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TRENDS

Renovating the chromoionophores and detection modes in carrier-based ion-selective optical sensors

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Abstract Ion-selective optical sensing is an important branch of analytical and bioanalytical chemistry. Conventional ion-selective optodes are based on H^+ chromoionophores. These sensors are known to be pH dependent and usually operated in a passive mode. In view of the applications in complex real samples, the sensors must exhibit not only excellent chemical selectivity but also the ability to eliminate the optical background interference such as autofluorescence and light scattering. In this article, recent advances to renovate the chromoionophores and detection modes to overcome the pH cross-response and to eliminate the background optical interference are summarized. Topics include sensors based on solvatochromic dyes, alternative chromoionophores, photoswitchable sensors, upconverting nanoparticles, luminescence decay time, and others.

Keywords Ionophore · Solvatochromic dyes · Spiropyran · Photoswitching · Upconverting · Luminescence decay time

Introduction

Carrier-based ion-selective optodes are initially recognized as the counterpart of ion-selective electrodes (ISEs), which is well-known for the quantification of small inorganic ions, including alkali and alkaline earth metal ions, transition metal ions, and various anions [1]. Compared with ISEs, optical sensors do not require the cumbersome reference electrodes and thus can be more easily miniaturized. Ion-selective optodes have gained increasing interests in recent years owing to their potential use in ultrasmall spaces, such as the interior of a cell [2–6]. In addition, compared with other conventional analytical instruments, including ion chromatography, atomic absorption (emission) spectroscopy, and electrophoresis, ion-selective optodes are relatively inexpensive and require much less or even no sample pretreatment (i.e., suitable for in situ measurements).

Ion carriers (also called ionophores) used in ion-selective optodes are capable of reversibly binding ions in a highly selective way [7]. However, the complexation reaction does not directly result in an optical signal change. Signal transducers are thus required for carrier-based ion-selective optical sensors. The classical signal transducer is known as H^+ chromoionophore, which is basically a highly lipophilic pH indicator [8–12]. The fundamental and applied aspects for ion-selective bulk optodes and miniaturized optodes based on H^+ chromoionophores have been extensively studied over the past few decades [1, 13–15]. However, applications in complex real samples such as body fluid and cells are still limited. The main difficulties are rooted in the signal transducing H^+ chromoionophores, which render the sensor pH dependent. In addition, the sensors are conventionally interrogated in passive modes, by measuring the UV-visible absorption or fluorescence intensities.

The pH of real complex samples can change with time and be sometimes unpredictable. Real samples can also be turbid, colored (even fluorescent), which renders simple intensity-based methods difficult to apply. In view of applications in real complex samples, it is challenging to overcome the drawbacks of conventional ion-selective optodes containing H^+ chromoionophores. During the past few decades, innovative

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researches have appeared worldwide aiming to tackle the problems, and remarkable progresses have been achieved. This article highlights recent advances to renovate the chromoionophores and detection modes of ion-selective optodes to render the sensors one step closer to be successfully applied in real complex samples. Future challenges and research trends will be pointed out along with the discussion.

Overcoming the pH cross-response for better chemical selectivity

Ion-selective optodes containing solvatochromic dyes

Because the H^+ chromoionophores are pH sensitive, ion-selective optodes are known to exhibit different sensor responses depending on the sample pH. The origin of the pH cross-response is the H^+ chromoionophores. Therefore, one attractive approach is to replace the H^+ chromoionophores with other pH-insensitive signal transducers. Solvatochromic dyes (SDs), also called polarity-sensitive dyes, provide one such opportunity. SDs are compounds well-known for their solvatochromic effect, exhibiting different absorption/emission spectra (and hence, color) depending on solvent polarity [16–19]. Some compounds have been developed into fluorescent probes to visualize cell membrane voltage and were coined voltage-sensitive dyes [20, 21].

Wolfbeis and co-workers first reported on hydrogel-based ion-selective sensors containing SDs [22–26]. A comparison between the sensing mechanisms of the two varieties of ion-selective optical nanosensors is shown in Fig. 1. Classic ion-selective optodes contain a H^+ chromoionophore (Ind), an ion exchanger (R^-), and an ionophore of choice (L). The sensor response is dictated by the ion transfer equilibrium. At a fixed pH, an increase in the analyte (M^{n+}) concentration (strictly, activity) will result in a decrease in the hydrogen ion concentration in the nanospheres and vice versa. The fraction of the protonated form of the H^+ chromoionophore ($HInd^+$) depends, therefore, on both the level of the target ion and sample pH. In contrast, the SD-based ion-selective nanosensors contain similar components except that the H^+ chromoionophore is replaced with SD. A change in the analyte concentration in the aqueous phase will result in the repartition SD. The sensor response is pH independent if the SDs do not undergo acid-base reactions within a certain pH range.

Hydrogel sensing films have been reported for ions including K^+, NH_4^+, NO_3^-, and Cl^-. Lipophilic droplets containing ionophore, ion exchanger, and SDs were trapped inside hydrogels. The overall sizes of the droplets were around 1 μm in diameter. The calibrations at physiological pH ranges showed only small deviations. The reported K^+ sensor containing valinomycin as the K^+ carrier exhibited a detection window from 0.1 to 50 mM and response time <3 min. The response range could potentially be adjusted by changing the droplet size and hydrophilicity of the dyes while the response time could also be shortened by reducing film thickness and the droplet diameter. Anion-selective sensors [23, 25] functioned on the co-extraction principle. In this case, cationic SDs were used instead of anionic SDs. In the pH range of 4.5 to 9.0, the fluorescence intensity decreases by around 3.5 %, which can be attributed to changes in the partitioning coefficient of the dye in the hydrogel/plasticizer system and, possibly, changing hydration of the hydrogel.

Based on the same sensing principle [27], developed ammonium-selective sensing films. The sensor contained nonactin as the ionophore for ammonium and an anionic SD cyanophenyl-doddecyl ether. The sensor responses were pH independent from pH 6 to 8. However, the sensors were merely about 2 times more selective for ammonium over potassium ion.

Recently, the use of SDs in carrier-based ion-selective optical sensors was revisited by Bakker and co-workers at the nanoscale [28–30]. Nanosensors for Na^+, K^+, and Ca^{2+} were successfully demonstrated. These nanosensors were composed of nanospheres (also known as nanoemulsions) prepared by solvent displacement [31]. Typically, the nanosensors exhibited average diameter from 50 to 100 nm with narrow size distributions, which dramatically increased the surface to volume ratio [21, 22]. As a result, the sensor response was found to be much faster (<1 s). The sensor responses were found to be nearly the same in nonbuffered water, 10 mM HCl, and 10 mM NaOH.

Other strategies: ion-selective chromoionophores, the exhaustive sensing mode and photonic crystals

Besides replacing the H^+ chromoionophores with SDs, a few other strategies have been proposed. As shown in Fig. 2, covalent linking the ionophore to a chromophore has led to chromoionophores selective to various ions. Binding to the recognition moieties often causes an optical signal change from the chromophores due to photo-induced electron transfer, intramolecular charge transfer and other mechanisms. If the chromoionophores are water soluble, they can be directly used in aqueous samples. These compounds are also known as synthetic ion indicators such as fluo-3 and sodium green. Although they have been characterized often in organic solvent such as acetonitrile (a [32] and b [33] in Fig. 2), hydrophobic chromoionophores can be embedded in lipophilic polymer films or nanospheres. Suzuki and co-workers reported on pH-independent fluorescent chemosensor for highly selective lithium ion sensing based on a chromoionophore (c in Fig. 2) containing tetramethyl-14-crown-4 moiety for lithium ion recognition and a coumarin moiety as the chromophore [34]. The sensor showed no pH cross-response in a wide range from pH 3 to 10. Recently, Lacour and co-workers

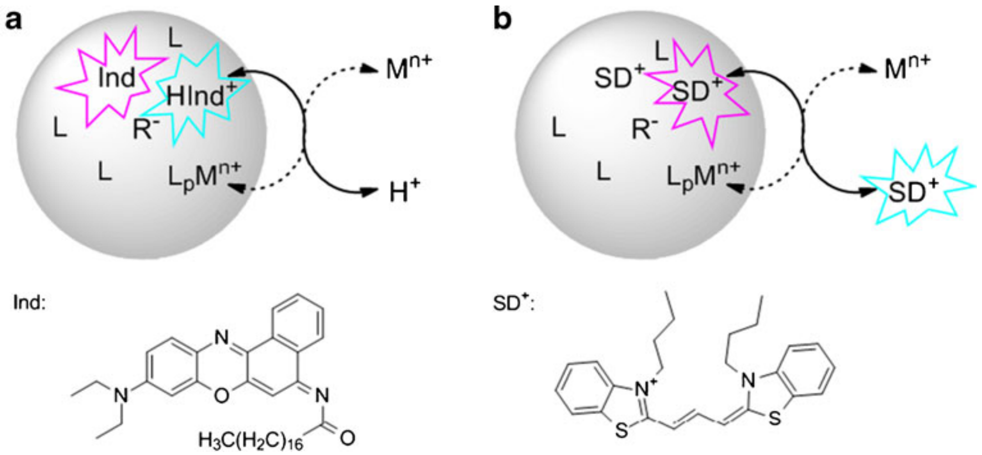


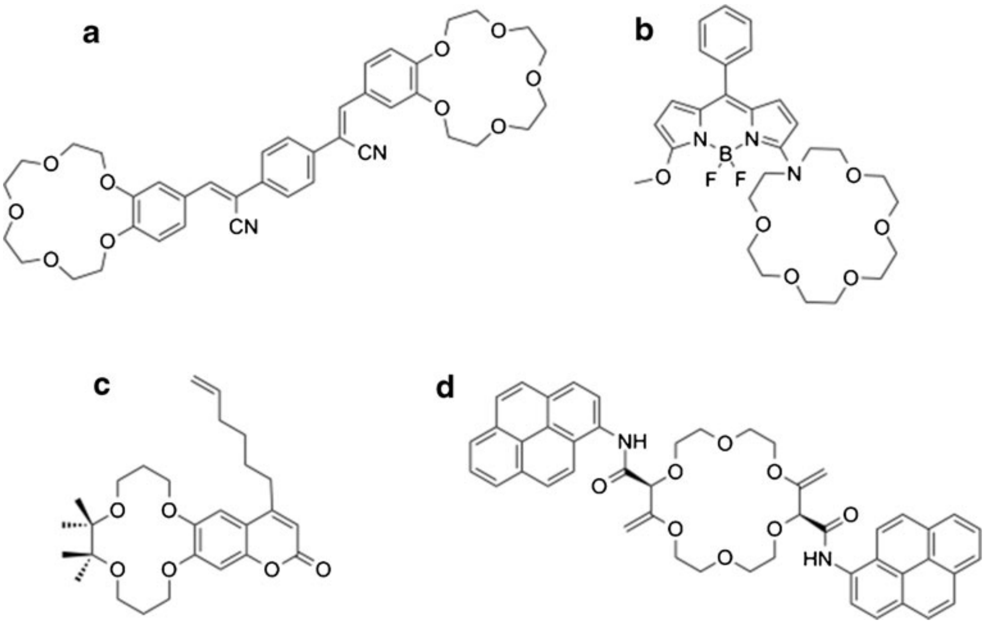
Fig. 1 A comparison of the signal transducing mechanisms between chromoionophore-based ion-selective nanosensors (**a**) and SD-based ion-selective nanosensors (**b**), where L is the ionophore, R^- is the ion exchanger, L_pM^{n+} is the complex formed between L and target ion M^{n+}, SD^+ is the solvatochromic dye, Ind and $HInd^+$ are the deprotonated and protonated chromoionophore, respectively. The purple and blue colors represent different absorption or fluorescence spectra. An example for the chemical structures of the chromoionophore and SD is shown

reported on pyrene modified polyether macrocycles (e.g., compound d in Fig. 2) for pH independent potassium ion sensing [35]. The chromoionophores were embedded in nanoemulsions and the pH independence was demonstrated between pH 4 and 10. There are a large number of synthetic ion-selective chromophores and an exhaustive summary is not possible in this article. Optodes containing these hydrophobic chromoionophores will require the use of ion-exchanger so that the target ions can be exchanged into the hydrophobic sensing phase. This, however, will lead to another reference ion, the concentration (activity) of which should be kept constant.

Bakker and co-workers have investigated the exhaustive sensing mode where all the analytes are consumed by the sensor during the detection step [36, 37]. In a limited pH range from non-buffered water (pH roughly 5.6) to pH 7.9, the signal readout is only dependent on the analyte concentration. However, since the exhaustive mode brings a dramatic alteration to the sample, it can be too aggressive in some cases where the analyte concentration is better left unchanged (e.g., intracellular measurements).

Photonic crystals have been lately applied in ion sensors as well [38–42]. If the matrix swells or shrinks, the diffracted wavelength from the crystals will be shifted. Asher and co-workers reported on a polymerized crystalline colloidal array containing covalently attached 8-hydroxyquinoline groups [39]. This material was able to bind with metal cations such as Cu^{2+}, Co^{2+}, Ni^{2+}, and Zn^{2+}. At low metal ion

Fig. 2 Examples of pH independent ion-selective chromoionophores suitable for use in polymeric optodes and nanosensors with selectivity to K^+ (**a**), (**b**), (**d**), and Li^+ (**c**)



concentrations (<1 μM), a blue shift in the diffracted light was observed whereas at high concentrations, a red shift was observed. To improve the chemical selectivity, the same group introduced 18-crown-6 ether into the polymerized colloidal array and found the material highly selective to Pb^{2+} [40]. Saito et al. copolymerized 4-vinylbenzo-18-crown-6 into periodically ordered porous gels for the selective detection of K^+ ions on similar principles [42]. Although the authors did not mention the pH interference, the sensors should be quite pH independent since there are no protonatable groups in 18-crown-6 ether. Recently, Hirsch and co-workers reported on a method for selective optical sensing and imaging of potassium ions using a sandwich assembly composed of layers of photonic crystals and an ion-selective membrane [38]. The poly(vinyl chloride) (PVC) membrane contained valinomycin to ensure excellent selectivity for K^+. This membrane was placed between the sample and the photonic crystals, allowing selective penetration of K^+ ions into the detection layer. The sensor responded to K^+ in the range from 0.1 to 100 mM, and since valinomycin is not pH sensitive, the sensor is expected to be pH independent as well.

Selectively retrieving the optical signal to overcome background interference

The selectivity of ion-selective optodes is generally understood as the ability to accurately quantify the target ions in the presence of the interfering ions. However, every optical measurement is confronted with the question of how to selectively retrieve the optical signal of interest. For complex real samples such as waste waters, cells, and body fluids, conventional intensity-based methods can become difficult to apply because of high autofluorescence and light scattering from the sample. To allow sensor application under such circumstances, researchers have been studying ion sensors that can either work in conventional or other interrogation modes.

Photoswitchable ion-selective optodes

Perhaps less well-known in the field of chemical sensors, detecting fluorescence signals selectively from individual emitter of interest has been a long-standing goal in the field of fluorescence microscopy. A few well-understood approaches have been proposed and successfully applied in bioimaging. Optical lock-in detection (OLID) images the correlation coefficient between the total fluorescence emission and an external reference signal from the photoswitchable fluorescent target over several cycles of dual-wavelength-driven optical switching [43, 44]. Synchronously amplified fluorescence image recovery (SAFIRe) images the amplitude of the fluorescence modulation resulting from modulating a secondary light source, which depopulates long-lived dark states of the fluorescent probe [45, 46]. Out-of-phase imaging after optical modulation (OPIOM) exploits the kinetic signature of a photoswitching fluorescent probe and use phase-sensitive detection to increase selectively and quantitatively its contrast [47, 48].

The most important premise to apply these methods in the area of chemical sensing is the participation of photoswitchable compounds. A photoswitchable sensor works in an active mode, that is, it can be switched on and off at defined times, allowing one to modulate the sensor signal and, consequently, correct for a non-modulated background signal. There have been a few research groups interested in photoswitchable optical sensors for ions. Byrne et al. have successfully attached spiropyran to polymethacrylic acid (PMMA) surface [49]. Irradiation with UV light converted the spiropyran into the merocyanine form, which was demonstrated to bind with Co^{2+}. The complexation shifted the absorbance of the active site and the color changed from purple to pink. With similar materials, reversible, photo-reversible binding and detection of H^+ ions was reported by the same group. Suzuki and co-workers reported on photo-reversible Pb^{2+}-complexation with a synthetic copolymer composed of N-isopropyl acrylamide and spiropyran acrylate [50]. The selectivity, however, still needs confirmation for chemical sensing purposes. Locklin and co-workers proposed a methacrylate-based spiropyran-containing copolymer as a colorimetric sensor to identify multiple metal ions in the concentration range from 1 μM to 100 mM [51, 52]. To summarize, the selectivity of these photoswitchable sensors was quite poor. The photoactived ring-opened merocyanine forms clearly lack high specificity to a certain target ion.

Recently, ionophores have been introduced into photoswitchable ion-selective optical sensors to drastically improve the chemical selectivity. Carrier-based photoswitchable ion sensors usually contain a photoswitchable compounds such as spiropyran, an ion-exchanger, and an ionophore of choice [53]. Spiropyran can be reversibly switched between two forms by UV and visible light [54]. The pKa value of the ring-opened form (ca. 8.6 in plasticized PVC membrane) is much higher than the ring-closed form (ca. 2.3 in plasticized PVC membrane) [55–57]. Taking advantage of the light-induced basicity change of spiropyran, Xie et al. reported on photodynamic optical sensors for Cl^- (Fig. 3), Na^+, and Ca^{2+} [58–61]. Figure 3 illustrates the principle for the chloride-selective photodynamic sensor. The sensor can be switched on by UV light (ca. 365 nm), where the mc form of the spiropyran started to function as a H^+ chromoionophore. Illumination with visible light is able to switch the sensor off. The sensor exhibited tunable response range to Cl^- and relatively fast switching kinetics (ca. 3 min) upon illumination with a low power LED. The group of Chumbimuni-Torres has reported visible light activated Ca^{2+} sensor with calcium ionophore and spiropyran attached to a polymer backbone [62]. Visible light is in principle more compatible with biological samples than UV light, which makes this

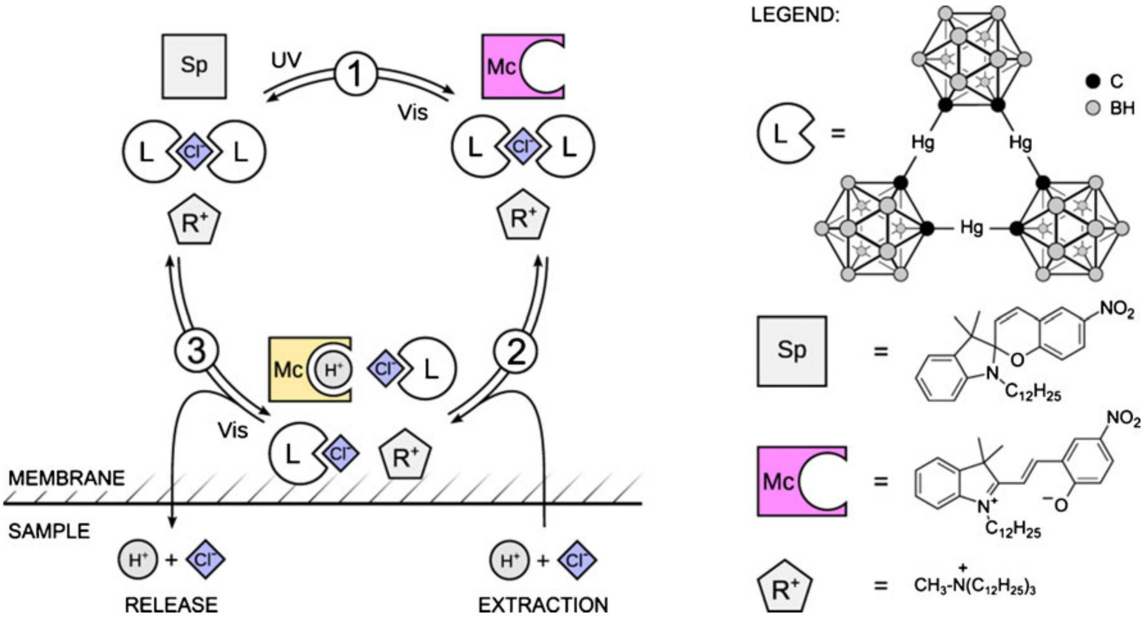


Fig. 3 Sensing mechanism of a photoswitchable chloride ion-selective optode and chemical structures of the active compounds. Reproduced from reference [58]. Copyright: American Chemical Society

work very attractive. However, the lower detection limit of 500 µM was not yet satisfactory. In addition, the activation time of ca. 35 min also needs to be shortened. Mistlberger et al. have reported on a photodynamic optical sensor for buffer capacity and pH based on hydrogel-incorporated spiropyran [63]. To apply the technique in real samples, the level of the reference ion must be defined and monitored (or fixed), since it still functions on the basis of ion-exchange.

Spiropyrans have been the most popular photoswitchable dyes used in the field so far. However, the photostability of spiropyran is not good enough. This will cause deterioration in repeatability and calibrations in the sensor signal. The spontaneous back reaction of spiropyran also makes it difficult to maintain the sensor in the ON state without the presence of light. Current photoswitchable ion sensors with spiropyran exhibit an ON-OFF switching cycle around several minutes [64–66], which will lead to a rather long sampling time for the techniques mentioned above, such as OPIOM and OLID. For these reasons, searching for other photoswitchable compounds with fast switching kinetics is very important for future development. Chumbimuni-Torres and co-workers showed that modification on the merocyanine with electron donating groups shortened the equilibrium time to the order of minutes [64]. Recently, the same group also reported on a carrier-based ion sensor containing a metastable photoacid, which was discovered by the group of Liao [67, 68]. Figure 4 shows the chemical structure and the visible light-induced photo-isomerization reaction. The equilibrium time for the sensor, however, was still around 10 min. In addition to the photoswitches mentioned above, there are a large number of photoswitchable compounds belonging to the other families, including azobenzenes, dithienylethenes, and fulgide. The applications of these photoswitchable compounds in ion-selective optodes are still to be exploited.

Upconverting nanoparticles for optical ion sensing

The use of near-infrared (NIR) excitation light (650 −1000 nm) represents another promising solution to eliminate background optical inference. NIR light can minimize the photo-damage while maximizing the penetration depth in biological samples. An excellent signal-to-noise ratio along with improved detection sensitivity can be achieved because of the lack of auto-fluorescence from biological materials. Upconverting nanomaterials exhibit unique properties, such as the emission at visible and NIR wavelengths, when excited with NIR laser sources, high photostability, and no blinking. For these reasons, upconverting nanoparticles have received enormous attention in designing various sensors and labels [69–73]. Carrier-based ion-selective optodes based on upconverting nanoparticles have been reported by Qin and co-workers [74]. By embedding upconverting nanorods into classic plasticized-PVC sensing films containing H^+ chromoionophore, ion exchanger, and ionophore, the authors successfully prepared NIR-excitable sensing films for pH and a range of metal ions [74, 75]. As shown in Fig. 5, the K^+ sensor exhibited a response range from 10 µM to 100 mM. Direct measurements of K^+ concentration in diluted blood samples were demonstrated. However, the relative signal change was small and the sensor showed a response time around 10 min.

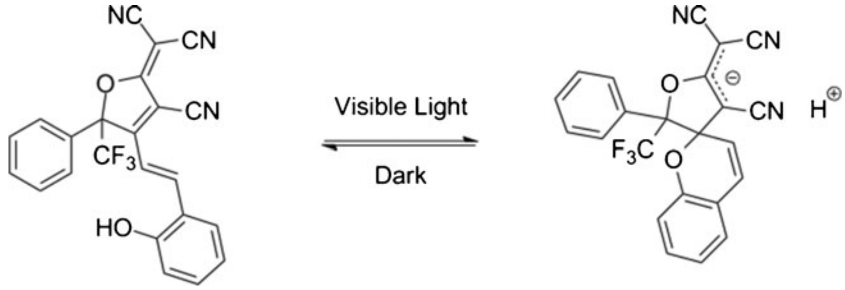


Fig. 4 Chemical structure and visible light induced photo-isomerization reaction of trifluoromethyl-phenyl-tricyano-furan (CF_3PhTCF) carbanion

The same group also reported Pb^{2+} selective sensing films based on similar principle [76]. Lead ions gave sensor responses in the concentration range from 1 μM to 10 mM at pH 5.

The role of the nanorods was to convert the NIR excitation light to green and red light that acted as excitation light for the H^+ chromoionophore. In principle, since there are two parts of emission light (greed and red) from the upconverting nanoparticles, one of them can serve as the internal reference. The authors used H^+ chromoionophores derived from Nile blue, which exhibited broad absorption spectra and low quantum yield. Perhaps an improved version can be achieved by choosing brighter dyes with narrow absorption bands that overlap with one of the emission bands from the upconverting nanoparticles.

Ion-selective optodes measuring luminescence decay time

Luminescence decay time measurement has the advantage of minimizing the effect of photon scattering in thick layers of sample. The application of this technique in carrier-based ion-selective optodes is so far quite limited. Earlier, Werner and co-workers reported on luminescence decay time based determination of potassium ions using a ruthenium(II) complex as proton donor [77]. The ruthenium(II) complex exhibited relatively long luminescence lifetimes (ca. 1 μs) and thus was a good choice as the donor of the energy transfer. At pH 8.7, the working function ranged from 1 to 100 mM KCl. The fluorescence lifetimes of synthetic fluorescent organic dyes are typically at nanosecond scale, requiring more advanced instrumentations to evaluate sensors containing these compounds

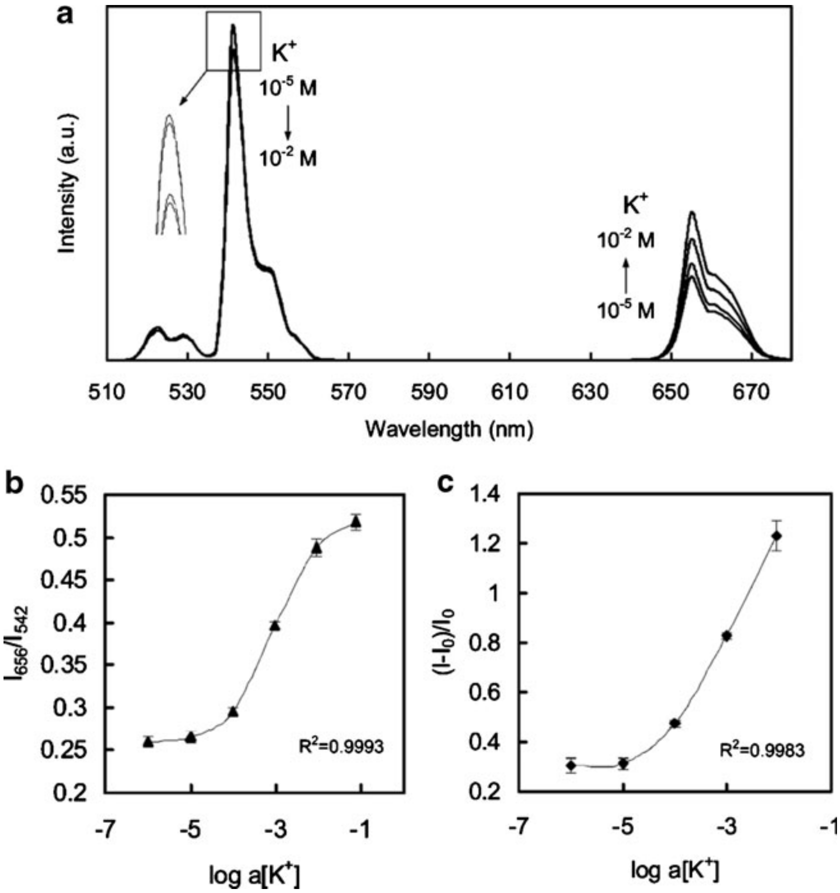


Fig. 5 **a** Upconversion luminescence spectra of the upconverting nanorod-based membrane with BME-44 toward potassium from 10^{-5} to 10^{-2} M at pH 7.4 upon excitation at 980 nm. **b** Response curve of the K^+ selective membrane by the intensity ratio of peak 656 nm to peak 542 nm. **c** Response curve of the K^+ selective membrane by monitoring the luminescent intensity at 656 nm. I_0 is the emission intensity of the membrane in a 10 mM pH 7.4 Tris-HCl buffer solution only. R^2 represents the correlation coefficients of linear fitting of each curve within the concentration range from 10^{-4} to 10^{-2} M. Reproduced from reference [75]. Copyright: American Chemical Society

[78]. A potential problem is, however, that both the complex and the pH-sensitive probe were not lipophilic enough. This could lead to dye leakage and signal deterioration over time. Lyophilized transition metal ion complexes should help prevent leaching of the dyes. The lack of pH indicators of sufficiently long excitation wavelength and excited-state lifetimes were the limiting factors for the development of appropriate decay time-based optodes. Recent advances in NIR pH probes have provided promising candidates for the luminescence decay time interrogation mode [32, 33, 79–81].

Outlook

Both the chemical selectivity and optical selectivity have to be met in order to apply carrier-based ion-selective optodes in complex real samples. This article summarized recent development to improve the chemical selectivity and overcome background optical interferences. However, many studies are proof-of-concept only and require further improvements.

The sensor response of ion-selective optodes containing SDs depends on the SDs between the aqueous and organic sensing phases. For application as in vitro assay, dye leakage and related dilution effect may not seem relevant if appropriate sample pretreatment and sensor calibrations are performed. For instance, the free potassium levels in diluted human blood plasma were successfully determined [29]. For other applications, such as intracellular experiments, or to fabricate reusable film-type sensor, dye leakage will be very problematic. Further work should try to overcome the dilution effect. Modification on the chemical structures of the SDs to decrease their hydrophilicity may be one solution. Lyophilized charged SDs may be confined to the interfacial region but will not leave the nanospheres. In addition, covalently attaching the SDs on the surface of the nanospheres will allow the dye to partition between the two phases but not leave the nanosensor as well. Instead of using freely dispersed nanospheres, nanospheres can be entrapped in hydrogels to make a reusable sensor. However, the dye leakage problem should be solved to avoid signal drifting.

To obtain the desired selectivity, sensitivity, and response range for chromoionophores that directly respond to ions (not H^+) is challenging. Most of the researches are based on rational design and trial-and-error process, which is fairly laborious. Perhaps computational modeling and high-content screening can facilitate the discovery of more chromoionophores and water-soluble fluorescent ion indicators.

The concepts of OLID, OPIOM, and SAFIRe can be applied on photoswitchable ion-selective optodes to evaluate their potentials to eliminate background optical interference. Meanwhile, the photoswitching kinetics should be further adjusted to match the optimal resonance conditions. Other photoswitches such as azobenzene and dithienylethenes may be able to meet the criteria. Miniaturized photoswitchable ion-selective optodes also deserve some attention. After miniaturization, the sensors could become a versatile platform for bioanalysis and bioimaging. The microsensors or nanosensors could potentially be prepared by incorporating the photoswitchable compounds, ionophores, and ion exchanger (if necessary) into organic/polymeric microspheres/nanospheres.

Nanosensors incorporating unconverting nanoparticles could serve as powerful bioimaging tools. They might exhibit extremely higher photostability and selectivity compared with synthetic fluorescent ion indicators. The nanosensors could potentially be prepared by coating the hydrophobic upconverting nanoparticles with ionophores and chromoionophores. Luminescence decay time measurement could benefit from the use of lyophilized donor molecules that exhibit long excited state lifetimes, with NIR chromoionophores as energy acceptor. Long excited state life time could also reduce the instrumental requirements and thus reduce the cost the sensors.

Overall, the field is full of life and elasticity with many aspects to be looked into. Some tasks may be very challenging and require step by step investigation. After all, "Rome was not built in one day."

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