

Communication

Ionophore-Based Potassium Selective Fluorescent Organosilica Nano-Optodes Containing Covalently Attached Solvatochromic Dyes

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Abstract: Fluorescent nanoprobe containing ionophores and solvatochromic dyes (SDs) were previously reported as an alternative to chromoionophore-based nano-optodes. However, the small-molecular SDs are prone to leakage and sequestration in complex samples. Here, we chemically attached the SDs to the surface of organosilica nanospheres through copper-catalyzed Click chemistry to prevent dye leakage. The nano-optodes remained well responsive to K⁺ even after exposure to a large amount of cation-exchange resin, which acted as a sink of the SDs. The potassium nanoprobe exhibited a dynamic range between 1 μM to 10 mM and a good selectivity thanks to valinomycin. Preliminary sensing device based on a nylon filter paper and agarose hydrogel was demonstrated. The results indicate that the covalent anchoring of SDs on nanospheres is promising for developing ionophore-based nanoprobe.

Keywords: ionophores; nanoprobe; potassium; ion-selective; fluorescence; nanosensors



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1. Introduction

Potassium ion (K⁺), a very important biological inorganic cation, can be detected with a variety of electrochemical and optical chemical sensors [1–7]. Ionophore-based ion-selective electrodes and optodes have been widely recognized because of the high selectivity, versatility, and robustness [8–13]. Recently, several research groups are interested in developing the nanoscale ion-selective optodes in the form of various nanoparticles [11,14–18]. The nano-optodes could share a similar sensing mechanism with polymer film-based bulk optodes where an increase of K⁺ concentration ([K⁺]) leads to the deprotonation of a pH indicator (H⁺ chromoionophore) in the nanospheres [19–21]. For example, the group of Bakker, Michalska, Clark, Cash, and our own have reported such nano-optodes based on different materials including Pluronic F-127, lipid covered plasticizer nanodroplets, conducting polymers, organosilicas, and quantum dots [14,15,22–29].

However, this approach is also known to suffer from a cross-response from sample pH changes. A solution to the problem was proposed by Bakker and coworkers to use solvatochromic dyes (SDs) as an alternative to the H⁺ chromoionophore [30–33]. The reported SDs included some commercial voltage-sensitive dyes, hemicyanines, and cyanines in the near infrared region (DTTC), which exhibited different absorption and fluorescence spectra in response to a change of the microenvironment of the dyes [34]. The SDs are typically charged and dissolve in water unless they are intentionally lipophilized. Water-soluble SDs could be lost due to the leakage from the nano-optodes during the measurements, especially when the sample contains species that attract the SDs through e.g., electrostatic force and hydrophobic interaction. Lipophilic SDs seem an improvement but dye leakage could still occur. For example, our experience with using the nano-optodes in cells indicated sequestration of SDs at the negatively charged cell mitochondria [30].

Here, we report K^+ nano-optodes with the SDs covalent anchored on the nanosphere surface. In this way, dye leakage was suppressed without compromising the response of the nanosensors. For the nano-optode to work, the SDs must be able to change their locations in response to the target ions. It was achieved here by attaching the SDs on the distal end of the amphiphilic poly (ethylene oxide) chains and anchored onto the organosilica nanospheres [29]. The performance of the resulting nano-optodes was investigated and the possibility of using the nano-optodes on Nylon filter paper was also demonstrated.

2. Materials and Methods

2.1. Reagents

Sodium tetrakis-[3,5-bis(trifluoromethyl)-phenyl] borate (NaTFPB), 1,3,5,7-tetramethyl-8-phenyl-4,4-difluoroboradiazaindacene (BODIPY), bis(2-ethylhexyl) sebacate (DOS), trimethoxy(propyl)silane, Pluronic F-127 (F127), and agarose (low gelling temperature) were obtained from Sigma-Aldrich. Silane (polyethylene glycol) azide (Si-PEG- N_3) was obtained from Ponsure Biological, China. Valinomycin was obtained from J&K, China. The cation exchange resin was purchased from Nanjing Herbaceous Biological Technology Company, China. The nylon film was obtained from Merk (Filter Type: 41 μ m Nylon Net, REF: NY4102500). All salts were analytical grade or higher. All solutions were prepared using deionized water (Milli-Q).

2.2. Synthesis of the Solvatochromic Dye SD

First, 136 mg of 4-(diethylamino)-2-(prop-2-yn-1-yloxy) benzaldehyde and 149 mg of 1-hexadecyl-4-methylpyridin-1-ium were dissolved in 5 mL of ethanol, and then 8 μ L of piperidine was added. The mixture was heated to 80 °C and stirred for 24 h under a nitrogen atmosphere and reflux. After cooling, the solvatochromic dye was separated by column chromatography, using dichloromethane-methanol as eluent. Yield: 22.72%, red solid. 1H NMR (400 MHz, $DMSO-d_6$) δ 8.71 (d, J = 6.7 Hz, 2H), 8.08–7.96 (m, 2H), 7.92 (s, 1H), 7.57 (d, J = 9.0 Hz, 1H), 7.17 (d, J = 16.0 Hz, 1H), 6.43 (d, J = 8.9 Hz, 1H), 6.36 (s, 1H), 4.98 (d, J = 2.0 Hz, 2H), 4.44–4.28 (m, 4H), 3.67 (s, 1H), 3.46–3.43 (m, 4H), 1.26 (s, 6H), 1.22 (s, 20H), 1.07 (d, J = 7.0 Hz, 6H), and 0.85 (s, 3H). More details about synthesis and structural characterization (1H NMR, ^{13}C NMR, and MS, Figures S2–S4) are shown in the Supplementary Materials.

2.3. Preparation of the Potassium Selective Organosilica Nano-Optodes

Firstly, organosilica nanospheres were fabricated by a modified Stöber method. 50 mg of Si-PEG- N_3 , 50 mg of F127, and 100 μ L of trimethoxy(propyl)silane were dissolved in 1 mL of methanol. Then the mixture was injected into 50 mL of deionized water, followed by injection of 100 μ L of ammonium hydroxide and stirring overnight. The resulting nanospheres were purified by dialysis for 3 days.

Secondly, the SD was linked to the nanospheres by Click reaction. A solution composed of 6 mg of $CuSO_4$, 13 mg of ascorbic acid, 0.75 mL of methanol were injected into 5 mL of organosilica nanospheres suspension, and then 1 mg of SD was added. The reaction was protected with N_2 under dark condition for overnight. After 3 days of dialysis, the excess SD dye was removed with cation exchange resin.

Finally, 0.01 mg of BODIPY, 0.064 mg of NaTFPB, and 0.32 mg of valinomycin were dissolved in 500 μ L of methanol. The mixture was added to 1 mL of nanospheres at a vortex speed of 1000 r/min, and then the solvent was blown with compressed air for 1 h to remove the methanol.

2.4. Preparation of Potassium Responsive Nylon Film

Firstly, 100 μ L of the ion-selective nanospheres were mixed with 1 mL of agarose (1% by weight) solution, and the mixture was uniformly dissolved by heating to 80 °C. The nylon film was immersed into the gel solution for a few seconds and then lifted out and placed on a confocal dish.

2.5. Instrumentation and Measurements

^1H NMR spectra and ^{13}C NMR spectra were recorded on a 400 MHz instrument from Bruker. Mass spectra were obtained on a Q-Exactive electrospray ionization mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). Fluorescence spectra measurements were measured using a fluorescence spectrometer (Fluoro Log 3, Horiba Jobin Yvon, Paris, France). TEM images were obtained on a transmission electron microscope. Confocal microscope images were taken by a $10\times$ objective on a laser scanning confocal microscope (LSM900 Zeiss, Oberkochen, Germany), using the 488 nm laser lines as excitation. The Hydrodynamic size of nanospheres was measured by a Zetasizer Nano ZSE (Malvern Instruments, Malvern, UK).

3. Results and Discussion

Figure 1 is an illustration of the composition of the nanoprobe and the sensing principle. The potassium ionophore valinomycin and the cation exchanger TFPB $^-$ were incorporated in organosilica nanospheres. The organosilica nanospheres were produced according to the classical Stöber method with F127 as the template, which produced more monodispersed nanospheres than that from small-molecule surfactants. The nanospheres were characterized with transmission electron microscopy (TEM, Figure S5) and dynamic light scattering (DSL). The average hydrodynamic diameter of the nanospheres was determined as 45.5 nm which is in good agreement of our previous study.

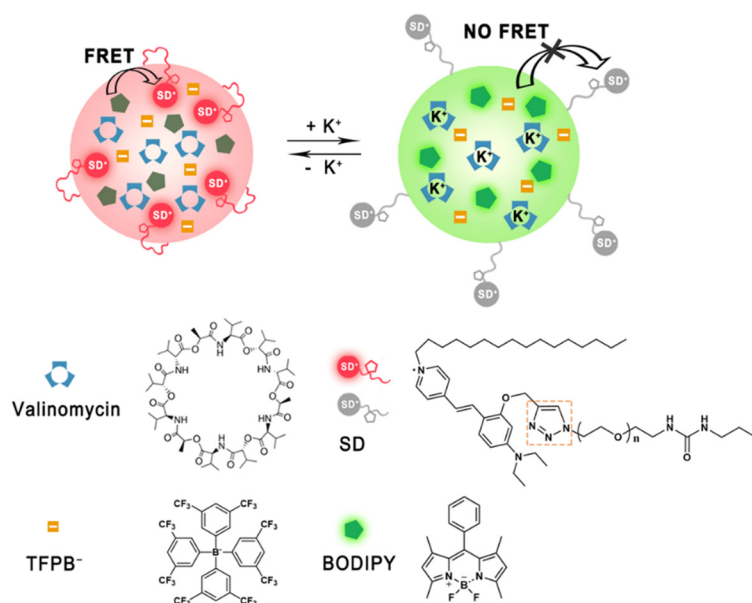


Figure 1. Schematic illustration of the K⁺ selective nano-optodes containing the ionophore valinomycin, the ion exchanger TFPB $^-$, and the covalently attached solvatochromic dye SD on the organosilica nanospheres. Fluorescence resonance energy transfer (FRET) is expected to occur between the reference dye BODIPY and SD. With increasing K⁺ concentration, FRET becomes less likely due to the increased distance between BODIPY and SD.

Poly (ethylene oxide) (PEO) chains were attached on the surface of the nanospheres. A fluorescent SD molecule bearing a propargyl group was linked to the distal end of the PEO chain through Click reaction. This covalent anchoring prevented the complete dye leakage from the nanospheres. Unreacted SDs after the Click reaction were removed with ion-exchange resin until no more adsorbed SDs were observed on the resins under a fluorescence microscope (Figure S6). The PEO chain contained around 250 units of ethylene oxide which could reach the length of roughly 75 nm long (assuming 0.3 nm for each segment). Therefore, the SD molecule could still change the location from the more hydrophobic surface to the hydrophilic aqueous phase. Similar with SDs in polymeric

nanospheres, a change of $[K^+]$ in the aqueous phase could cause a change of location of the SD as illustrated in Figure 1. When SDs move from the organic to the aqueous phase, a decrease of fluorescence intensity is expected to be similar to previous ionophore-based nano-optodes containing SDs. To provide a more accurate signal for quantitation, we also added a hydrophobic inert fluorescent dye BODIPY as a reference dye. The fluorescence emission spectrum of BODIPY and the absorption spectrum of SD exhibited pronounced overlap (Figure 2), leading to fluorescence resonance energy transfer. When the SDs move toward the aqueous phase, BODIPY and SD became farther apart, and less FRET is expected.

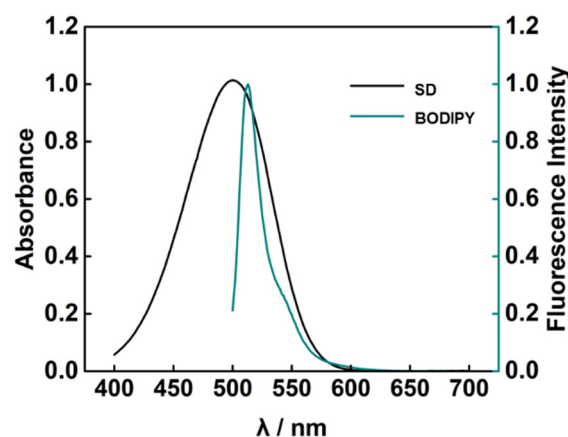


Figure 2. The overlay of the normalized fluorescence emission spectrum of BODIPY (excitation: 480 nm) and the absorption spectrum of SD.

As shown in Figure 3a, when the nanospheres were excited at 480 nm, an emission peak around 600 nm was observed corresponding to the SD. Another emission peak corresponding to BODIPY was also observed at 515 nm, bringing simplicity of signal readout with excitation at one wavelength. As $[K^+]$ in the sample increased, a gradual decrease of the emission intensity occurred. A sigmoidal response curve was obtained by the ratio of fluorescence intensity at 598 nm and the fluorescence intensity at 515 nm (Figure 3b). The response was ascribed to the change of microenvironment of SDs. Moreover, the emission of BODIPY at 598 nm was gradually restored, indicating less FRET between BODIPY and SD. However, the dyes cannot be freely dissolved because they are covalently anchored on the nanospheres. The selectivity of the nanospheres was confirmed and shown in Figure 3c, the interference of other ions including Na^+ , Mg^{2+} , and Ca^{2+} was very small up to 0.1 M. The dynamic response range of $[K^+]$ from 10^{-5} to 10^{-2} mM and the excellent selectivity rendered the nanospheres promising for analysis in biological and environmental samples.

Previous SD-based nano-optodes were shown pH-independent in polymer nanospheres which is considered advantageous over chromoionophore-based nano-optodes. The influence of pH was also investigated on the organosilica nanospheres containing SD, TFPB, and valinomycin. As shown in Figure 4, the K^+ response was not completely independent of pH. When pH changed from 5.1 to 7.1, there was less decrease of the relative decrease of fluorescence at 598 nm as indicated by I/I_0 . This implied that SD was more easily exchanged to the aqueous phase, which is still not understood. When pH went from 7.1 to 8.3, SD became more difficult to enter the aqueous phase, which could be explained by the more negative surface charge of the organosilica nanospheres as the pH became 7.1. Compared with chromoionophore-based optodes, the nanospheres reported in this work still exhibited less influence of pH on the K^+ response range.

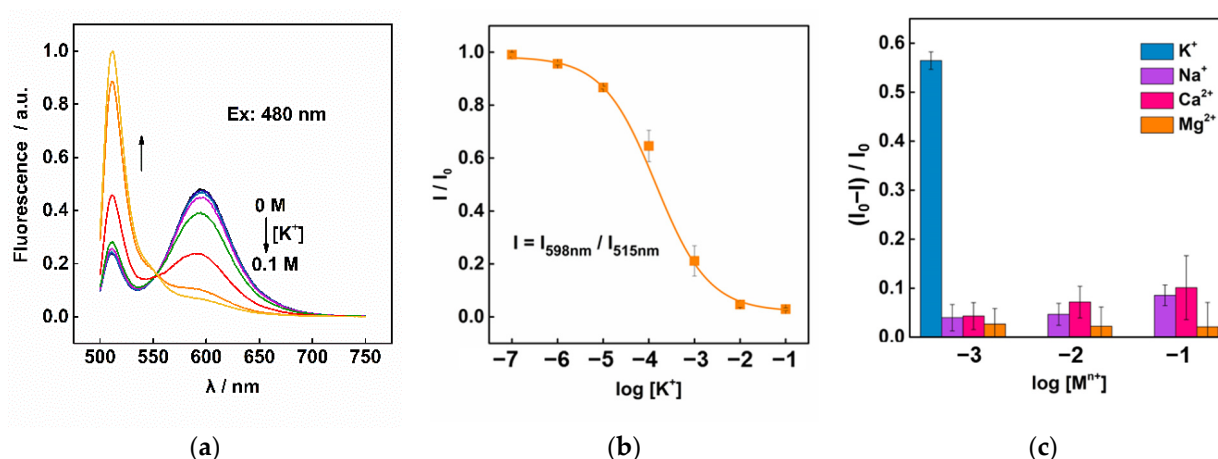


Figure 3. (a) Fluorescence emission spectra of the K⁺-selective nano-optodes excited at 480 nm with increasing K⁺ concentration as indicated; (b) fluorescence calibration curve of the K⁺-selective nano-optodes at different K⁺ concentrations; I_0 represents initial value (without K⁺) of the intensity ratio between 598 and 515 nm. (c) Selectivity of K⁺-selective nano-optodes over Na⁺, Ca²⁺, and Mg²⁺.

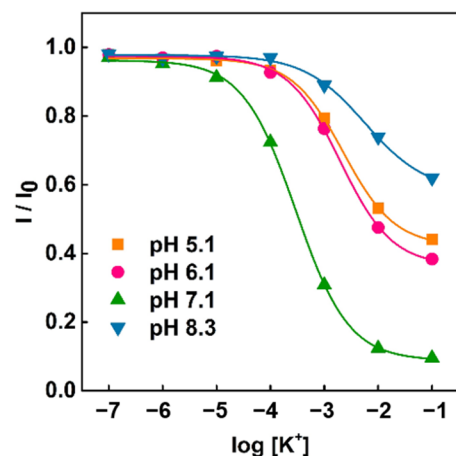


Figure 4. Fluorescence response of the K⁺-selective nano-optodes at different pH as indicated. Excitation and emission are the same as in Figure 3.

We also attempted to deposit the K⁺ selective nanospheres on nylon filter paper. As shown in previous research, paper-based sensing devices are inexpensive, portable, and user-friendly. In this work, the K⁺ selective nanospheres were first dispersed in an agarose solution (1% *w/w*) above the gelling temperature (Figure 5a). The filter paper was then dipped into the solution to absorb the particles. After cooling to room temperature, the agarose hydrogel formed, and this prevented the escape of the nanospheres from the paper. Figure 5b shows the microscopic images of the filter paper in bright-field and fluorescence mode. A layer of hydrogel was trapped in the grids of the paper where the fluorescence of the nanospheres was observed. The K⁺ response of the paper quantified from the emission of SDs is shown in Figure 5c. During the measurements, the pH of the samples was controlled with buffers at pH 7. Similar to the nanospheres in solution, increasing the [K⁺] caused a decrease of fluorescence intensity. Here, we observed that the green emission from BODIPY was less sensitive due to adsorption by the nylon filter. Therefore, only the emission intensity from the SDs was used for quantitative analysis. Because BODIPY was physically adsorbed on the organosilica nanospheres, they could be transferred to other locations such as the hydrophobic nylon surface. This again shows the importance of the covalent attachment strategy as we did to the SDs. The results also indicated that the K⁺ nanoprobe also could be used besides in aqueous suspension.

Although reversible use is achievable, the nano-optodes and paper-based device were designed to be disposable because of the low cost and ease of preparation.

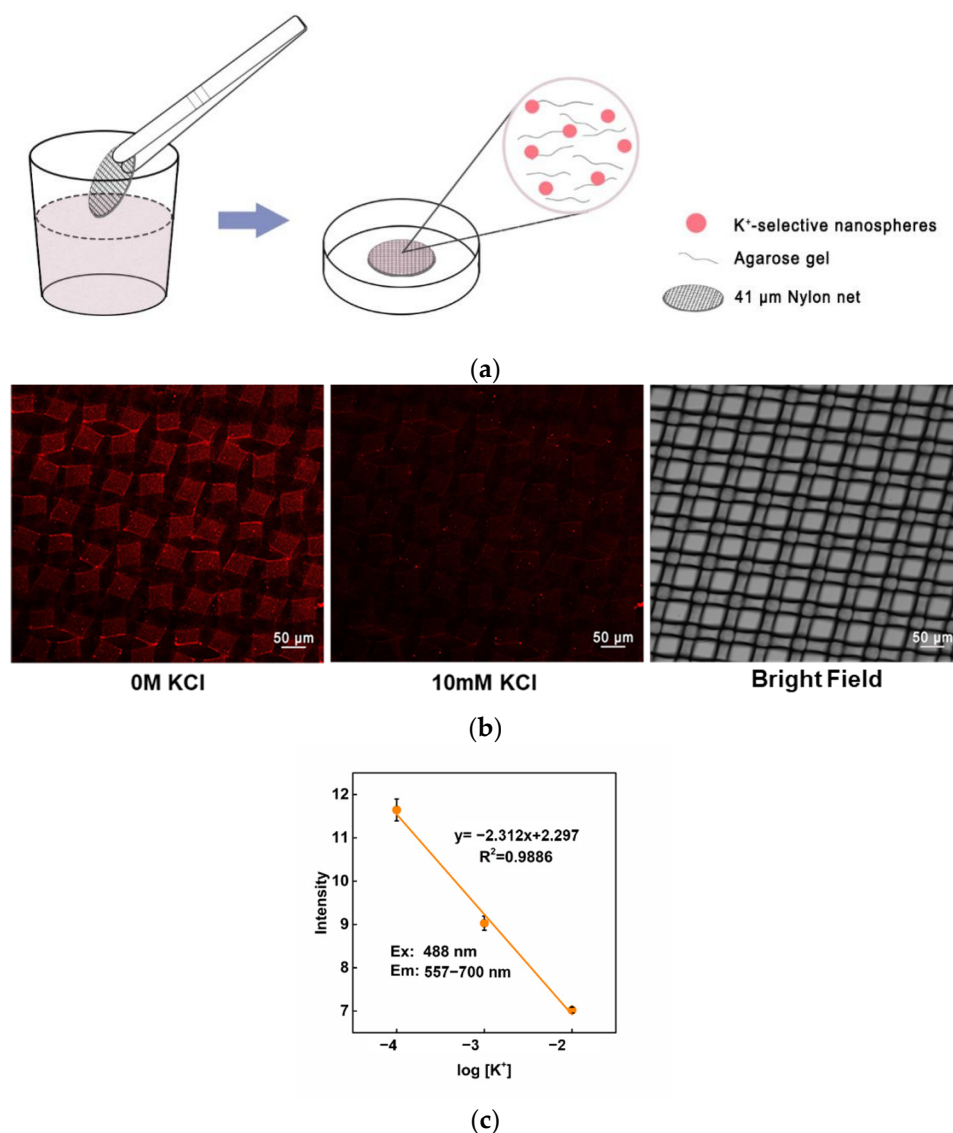


Figure 5. (a) Preparation process of a nylon filter paper containing the K⁺ nano-optodes immobilized in agarose hydrogel; (b) fluorescence confocal microscope images for the K⁺ sensing paper in fluorescence (with 0 and 10 mM KCl) and bright-field mode; (c) the K⁺ response of the paper quantified from the red emission (557 to 700 nm) intensity of SDs. Excitation: 488 nm.

4. Conclusions

To summarize, a K⁺ selective nano-optodes was presented based on organosilica nanospheres. The nanospheres contained valinomycin, the ion-exchanger TFPB, and a SD covalently linked to the surface of the nanospheres through a PEG chain. Therefore, the SDs were not able to freely dissolve into the aqueous sample solution, which is advantageous over previous nano-optodes containing SDs. Further, the organosilica nanospheres showed good selectivity to K⁺ and was deposited on nylon filter paper in an attempt to make portable sensing device. The obtained K⁺ sensing paper was successfully prepared by trapping of a layer of agarose hydrogel containing the nano-optodes. However, it was also noted that sample pH change still influences the response range of K⁺, which is not observed in on nano-optodes based on Pluronic F-127 and plasticizer. This means the matrix material is indeed important for the performance of ion-exchange based nano-optodes. To further suppress the pH interference, the organosilica matrix could be replaced with

other materials and the SDs could be covalently linked to the distal end of block copolymers such as poloxamers. Research in this direction is continued in the lab.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/chemosensors10010023/s1>, Figure S1: Synthesis of the solvatochromic dye (SD); Figure S2: ¹H NMR spectra for SD; Figure S3: ¹³C NMR spectra for SD; Figure S4: Mass Spectroscopy for SD; Figure S5: Transmission electron microscopy (TEM) and dynamic light scattering (DLS) image for the nanospheres; Figure S6: The fluorescence microscope images of cation exchange resin adsorbed different solutions.

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References

- Bakker, E.; Bühlmann, P.; Pretsch, E. Carrier-Based Ion-Selective Electrodes and Bulk Optodes. 1. General Characteristics. *Chem. Rev.* **1997**, *97*, 3083–3132. [\[CrossRef\]](#)
- Ng, R.H.; Sparks, K.M.; Statland, B.E. Colorimetric Determination of Potassium in Plasma and Serum by Reflectance Photometry with a Dry-Chemistry Reagent. *Clin. Chem.* **1992**, *38*, 1371–1372. [\[CrossRef\]](#)
- Brasuel, M.; Kopelman, R.; Miller, T.J.; Tjalkens, R.; Philbert, M.A. Fluorescent Nanosensors for Intracellular Chemical Analysis: Decyl Methacrylate Liquid Polymer Matrix and Ion-Exchange-Based Potassium PEBBLE Sensors with Real-Time Application to Viable Rat C6 Glioma Cells. *Anal. Chem.* **2001**, *73*, 2221–2228. [\[CrossRef\]](#) [\[PubMed\]](#)
- Koronczi, I.; Reichert, J.; Heinzmann, G.; Ache, H.J. Development of a submicron optochemical potassium sensor with enhanced stability due to internal reference. *Sens. Actuators B Chem.* **1998**, *51*, 188–195. [\[CrossRef\]](#)
- Kong, D.-M.; Ma, Y.-E.; Guo, J.-H.; Yang, W.; Shen, H.-X. Fluorescent Sensor for Monitoring Structural Changes of G-Quadruplexes and Detection of Potassium Ion. *Anal. Chem.* **2009**, *81*, 2678–2684. [\[CrossRef\]](#) [\[PubMed\]](#)
- Shen, Y.; Wu, S.-Y.; Rancic, V.; Aggarwal, A.; Qian, Y.; Miyashita, S.-I.; Ballanyi, K.; Campbell, R.E.; Dong, M. Genetically encoded fluorescent indicators for imaging intracellular potassium ion concentration. *Commun. Biol.* **2019**, *2*, 18. [\[CrossRef\]](#) [\[PubMed\]](#)
- Nguyen, B.T.T.; Ang, J.Q.; Toh, C.-S. Sensitive detection of potassium ion using Prussian blue nanotube sensor. *Electrochem. Commun.* **2009**, *11*, 1861–1864. [\[CrossRef\]](#)
- Mistlberger, G.; Crespo, G.A.; Bakker, E. Ionophore-Based Optical Sensors. *Annu. Rev. Anal. Chem.* **2014**, *7*, 483–512. [\[CrossRef\]](#)
- Kisiel, A.; Maksymiuk, K.; Michalska, A. Capsules as ion-selective optodes—Maximizing sensitivity of ion-selective optodes. *Sens. Actuators B Chem.* **2018**, *273*, 1730–1734. [\[CrossRef\]](#)
- Rong, G.; Kim, E.H.; Poskanzer, K.E.; Clark, H.A. A method for estimating intracellular ion concentration using optical nanosensors and ratiometric imaging. *Sci. Rep.* **2017**, *7*, 10819. [\[CrossRef\]](#)
- Ruckh, T.T.; Mehta, A.A.; Dubach, J.M.; Clark, H.A. Polymer-Free Optode Nanosensors for Dynamic, Reversible and Ratiometric Sodium Imaging in the Physiological Range. *Sci. Rep.* **2013**, *3*, 3366. [\[CrossRef\]](#)
- Kondratyeva, Y.O.; Tolstopjatova, E.G.; Kirsanov, D.O.; Mikhelson, K.N. Chronoamperometric and coulometric analysis with ionophore-based ion-selective electrodes: A modified theory and the potassium ion assay in serum samples. *Sens. Actuators B Chem.* **2020**, *310*, 127894. [\[CrossRef\]](#)
- Johnson, R.D.; Bachas, L.G. Ionophore-based ion-selective potentiometric and optical sensors. *Anal. Bioanal. Chem.* **2003**, *376*, 328–341. [\[CrossRef\]](#)
- Kłucińska, K.; Stelmach, E.; Kisiel, A.; Maksymiuk, K.; Michalska, A. Nanoparticles of Fluorescent Conjugated Polymers: Novel Ion-Selective Optodes. *Anal. Chem.* **2016**, *88*, 5644–5648. [\[CrossRef\]](#) [\[PubMed\]](#)
- Ferris, M.S.; Katageri, A.G.; Gohring, G.M.; Cash, K.J. A dual-indicator strategy for controlling the response of ionophore-based optical nanosensors. *Sens. Actuators B Chem.* **2018**, *256*, 674–681. [\[CrossRef\]](#)
- Stelmach, E.; Kłucińska, K.; Maksymiuk, K.; Michalska, A. Rational design of nanopotodes architecture—Towards multifunctional sensors. *Talanta* **2019**, *196*, 226–230. [\[CrossRef\]](#)

17. Dailey, A.L.; Greer, M.D.; Sodha, T.Z.; Jewell, M.P.; Kalin, T.A.; Cash, K.J. LipiSensors: Exploiting Lipid Nanoemulsions to Fabricate Ionophore-Based Nanosensors. *Biosensors* **2020**, *10*, 120. [[CrossRef](#)] [[PubMed](#)]
18. Ozaydin-Ince, G.; Dubach, J.M.; Gleason, K.K.; Clark, H.A. Microworm optode sensors limit particle diffusion to enable in vivo measurements. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 2656. [[CrossRef](#)] [[PubMed](#)]
19. Krause, C.; Werner, T.; Huber, C.; Wolfbeis, O.S. Emulsion-Based Fluorosensors for Potassium Featuring Improved Stability and Signal Change. *Anal. Chem.* **1999**, *71*, 5304–5308. [[CrossRef](#)] [[PubMed](#)]
20. Bakker, E.; Lerchi, M.; Rosatzin, T.; Rusterholz, B.; Simon, W. Synthesis and characterization of neutral hydrogen ion-selective chromoionophores for use in bulk optodes. *Anal. Chim. Acta* **1993**, *278*, 211–225. [[CrossRef](#)]
21. Lee, C.H.; Folz, J.; Zhang, W.; Jo, J.; Tan, J.W.Y.; Wang, X.; Kopelman, R. Ion-Selective Nanosensor for Photoacoustic and Fluorescence Imaging of Potassium. *Anal. Chem.* **2017**, *89*, 7943–7949. [[CrossRef](#)]
22. Kisiel, A.; Baniak, B.; Maksymiuk, K.; Michalska, A. Ion-selective reversing aggregation-caused quenching—Maximizing optodes signal stability. *Talanta* **2020**, *220*, 121358. [[CrossRef](#)] [[PubMed](#)]
23. Wang, R.; Du, X.; Ma, X.; Zhai, J.; Xie, X. Ionophore-based pH independent detection of ions utilizing aggregation-induced effects. *Analyst* **2020**, *145*, 3846–3850. [[CrossRef](#)]
24. Di, W.; Tan, X.; Calderon, I.A.C.; Reilly, A.E.N.; Niedre, M.; Clark, H.A. Real-time particle-by-particle detection of erythrocyte-camouflaged microsensor with extended circulation time in the bloodstream. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 3509. [[CrossRef](#)] [[PubMed](#)]
25. Balaconis, M.K.; Clark, H.A. Biodegradable Optode-Based Nanosensors for in Vivo Monitoring. *Anal. Chem.* **2012**, *84*, 5787–5793. [[CrossRef](#)] [[PubMed](#)]
26. Ruckh, T.T.; Skipwith, C.G.; Chang, W.; Senko, A.W.; Bulovic, V.; Anikeeva, P.O.; Clark, H.A. Ion-Switchable Quantum Dot Förster Resonance Energy Transfer Rates in Ratiometric Potassium Sensors. *ACS Nano* **2016**, *10*, 4020–4030. [[CrossRef](#)]
27. Sahari, A.; Ruckh, T.T.; Hutchings, R.; Clark, H.A. Development of an Optical Nanosensor Incorporating a pH-Sensitive Quencher Dye for Potassium Imaging. *Anal. Chem.* **2015**, *87*, 10684–10687. [[CrossRef](#)] [[PubMed](#)]
28. Jewell, M.P.; Greer, M.D.; Dailey, A.L.; Cash, K.J. Triplet-Triplet Annihilation Upconversion Based Nanosensors for Fluorescence Detection of Potassium. *ACS Sens.* **2020**, *5*, 474–480. [[CrossRef](#)]
29. Du, X.; Yang, L.; Hu, W.; Wang, R.; Zhai, J.; Xie, X. A Plasticizer-Free Miniaturized Optical Ion Sensing Platform with Ionophores and Silicon-Based Particles. *Anal. Chem.* **2018**, *90*, 5818–5824. [[CrossRef](#)]
30. Xie, X.; Gutiérrez, A.; Trofimov, V.; Szilagyi, I.; Soldati, T.; Bakker, E. Charged Solvatochromic Dyes as Signal Transducers in pH Independent Fluorescent and Colorimetric Ion Selective Nanosensors. *Anal. Chem.* **2015**, *87*, 9954–9959. [[CrossRef](#)]
31. Xie, X.; Szilagyi, I.; Zhai, J.; Wang, L.; Bakker, E. Ion-Selective Optical Nanosensors Based on Solvatochromic Dyes of Different Lipophilicity: From Bulk Partitioning to Interfacial Accumulation. *ACS Sens.* **2016**, *1*, 516–520. [[CrossRef](#)] [[PubMed](#)]
32. Wang, L.; Xie, X.; Zhai, J.; Bakker, E. Reversible pH-independent optical potassium sensor with lipophilic solvatochromic dye transducer on surface modified microporous nylon. *Chem. Commun.* **2016**, *52*, 14254–14257. [[CrossRef](#)] [[PubMed](#)]
33. Wang, L.; Bakker, E. A tunable detection range of ion-selective nano-optodes by controlling solvatochromic dye transducer lipophilicity. *Chem. Commun.* **2019**, *55*, 12539–12542. [[CrossRef](#)] [[PubMed](#)]
34. Klymchenko, A.S. Solvatochromic and Fluorogenic Dyes as Environment-Sensitive Probes: Design and Biological Applications. *Acc. Chem. Res.* **2017**, *50*, 366–375. [[CrossRef](#)] [[PubMed](#)]