescence spectrophotometer with a xenon lamp as the excitation source. The slits widths for excitation and emission were set to 3.0 nm, 5.0 nm, respectively. The mass spectra of the samples were measured on an LCMS-IT-TOF using methanol as solvent. High-performance liquid chromatography (HPLC) analyses were conducted on a Shimadzu HPLC system, equipped with LC-20AD solvent delivery unit, SIL-20A autosampler and a SPD-M20A photodiode array detector. The methanol/water (80:20, v/v) was used as mobile phases.

Synthesis of Probe CIL. The proposed fluorescent probe CIL could be easily synthesized according to a literature method by the acid-base neutralization[36] between curcumin and tetrapropylammonium hydroxide without any poisonous by-product (Scheme 2). In brief, the curcumin precursor (0.05 g, 0.14 mmol) was dissolved in 30 mL ethanol. Then the aqueous solution of tetrapropylammonium hydroxide (ratio 1:1) was added to the system. The mixture was stirred for 24 h at room temperature, and then desirable CIL-based probe was obtained after drying using a high vacuum pump. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.35 (d, J=11.6 Hz, 2H), 7.02 (s, 2H), 6.94 (d, J=8.2 Hz, 2H), 6.51−6.31 (d, J=59.2 Hz, 4H), 5.74 (s, 1H), 3.73 (s, 6H), 3.15–3.05 (m, 8H), 1.65–1.53 (m, 8H), 0.88

(t, J=7.2 Hz, 13H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 183.13, 150.34, 148.22, 140.77, 125.84, 123.38, 120.71, 115.86, 111.27, 100.90, 59.25, 55.68, 14.81, 10.56 ppm. Elemental analysis: Calcd. for $C_{33}H_{47}NO_6$ (553.75): C, 71.61; H, 8.49; N, 2.53; Found: C, 71.56; H, 8.38; N, 2.20.

Detection of BPO in solution state. The standard solutions of CIL probe (1.0 mM) and BPO (5 mM) were prepared in ethanol. All solutions of fluorescence and UV-vis measurements were freshly prepared in ethanol. In test system, 0.25 mL stock solution of CIL probe (0.05 mM) and various volume standard solution of BPO were mixed. The final volume was adjusted to 5 mL with ethanol. The fluorescence and UV-vis spectra of the mixture solution were collected after sonication for 10 min and incubation for 60 min at room temperature.

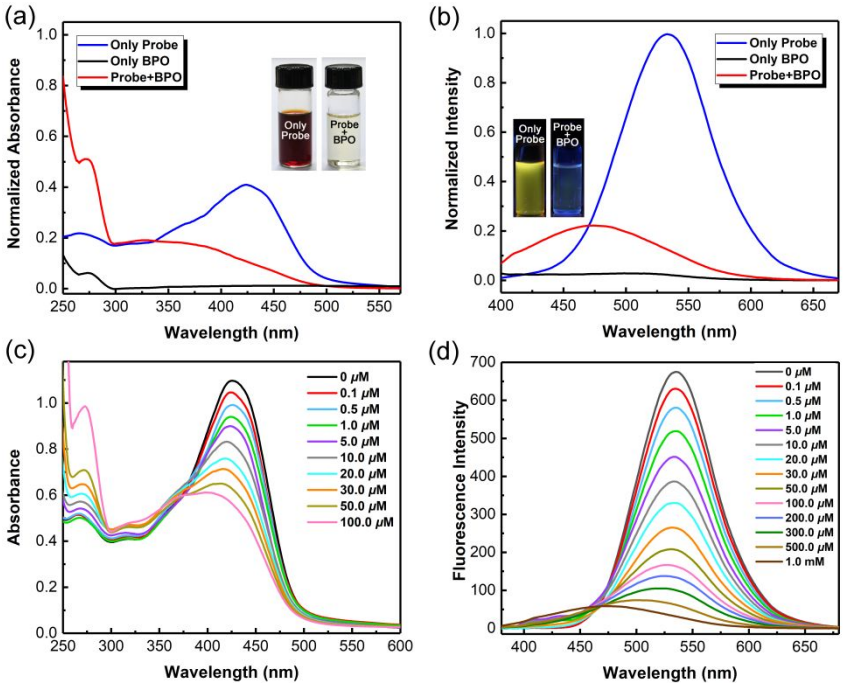


Fig 1. (a) UV-vis absorption and (b) fluorescence emission spectra of CIL probe, BPO and CIL probe in the presence of 300.0 μM BPO in ethanol, λ_{ex} = 365 nm; the inset shows photographs of changes of color and fluorescence under day light and UV light (365 nm). (c) UV-vis absorption and (d) fluorescence emission spectra of the solutions of CIL probe with various concentrations of BPO, including 0, 0.1, 0.5, 1.0, 5.0, 10.0, 20.0, 30.0, 50.0, 100.0 μM in UV-vis spectra; 0, 0.1, 0.5, 1.0, 5.0, 10.0, 20.0, 30.0, 50.0, 100.0, 200.0, 300.0, 500.0 μM and 1.0 mM in fluorescence spectra.

Detection of BPO in real samples. Wheat flour and benzoyl peroxide gel were selected as the real samples. First, 0.10 g wheat flour and an appropriate volume of BPO standard solution (0, 5, 10, 20 μM) were added into 1 mL CIL probe stock solution, and then a final volume was adjusted to 5 mL with ethanol. For benzoyl peroxide gel, 0.10 g gel and 0.20 mM CIL probe were mixed into ethanol. All mixture solutions were incubated at room temperature for 60 min and centrifuged at 5000 rpm for 10 min. The supernatants were tested by UV-vis absorption and fluorescence spectra with λ_{ex} = 365 nm.

RESULTS AND DISCUSSION

Characterization of CIL Probe. The structure of the obtained probe CIL was characterized by ^{1}H and ^{13}C NMR, FT-IR and elemental analysis. Compared with the ^{1}H NMR spectrum of curcumin (Fig S1), some new signals at 0.86−3.15 ppm appeared, which were attributed to the proton of the —CH_3 and —CH_2 group of TPAH parent material. Furthermore, the chemical shift from at 9.67 ppm to at 4.83 ppm was allocated to the proton of phenol groups of curcumin, and shape of the peak changed from sharp to broad visibly. The electron pairs of negative ion are speculated to be delocalized after the reaction and shared among the whole conjugate system with the affection of proton activity belonged to the phenol. The slight shifts can also be observed in ^{13}C NMR spectrum (Fig S1). In the FT-IR spectra of curcumin and probe CIL (Fig S2), the new peaks observed at 2828−2970 cm^{-1} were assigned as the symmetric and asymmetric stretching vibration of C−H groups of tetrapropylammonium. The remarkable blue-shifted from at 1697 cm^{-1} to at 1575 cm^{-1} was ascribed to the characteristic peak of C=O group of curcumin substrate. The stretching vibration of C=C group was observed at 1626 cm^{-1} and the aromatic C=C stretching vibration was found at 1474 cm^{-1}. The product was further confirmed by elemental analysis. All these results suggested the probe CIL was successfully synthesized.

Detection of BPO by Colorimetric Signal and Fluorescent Signal. To verify the effective interaction between the probe CIL and BPO system, we tested the response of probe CIL in the absence and presence of BPO by UV-vis absorption and fluorescence spectra. The detecting behavior of probe CIL toward BPO were presented in Figure 1. In UV-vis absorption spectra (Fig 1a), the probe CIL displayed a strong absorption at 426 nm due to π–π* transition of the extended conjugated system[37]. Interestingly, after addition of BPO, the original absorption peak of probe CIL at 426 nm almost disappeared and the peak intensity at 270 nm increased significantly. It means that a redox reaction may occur when the addition of BPO. Meanwhile, a significant color change of the system from blood red to nearly colorless can be observed by naked

eyes, as demonstration in the inset of Fig 1a. The result indicates that the prepared CIL can be used as a colorimetric probe for BPO detection.

The response of CIL probe to BPO also tested by fluorescent strategy. As shown in Fig 1b, in the absence of BPO, the probe CIL shows a maximal fluorescence emission at 544 nm with the excitation wavelength at 365 nm. While once probe CIL meets BPO, vary weak fluorescence emission intensity was found at about 470 nm. It means that the addition of BPO induces the behavior of a specific fluorescence quenching in probe CIL, accompanied by a distinct visual change from bright-yellow to colorless under the UV light illumination (365 nm) in the dark (in the inset of Fig 1b). Interestingly, the emission peak undergoes blue-shift from 544 nm to 470 nm compared to the original CIL probe system. This specific change could be attributed to efficient redox reaction between CIL and BPO, which would induce deterioration of CIL probe and destruction of conjugated system. These fluorescent evidences were consistent with the observation from UV-vis absorption spectra. The results demonstrated that BPO can be simple identified by CIL-based fluorescence probe.

Analytical Performance of Probe CIL for BPO Detection. To evaluate the activity of the CIL-based sensor for BPO detection, we conducted the gradient experiments of CIL probe with various concentrations of BPO under the optimal conditions (the optimal conditions are shown in Supporting Information). As illustrated in Fig 1c, with an increase in the concentrations of BPO, the peaks of reaction solutions exhibited a downward trend at 426 nm, and instead rise at 270 nm in UV-vis absorption spectra. Meanwhile, a new absorption peak emerged at 367 nm upon the addition of BPO. The changes of fluorescent signals for BPO response were also studied (Fig 1d). It can be seen that the fluorescence intensity of the systems gradually decreases and the fluorescence response regularly blue-shifts with the concentrations of inserted BPO increases. Photographs of probe CIL with various concentrations of BPO under day light and UV light (365 nm) were shown in Fig 2. The changes are visualized and the presence of BPO can

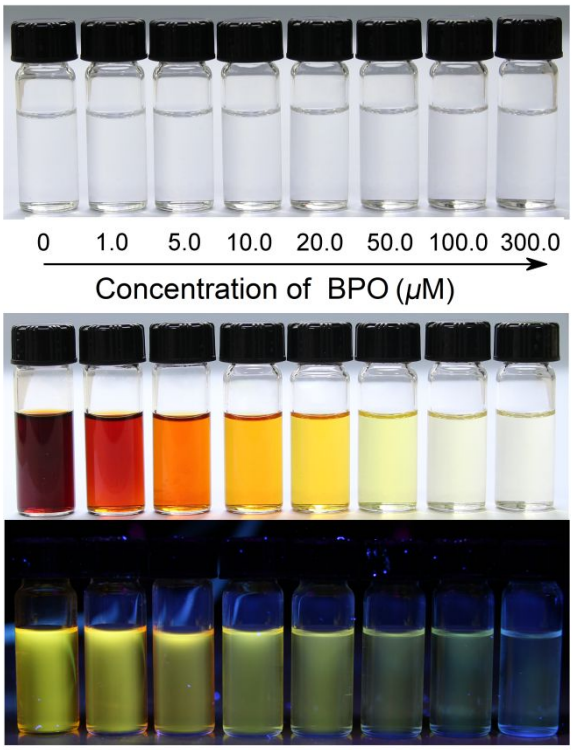


Fig 2. Photographs of various BPO concentrations in presence of 0.2 mM CIL under day light and UV light (365 nm), BPO concentrations including: 0, 1.0, 5.0, 10.0, 20.0, 50.0, 100.0 and 300.0 μM.

be direct recognized by naked eyes. These observations proved that the as-prepared CIL possesses an excellent sensitivity to BPO. The relationship between changes in fluorescence intensity ($\Delta F = F_0 - F$) and various BPO concentrations was depicted in Fig 3a. The linear correlation equation was shown as $\Delta F = 177.7C_{BPO} + 2.063$ ($R^2 = 0.995$). The detection limit toward BPO by the fluorescent strategy used is 10 nM (n = 5), which was lower than previous reported probes for BPO. The detection limits of published literature in this field were summarized in Table S1. The time-dependence kinetic measurement was also established by UV-vis spectroscopy (Fig 3b) and it further demonstrates the great sensitivity of CIL probe in BPO monitoring.

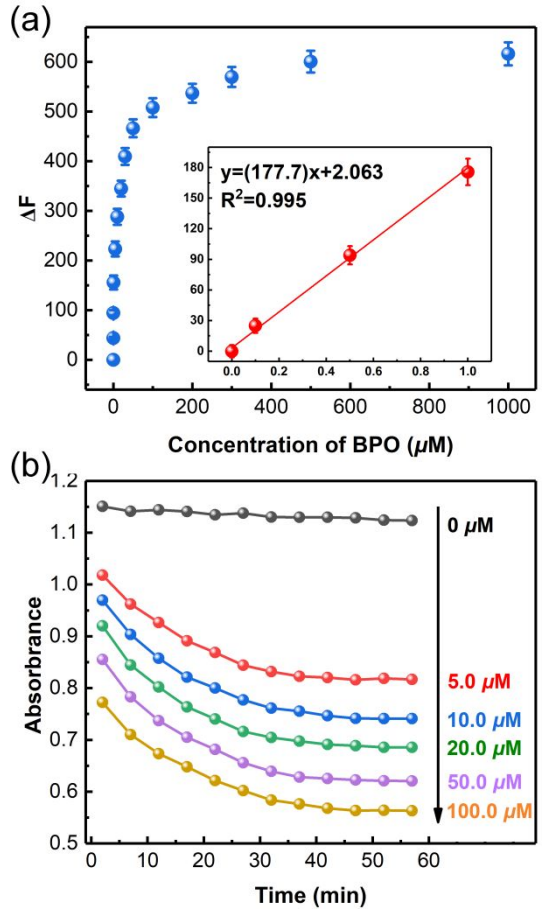


Fig 3. (a) Change trend of fluorescence intensity (ΔF) in the presence of various BPO concentrations; the inset shows the linear relationship between fluorescence intensity (ΔF) and BPO concentrations. (b) Time-dependence kinetic measurement of UV-vis response of CIL probe toward different BPO concentrations from 0 to 100.0 μM.

Specificity of CIL toward BPO. Specificity of probe is considered to be of great significance for its practical application. To confirm the specificity and selectivity of method proposed toward BPO, we examined the effects of various potential disturbances in parallel by control experiments. The results demonstrated that BPO could be identified by CIL specifically. As shown in Fig 4, under same conditions, only BPO can produce a dramatic fluorescence quenching and blue-shift behavior, whereas the other interference tested including common oxidants hardly changed in fluorescence spectra. More importantly, compared to BPO, H_2O_2 do not show these unique behaviors. This shows that the used probe can eliminate the interference of H_2O_2 in BPO detection process. To verify this, fluorescence spectra of different H_2O_2 concentrations (10 μM to 300 μM) were collected under optimum conditions. As shown in Fig S5, fluorescence quenching and blue shift were not observed with the increase of H_2O_2 concentration. To the best of our knowledge, this is the first time to eliminate the interference of H_2O_2 in fluorescent method for BPO sensing. Cumyl hydroperoxide (CHP), a substance similar to H_2O_2, also has no interference with the fluorescence detection of BPO (the structure was shown in Scheme 2). The

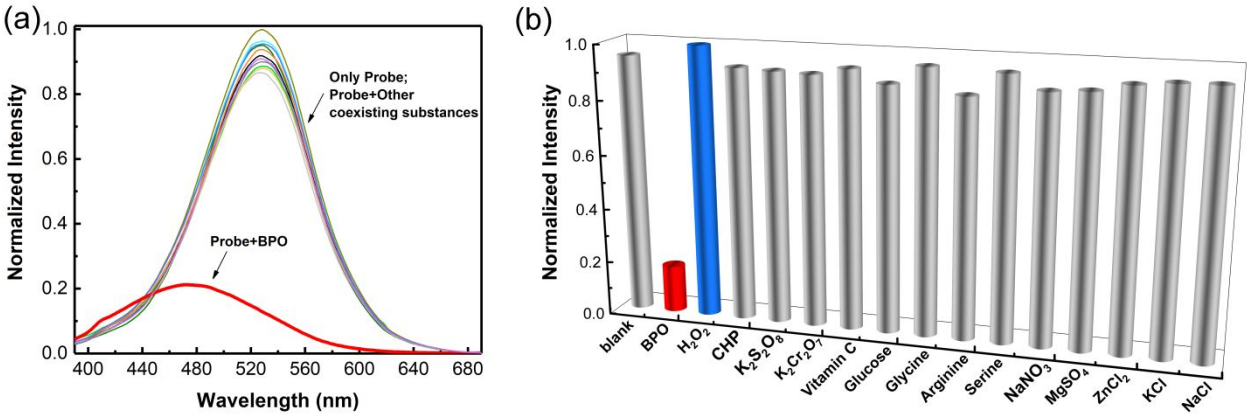


Fig 4. (a) Fluorescence emission spectra (λ_{ex} = 365 nm) of CIL probe and its mixture with various coexisting substances including 50.0 μM of BPO, CHP, $K_2S_2O_8$, $K_2Cr_2O_7$, vitamin C, glucose, glycine, arginine, serine, $NaNO_3$, $MgSO_4$, $ZnCl_2$, KCl, NaCl, and 10.0 μM of H_2O_2. (b) Fluorescence intensity of CIL probe in the presence of 10.0 μM H_2O_2, 50.0 μM BPO and other coexisting substances.

FT-IR analysis of products formed further proved the specific interaction between CIL and BPO (Fig S6, S7). The results suggested that the CIL-based sensor possesses a strong specificity and selectivity.

Mechanism Studies. To explore the possible mechanism of CIL probe for selective response with BPO, the reaction products formed were conducted to FT-IR, ^{1}H NMR and HPLC-MS analyses. In the FT-IR spectra of products of CIL with various BPO ratios (Fig S8), a new signal peak appeared at 1690 cm^{-1} with the increase of BPO. Compared with the original BPO, the peaks assigned to the C=O bond of BPO at 1781 cm^{-1} and 1756 cm^{-1} disappeared (Fig S6). This indicated that the chemical structure of BPO was broken and a new substance, benzoic acid, may be formed. To prove this, the FT-IR spectra of benzoic acid and the mixture of benzoic acid and CIL were recorded. As displayed in Fig 5, C=O group of benzoic acid was observed at 1678 cm^{-1} in pure sample and at 1690 cm^{-1} in CIL atmosphere. This is consistent with the new peak of the product formed between CIL and BPO. Moreover, the characteristic C−H vibrations of benzoic acid at 2544 cm^{-1} to 3069 cm^{-1} can be all found in the FT-IR spectrum of the product. The benzoic acid also was observed in HPLC-MS

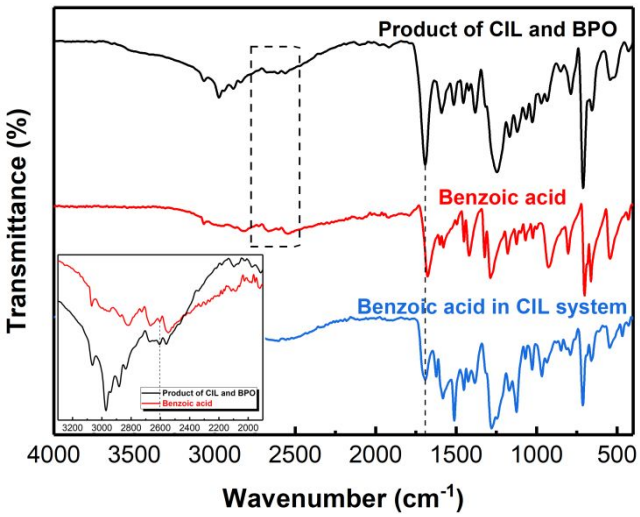


Fig 5. FT-IR spectra of benzoic acid, the mixture of benzoic acid and CIL, and the product formed after the reaction of CIL probe with BPO.

spectrum of the product at 121.0312 ([benzoic acid − H]$^-$: m/z calcd. 121.0325, found 121.0312) (Fig S9). In addition, benzoic acid was further verified as a product by NMR analysis. As shown in Fig S10, the proton peaks of benzoic acid were found in ^{1}H NMR spectrum of product at 7.35, 7.41, and 7.90 ppm. The proton of carboxyl group of benzoic acid was not observed because of the alkaline environment of CIL system. These data confirmed our conjecture.

Assays of Real Wheat Flour and Drug Samples. Many countries have resolutely banned BPO as a food additive in wheat flour, while there are still some businesses having violations to their profitableness. Therefore, the quantitative detection of BPO in real samples is of prime important for ensuring the safety of humanity and environment. To confirm the practical applicability of CIL probe for BPO, we determined the recovered BPO concentrations in real samples matrix. The results are encouraging in wheat flour and benzoyl peroxide gel (a drug containing 50 mg BPO per gram for acne). In wheat flour samples, 10.00 μM, 20.00 μM BPO were added, and 9.94 μM, 20.45 μM were found by testing, respectively. Furthermore, a lower content of BPO (5.00 μM) was tested through the same strategy and similar result could be obtained (5.06 μM was found). The great recoveries of the tests close to 100.0% were obtained, and the relative error no more than 3% (Fig S11, S12 and Table S2). For benzoyl peroxide gel sample, an obvious color change was observed upon the addition of gel into the probe solution (Fig S13, S14 and Table S2). The BPO was found from our test to be 5.03 mg in the 0.10 g gel, which was consistent with available data in the instructions of benzoyl peroxide gel commercially (Table S2). The method adopted was proved by HPLC analysis (Table S2). All results indicate that CIL probe is feasible for quantitative analysis of BPO in real samples.

Portable Detector Applies. After demonstrating that the CIL probe has an excellent performance for BPO sensing, we fabricated a portable device to realize a convenient and real-time detection. The CIL solution of appropriate concentration (1.0 mM) was poured into a pushing liquid atomizer, and its ability to identify BPO in real samples was measured. The results of the tests were showed in Fig 6. The CIL liquid sensor designed could be well atomized and distributed on the surface of wheat flour samples. The change of color and fluorescence can be easily observed with naked eyes. It is worthy to mention that the UV analyzer can be replaced by miniature and carriable ultraviolet flashlight (365 nm) purchased commercially, and the atomizer can still effectively display fluorescent signal. As an alternative device, the atomizer designed can meet the requirements of rapid and local monitoring of BPO without any specialized equipment and extra pretreat-ment. The initial results have proved that CIL-based liquid atomizer can be employed as a portable device for the detec-tion of BPO in real samples.

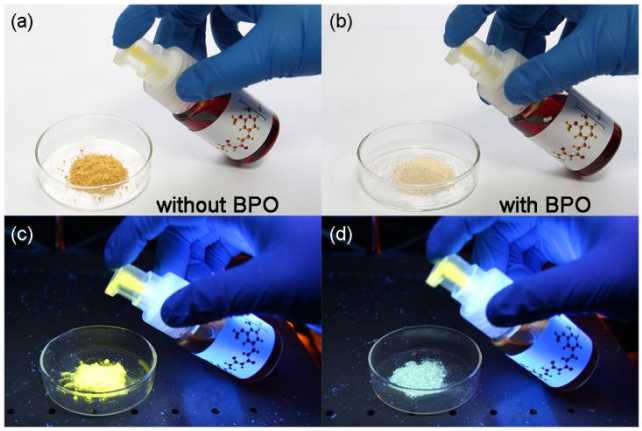


Fig 6. Photographs of wheat flour in the absence and presence of BPO after spraying and incubating for an hour using the liquid atomizer device; (a) and (c) showed the wheat flour without BPO in day light and UV light, respectively; (b) and (d) showed the wheat flour containing 500.0 μM BPO in day light and UV light, respectively.

CONCLUSIONS

In summary, a novel IL probe derived from biomass curcumim has been firstly designed and prepared. With the obvious color and prominent optical properties, the CIL can simultaneously provide colorimetric and fluorescent signals, and enable the detection limit of BPO at ultra-low level of 10 nM. The BPO triggered a unique behavior of fluorescence quench and emission peak blue-shift, whereas other interferences including H_2O_2 do not have this phenomenon. The excellent specificity and selectivity allowed the successfully detection of BPO in real samples such as wheat flour and antibacterial agent. In addition, a promising spot test device based on atomizer was fabricated, which can satisfy the demands as portable detectors. The BPO in samples could be identified conveniently and reliably by the CIL atomizer. In our work, we first achieved specific detection of BPO without the disturbance of H_2O_2 by CIL probe proposed.

ASSOCIATED CONTENT

Supporting Information

The NMR and FT-IR spectral analyses (Fig S1, S2), optimization of operation conditions (Fig S3, S4), the fluorescence spectra of various H_2O_2 concentrations (Fig S5), the FT-IR analysis of products (Fig S6–S8), HPLC-MS and ^{1}H NMR spectrum of product (Fig S9, S10), BPO detection in real samples (Fig S11–S14, and table S2). Summary of published literature (table S1).

The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through Q.-H.Z., G.-H.Z., G.-H.T. and L.Z.. L.H., G.-H.T. and W.-L.Y. designed the project. Q.-H.Z., and W.-L.Y. performed the experiments and analyzed the data. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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