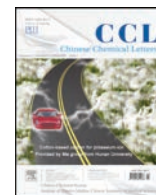




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Communication

Cyclodextrin derivatives functionalized highly sensitive chiral sensor based on organic field-effect transistor

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ARTICLE INFO

Article history:

Received 26 March 2019

Received in revised form 18 April 2019

Accepted 30 April 2019

Available online 1 May 2019

Keywords:

Chiral discrimination

OFET

Sensor

 β -Cyclodextrin derivatives

Real-time detection

Quantitative detection

ABSTRACT

Novel highly sensitive chiral organic field-effect transistors (COFET) were developed by directly assembling imidazolium 3,5-dimethylphenylcarbamoylated- β -cyclodextrin (Im⁺-Ph- β -CD) and 3,5-dimethylphenylcarbamoylated- β -CD (Ph- β -CD) respectively onto the semiconductor layer as sensing units. The Im⁺-Ph- β -CD/COFET afforded better enantioselectivity and a lowest detection concentration of 10⁻¹⁸ L/mol as well as the potentiality in quantitative analysis of commercial medicines.

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Chirality is a widespread feature in nature, and the discrimination of enantiomers has become an area of interest in chemistry and biology science as well as medical, food and pharmaceutical industries [1,2]. Organic field-effect transistor (OFET) has rapidly developed as one of the most attractive and powerful techniques for chem- and bio-sensing due to its advantages such as rapid response, high sensitivity, low cost and on-line analysis [3]. The most widely used approach to construct OFET-based sensor is modification of the gate by sensing materials, and the detection signal derives from the change of the threshold voltage or the on-state transconductance of the OFET after analytes are captured [4–7]. However, the recognition of chirality usually depends on weak intermolecular interactions such as hydrogen bonds, π - π interactions and inclusions, which is hard to generate strong electric signals by gate-inducing effect. Modification of semiconducting layer using chiral selector could transduce the interaction more directly between the enantiomers and chiral selectors to the changed conductance of the semiconductors, which could be expected to afford high sensitivity.

Herein, OFET based chiral sensors (COFETs) were fabricated by directly assembling of β -cyclodextrin (β -CD) derivatives, namely mono-6-deoxy-6-(1-allylimidazolium)-per(3,5-dimethyl)-phenylcarbamoylated- β -CD (Im⁺-Ph- β -CD) and its analog per(3,5-

dimethyl)phenylcarbamoylated- β -CD (Ph- β -CD) on the copper hexadecafluorophthalocyanine (F₁₆CuPc) semiconducting layer directly. The positively charged imidazolium moiety of Im⁺-Ph- β -CD could provide more action sites and enantioselective electrostatic interaction, which benefits the chiral recognition in addition to the inclusion complexation. Ultra-sensitive chiral discrimination was achieved with a lowest detection concentration (LDC) of 1 amol/L, arising from the high affinity constant between enantiomer and cationic CD as well as the amplification effect of the hydrogen-bonding network of Im⁺-Ph- β -CD. In addition, the potentiality for practical applications of the COFET was proved by analysis of a commercial medicine ibuprofen (Ibu).

Im⁺-Ph- β -CD was synthesized by cationization of mono-6-tosyl- β -CD with 1-allylimidazole followed by functionalization with 3,5-dimethylphenyl isocyanate. And Ph- β -CD was synthesized by directly derivating β -CD with 3,5-dimethylphenyl isocyanate. Detail synthesis procedure and characterization are shown in Supporting information (Scheme S1). The fabrication of the COFETs with a top-contact/bottom-gate architecture is shown in Supporting information (The fabrication of the COFETs) and the electrical characteristics of the OFET were measured by an electronic probe station with two Keithley 2400 sources in ambient conditions at room temperature (Fig. S1 in Supporting information).

The elemental composition of the semiconducting layer before and after CD derivatives assembly was detected by X-ray photoelectron spectroscopy (XPS). As shown in Table S1 and Fig. S2 (Supporting information), N%, F% and Cu% decreased while

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% and O% increased obviously after the modification of CD derivatives on the $F_{16}CuPc$ semiconducting layer, indicating the successful assembly of $Im^+-Ph-\beta-CD$ and $Ph-\beta-CD$ on the $F_{16}CuPc$ surface based on hydrophobic interaction, which benefits from the introduction of the hydrophobic isocyanato groups on CDs. The surface morphology of the device channel without and with CD derivatives was investigated by atomic force microscopy (AFM). As shown in Fig. S3 (Supporting information), the $F_{16}CuPc$ form a polycrystalline film with shape of fishbone. After modification with CD derivatives, the grain boundary of $F_{16}CuPc$ film is filled with CD derivatives hence reduces the roughness of the surface. The fishbone morphology of $F_{16}CuPc$ is still faintly visible for $Im^+-Ph-\beta-CD$ immobilized device while $Ph-\beta-CD$ modified device exhibits a different feature as amorphous film. This indicates the $Im^+-Ph-\beta-CD$ forms thinner film than $Ph-\beta-CD$ since its higher polarity makes the solution form wider spread on the polar surface of $F_{16}CuPc$ film in the assembly process, which is supported by the larger water contact angle (Fig. S3 in Supporting information). The higher affinity of the $Im^+-Ph-\beta-CD$ to $F_{16}CuPc$ could be ascribed to the possible dipole-dipole interaction between the positive charged imidazolium and electronegative F atom. Then, the electrical characteristics of OFET without and with CD derivatives were investigated. As shown in Fig. 1, no significant change is observed for $Ph-\beta-CD$ immobilized device. While the device with $Im^+-Ph-\beta-CD$ shows declined saturated drain current, which is consistent with the expectation that attached positive charged species lead to lower conductance in n-channel transistors due to the n-type doping effect related to the induced polarization [8,9]. That could be also supported by the reduced threshold voltage.

The chiral discrimination ability of the COFET was evaluated with four pairs of enantiomers include D-phenylalanine (D-Phe), L-phenylalanine (L-Phe), 2-chloro-D-mandelic acid (D-CA), 2-chloro-L-mandelic acid (L-CA), L-(+)-mandelic acid (L-MA), D-(-)-mandelic acid (D-MA), D-(+)-3-phenyllactic acid (D-PA), L-(-)-3-phenyllactic acid (L-PA). Aqueous solutions of enantiomers with concentration from 10^{-20} mol/L (0.01 amol/L) to 10^{-9} mol/L (1 nmol/L) were delivered alternately to the fluid cell at a flow rate of 400 μ L/min by a peristaltic pump and the time interval of each concentration was around 30 s. The solutions errors were calculated and presented in Supporting information ("Calculation of the solution error" Scheme S2 and Table S2 in Supporting information) [10]. Between each concentration, the enantiomer solution was switched to deionized water (D.I. water)

to allow the current to drop to baseline. The real-time sensing performance of the COFETs was measured at the condition of $V_G = V_{DS} = 2$ V. As shown in Fig. 2, both COFETs exhibit chiral discrimination capability to the four pairs of enantiomers. The $Im^+-Ph-\beta-CD/COFET$ shows better chiral resolution than $Ph-\beta-CD/COFET$, which suggests the positive contribution of the charged imidazolium moiety. Since all the carboxylic acids have pKa in the range of 3.0–4.0 and Phe has a pI as 5.48, all the analytes could sufficiently dissociate at the measured condition. As a result, enantioselective electrostatic interaction between the analytes and the positively charged CD could contribute to the chiral recognition in addition to the inclusion complexation to afford better resolution [11]. For $Im^+-Ph-\beta-CD/COFET$, Phe and PA could be well resolved at 0.1 amol/L while MA and CA are discriminated at 1 amol/L, which reveals the good sensing ability of as-prepared COFET and 1 amol/L can be taken as the lowest detection concentration (LDC) of the COFET. The relatively lower resolution for MA and CA with chiral carbon linked to the aromatic ring directly, could be ascribed to less flexibility of the molecule due to the short alkyl chain [11]. The possible mechanism which enables the such low LDC of the $Im^+-Ph-\beta-CD/COFET$ (0.1 amol/L) was investigated. The affinity constant (K) for D-Phe and L-Phe is calculated according to the calibration curves (Fig. S5 in Supporting information) which is $(6.43 \pm 0.32) \times 10^9$ L/mol and $(5.87 \pm 0.52) \times 10^9$ L/mol, respectively. The high affinity constants suggest the strong interaction between $Im^+-Ph-\beta-CD$ and Phe, which profits from the extended CD cavity and lead to high sensitivity. What is more, the carbonyl groups and amino groups of the $Im^+-Ph-\beta-CD$ could be expected to form H-bonding between adjacent CD molecules to form a network [12–14] (Fig. S6 in Supporting information). As a result, the inclusion energy between Phe and one CD molecule could be transferred to its neighbors and propagate in the whole sensing layer through the H-bonding network to afford signal amplification [12]. In brief, the high affinity constant and the H-bonding network guarantee the high sensitivity of the COFET. Finally, the repeatability of the COFET was evaluated. As shown in Fig. S4 (Supporting information), 0.1 amol/L and 1 amol/L Phe solutions were injected for three times respectively in succession, the current kept at stable stage respectively.

Finally, a commercial medicine ibuprofen (Ibu) was used to evaluate the sensing ability of the COFET for its practical application. As shown in Figs. 3A and B, the COFET well discriminates Ibu enantiomers at 1 amol/L and shows composition

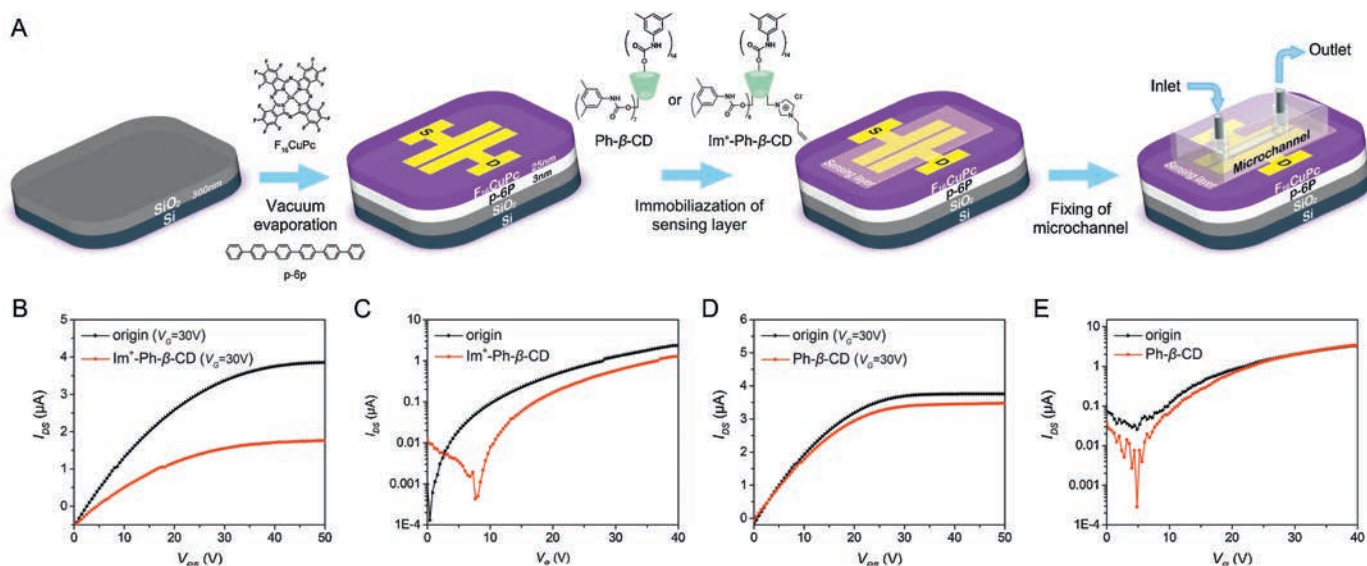


Fig. 1. (A) The architecture and fabrication process of the COFETs. The (B) output and (C) transfer curves of the OFET with $Im^+-Ph-\beta-CD$. The (D) output and (E) transfer curves of the OFET with $Ph-\beta-CD$.

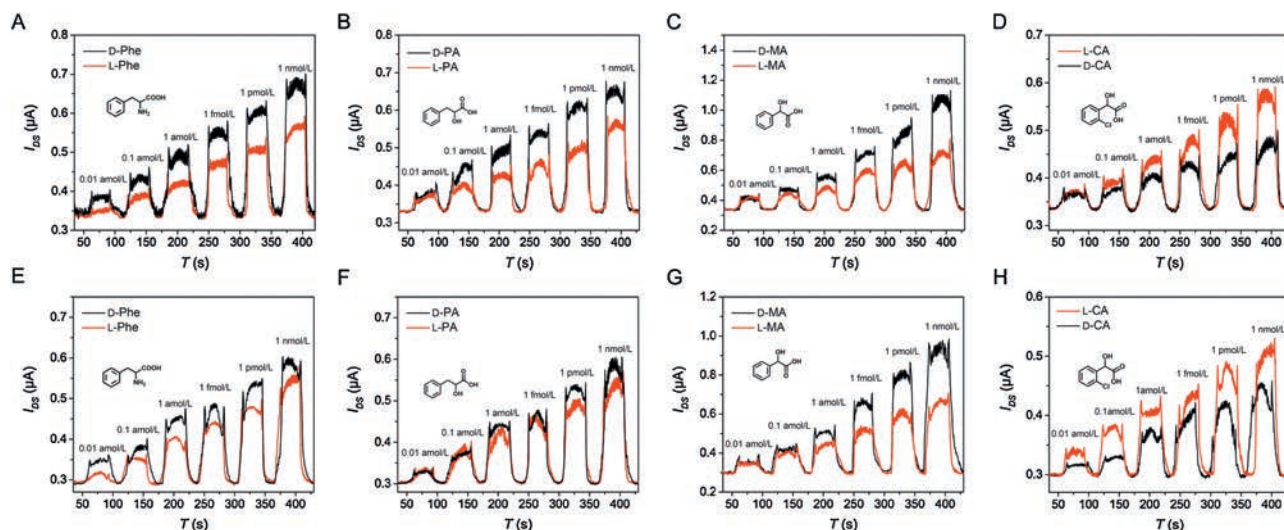


Fig. 2. The real-time sensing of the Phe (A), PA (B), MA (C) and CA (D) by $\text{Im}^+\text{-Ph-}\beta\text{-CD/COFET}$ and the real-time sensing of the Phe (E), PA (F), MA (G) and CA (H) by $\text{Ph-}\beta\text{-CD/COFET}$ from 0.01 amol/L to 1 nmol/L.

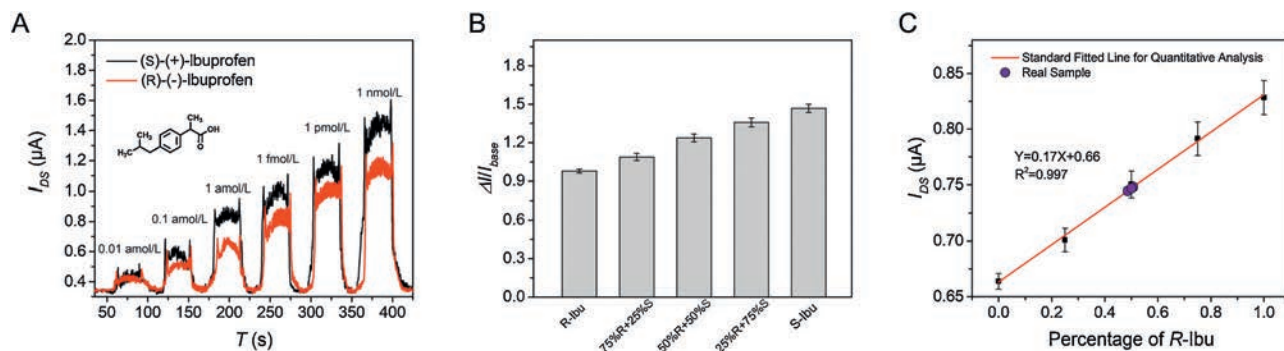


Fig. 3. The sensing response to (A) Ibu enantiomers and (B) their mixtures (total concentration is fixed at 1 amol/L). (C) Quantitative detection of ibuprofen in "Ibuprofen Sustained-release Capsules" (The error bar is obtained by the average of all stable data points except the current attenuation of five replicate test data).

dependent response to the mixture of Ibu enantiomer, which indicates its good chiral sensing ability and potentiality in quantitative analysis. A good linear relationship between current and composition of Ibu was fitted and showed in Fig. 3C. Then, a quantitation analysis of a commercial medicine "Ibuprofen Sustained-release Capsules" containing Ibu enantiomers was performed. The pure Ibu enantiomers with a melting point of 72–73 °C were obtained by triturating the main components of the capsule and washing with D.I. water for three times to remove the impurities. The composition of *R*-Ibu is determined by the COFET as 49.8% for three repeated experiments (Fig. 3C). The result is close to the HPLC analysis (49.73%) as shown in Fig. S7 (Supporting information), which proves the quantitative analysis ability and the potential for practical applications of the COFET.

In conclusion, we fabricated novel chiral sensors based on OFET by employing a positively charged $\beta\text{-CD}$ derivative ($\text{Im}^+\text{-Ph-}\beta\text{-CD}$) and its analog $\text{Ph-}\beta\text{-CD}$ as the sensing layer respectively to functionalize the F_{16}CuPc semiconductor layer. The device with $\text{Im}^+\text{-Ph-}\beta\text{-CD}$ exhibited better chiral sensing ability than that of $\text{Ph-}\beta\text{-CD}$ at low concentration, which benefits from the positive contribution of the charged imidazolium group to the discrimination of the negatively charged enantiomers. The $\text{Im}^+\text{-Ph-}\beta\text{-CD/COFET}$ showed a LDC of 1 amol/L and composition dependent response to enantiomer mixtures, which reveals its ability and

potentiality for highly sensitive quantitative enantiomeric analysis of commercial medicines.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (No. 21575100) and Tianjin Research Program of Application Foundation and Advanced Technology (Nos. 18JCZDJC37500, 17JCYBJC20500).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ccl.2019.04.074>.

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