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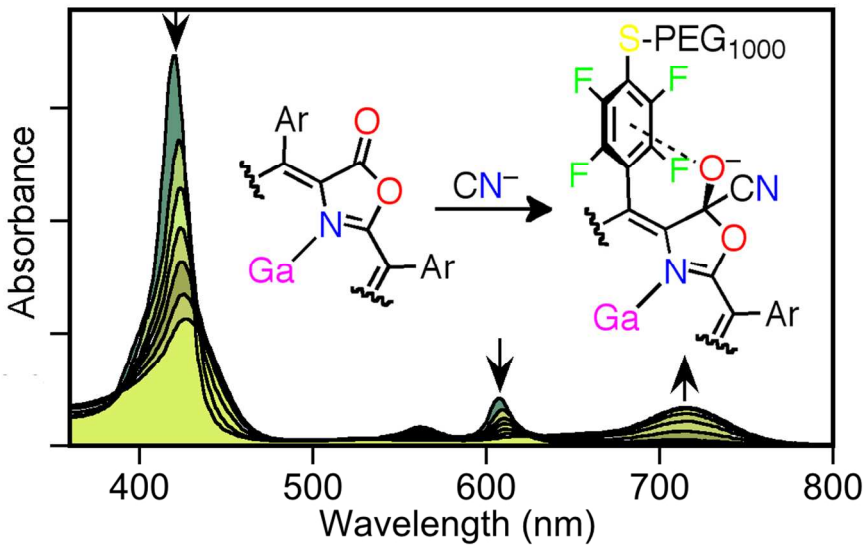

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ARTICLE

PEGylated *meso*-arylporpholactone metal complexes as optical cyanide sensors in water‡

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The colorimetric cyanide sensing ability of free base porpholactone, a pyrrole-modified porphyrin in which a porphyrin β,β'-double bond was replaced by a lactone functionality, and its zinc(II), platinum(II), and gallium(III) complexes in aqueous solution are reported. Water-solubility of the parent *meso*-pentafluorophenyl-derivatized porphyrinoids was assured by PEGylation of the *p*-aryl position using a nucleophilic aromatic substitution reaction with thiol-terminated PEG chain. A central metal-dependent sensing mechanism was revealed: While the CN^- adds to the zinc(II) complex as an axial ligand, resulting in a minor response in its UV-vis spectrum, it undergoes a nucleophilic addition to the lactone moiety in the platinum(II) and gallium(III) complexes, leading to a much more prominent optical response. Nonetheless, these chemosensors are less sensitive than many other sensors reported previously, with detection limits at pH 7 for the zinc, gallium, and platinum complexes of 2 mM (50 ppm), 240 μM (6 ppm), and 4 mM (100 ppm), respectively. The gallium(III) complex is weakly fluorescent (ϕ = 0.8%) and cyanide addition leads to fluorescence intensity quenching; the cyanide adduct responds with a fluorescence switch-on response but the signal is weak ($\phi < 10^{-2}$%). Lastly, we report on the fabrication of a unique optical cyanide-sensing membrane. The PEGylated gallium-complex was incorporated into a Nafion® membrane (on a PTFE carrier film). It was shown to be stable over extended periods of time and exhibiting a reversible and selective response within minutes to cyanide, with a 5 mM (130 ppm) detection limit. This largely fundamental study on the ability to utilize the once rare but now readily available class of pyrrole-modified porphyrins as chemosensors highlights the multiple principle ways this chromophore platform can be modified and utilized.

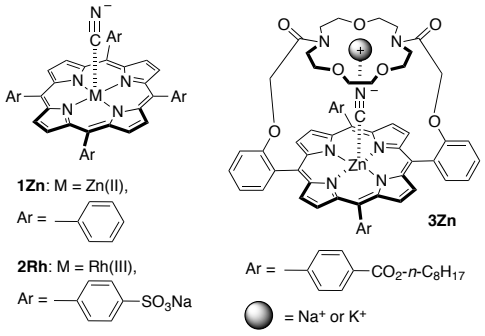
Introduction

The high toxicity of cyanide (CN^-), combined with its wide-spread technical use, urge the development of sensing methods for this anion.[1] As little as 0.5-3.5 mg cyanide per kg of body weight are lethal to humans.[1, 2] Cyanide inhibits cellular respiration. The primary toxic effect of cyanide lies in its ability to strongly bind to iron in heme proteins, whereby the crucial target in the mammalian body is cytochrome *c* oxidase.

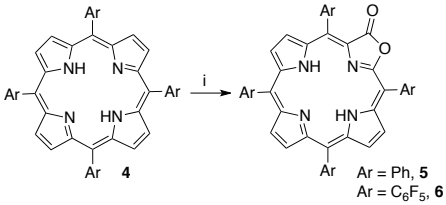
Cyanides (typically in the form of cyanogenic glycosides) are widespread in nature. They occur in certain seeds and fruit stones, such as those of apple, mango, peach, and bitter almonds, and in cassava, bamboo shoots, and linseed.[1, 2] Large quantities of cyanides are used in industry, e.g., in the synthesis of plastics, inks, fertilizers, nylon, fishing, tanning, gold mining, for the case hardening of steel, and in metal electroplating.[1, 2] Its wide-spread use raises the risk for accidental or intentional release into the water stream. The WHO recommended limit for cyanide in drinking water is 0.07 mg/L.[2]

Optical chemosensors hold much appeal for the simple and rapid chemoselective detection of many analytes,[3, 4] including cyanide. The current state of the art of colorimetric and fluorometric cyanide chemosensing methods was recently reviewed.[1] Some of the detection methods rely on hydrogen bonding interactions but they frequently suffer from poor selectivity with respect to other anions.[5-8] Reaction-based sensors (or non-reversible chemidosimeters) take advantage of the nucleophilicity of cyanide toward electron-poor carbonyl groups (or derivatives) attached to a chromophore,[5-15] the strong affinity of cyanide for metal ions,[16-20] the ability of cyanide to form Lewis acid-base pairs with triarylboranes,[21] or the ring-opening of a pyrylium moiety. The resulting changes of the optical spectra or luminescence lifetimes upon cyanide addition were tracked.[1, 18] Even though real life cyanide detection is, in most cases, expected to take place in water, most sensors reported to date require organic solvents or a mixture of an organic solvent with some water.[1, 6, 8-10, 13, 21] Only a few sensors were reported to operate in a purely aqueous system.[16, 17, 19, 20]

For their strong colors, fluorescence, electrochemical activity, ability to coordinate to a variety of metals, and chemical stability, porphyrins and many other porphyrinoids are well suited for use in sensing applications.[22-27] Metalloporphyrins can act as cyanide sensors because of the intrinsic affinity of cyanide for some metals coordinated to the porphyrin, such as zinc, rhodium, copper, silver and gold, thus exchanging or adding axial ligands.[28-33] In this fashion, [*meso*-tetraphenylporphyrinato]zinc(II) (**1Zn**),[29, 33] [*meso*-tetrakis(4-carboxyphenyl)porphyrinato]copper(II),[30] or [*meso*-tetrakis(4-sulfonatophenyl)porphyrinato]rhodium(III) (**2Rh**)[28] were used for the optical detection of cyanide (Figure 1). One refined approach utilized a two-point recognition of sodium or potassium cyanide by zinc porphyrin crown ether conjugate **3Zn**.[31, 32] However, the coordination of the cyanide to the central metal generally elicits only modest changes to the optical spectra of the metalloporphyrins, diminishing their practicality as sensors (see also below).[28-33]



Porpholactones **5** are derived from porphyrins **4** by replacement of a β,β'-double bond with a lactone functionality; in effect, a pyrrole moiety was exchanged for an oxazolone.[26, 34-37] Though known for some time,[34, 35] they have only more recently become readily available along two complementary routes: The one-step Ru-catalyzed direct oxidation of a porphyrin,[38] or a two-step route involving the OsO_4-mediated dihydroxylation of a porphyrin, followed by MnO_4^--oxidation of the intermediate dihydroxychlorin (Scheme 1).[26, 37, 39, 40] Both pathways produce the porpholactones **5** and **6** in good yields.



Scheme 1. Formation of tetraarylporpholactone **5** and **6** by oxidation of the corresponding porphyrins **4**. *Reaction Conditions:* (i) for R = Ph:[26, 37, 41] 1. OsO_4, pyridine, $CHCl_3$, r.t., up to 7 d; 2. H_2S, followed by column chromatography; 3. Cetyltrimethylammonium permanganate (CTAP), CH_2Cl_2, r.t., 12 h, followed by column chromatography. (ii) For R = C_6F_5:[40] 1. OsO_4, pyridine, $CHCl_3$, r.t., 24 h, then removal of ~50% solvent by rotary evaporation; 2. Addition of a saturated MeOH/H_2O (1:1) solution of $NaHSO_3$ to the reaction mixture, r.t., up to 2 d, followed by column chromatography; 3. CTAP, CH_2Cl_2, r.t., ~3 h, followed by column chromatography.

The introduction of the external lactone functionality into the chromophore influences its electronic properties.[35, 37] The lactone functionality can also serve as a synthetic handle toward the generation of other porphyrinoids.[27, 37, 42, 43] Most important in the current context, the lactone functionality at the periphery of the macrocycle is electronically strongly coupled to the chromophore. This renders porpholactones to be excellent sensor platforms: The lactone moiety serves as the key functionality in the use of **6Pt**, and related derivatives, as high pH indicators.[26, 44] At pH values above 11.5, hydroxide attacks the lactone carbonyl group, forming a cyclic orthoester anion. This sp^2-to-sp^3 conversion of the lactone β-carbon induces a ~100 nm red-shift of the optical spectrum. Interestingly, the presence of the lactone moiety also indirectly influences the sensing ability of the chromophore as the [porpholactonato]platinum(II) complex **6Pt** proved to be a more effective oxygen-sensing dye in pressure-sensing paints than the corresponding porphyrin platinum complex.[45-47] We have recently also demonstrated that the porpholactone chromophore can be modulated by conversion to a thionolactone.[27] The hypochlorite-selective conversion of the non-fluorescent thionolactone to the fluorescent lactone forms the basis for the use of thionoporpholactones as fluorescence-based chemodosimeters for hypochlorite.[27]

Herein we report the evaluation of a number of metalloporpholactone derivatives as colorimetric and fluorimetric cyanide sensors, whereby we directly compare the effectiveness of cyanide sensing by coordination to a central metal (in the case of the Zn(II) complexes) or by nucleophilic attack on the lactone carbonyl group (in the free base and Pt(II) and Ga(III)Cl complexes). Importantly, the particular *meso*-pentafluorophenyl-substituted porpholactones utilized are readily susceptible to conversion to novel water-soluble derivatives. Thus, we report on the selective and sensitive detection of cyanide in pure water. Lastly, we report on the incorporation of the sensitive [porphyrinato]gallium(III) chloride-based sensor dye into a Nafion® membrane, resulting in the formation of chemically robust optical cyanide sensor membranes.

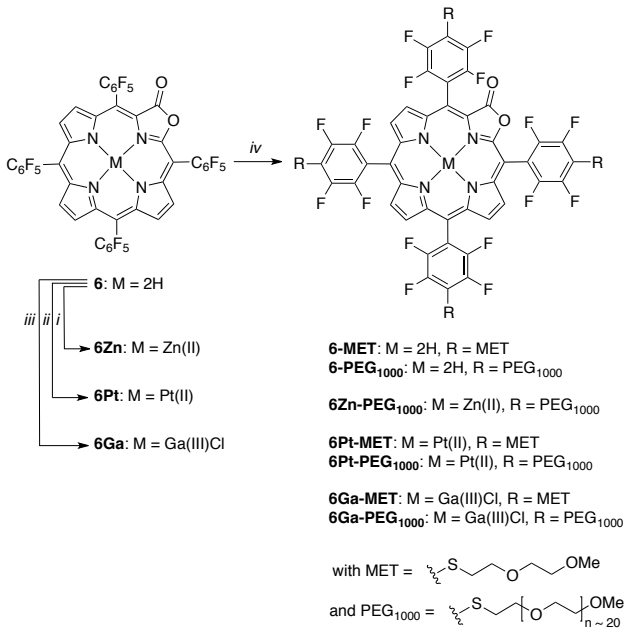
Results and Discussion

Syntheses of Metalloporpholactones 6M

The metalloporpholactones, known **6Zn**, **6Pt**[26, 36, 44] and novel derivative **6Ga**, were synthesized by metalation of free base *meso*-tetrakis(pentafluorophenyl)porpholactone **6** using standard reaction conditions (in case of **6Ga**, microwave heating) (Scheme 2).[48-50] The novel gallium(III) complex showed all the expected spectroscopic and analytical properties (see ESI). It was prepared as the square pyramidal complex carrying an axial chloride ligand, thus forming an overall neutral complex.

Synthesis of PEGylated Metalloporpholactones 6M-MET/6M-PEG$_{1000}$

meso-Pentafluorophenyl groups are susceptible to a nucleophilic aromatic substitution of the *p*-F atom with soft nucleophiles, such as sulfides. This reaction was frequently utilized to functionalize porphyrins.[51-57] We have also shown that *meso*-pentafluorophenyl-substituted oxazolochlorins are susceptible to this reaction, allowing the preparation of water-soluble derivatives when using thiol-terminated PEG chains as nucleophiles.[58] As expected, the related *meso*-pentafluorophenyl-substituted metalloporpholactones **6M** are also susceptible to this reaction. Thus, reaction of **6M** with at least a 4-fold molar excess of 2-(2-methoxyethoxy)ethanethiol (MET-H) under basic conditions (33% NEt_3 in DMF) provided **6M-MET** in excellent yields (Scheme 2).



Scheme 2. Formation of metalloporpholactones **6M** by insertion of metal ions into free base lactone **6** and formation of the PEGylated derivatives. *Reaction Conditions:* (i) $Zn(OAc)_2$/MeOH, $CHCl_3$, reflux; (ii) $Pt(acac)_2$, PhCN, reflux; (iii) $GaCl_3$, $NaOAc{\cdot}3H_2O$, CH_3CO_2H, MW; (iv) H-MET or H-PEG$_{1000}$, DMF, NEt_3 (2:1), reflux.

The clean and diagnostic ^{1}H NMR spectra of these compounds confirmed the presence of four short MET chains. However, full water-solubility could not be achieved with the short chains. We therefore reacted **6M** with a longer thiol-terminated PEG of average molecular weight of 1000 amu, PEG$_{1000}$. However, the molecular weight heterogeneity of the longer PEG chains made the characterization of the resulting less homogenous products more difficult. ESI-MS allowed only the detection of peak clusters around a mass that suggested tetra-substitution had taken place and the ^{1}H NMR of the compounds was dominated by the large number of methylene protons. On the other hand, the products **6M-PEG$_{1000}$** proved to be freely water-soluble. They also possessed optical spectra that were comparable to those of the parent compounds in organic solvents (see below). In the sensing experiments described in the following, we use only the PEG$_{1000}$ derivatives in purely aqueous solutions (or aqueous phosphate buffers).

Optical Properties of 6M and their PEGylated Derivatives

As described previously, the UV-vis spectra of free base porpholactones in organic solvents are porphyrin-like, and those of their metal complexes possess characteristics of metallochlorins.[35, 37] The introduction of the thiol PEG chains to the *meso*-aryl groups of the porpholactones affects their optical spectra only to a minor degree: The spectra do not change their characteristic shapes but blue-shift their absorption peak maxima a few nm. The compounds are subject to larger, but overall still small, solvochromic shifts. Taken together, the high-energy bands in the UV-vis spectrum of **6-PEG$_{1000}$** in water (λ_{max} values at 417, 514, 552, 589, and 643 nm; Figure 1A) are up to 11 nm bathochromically shifted compared to the corresponding bands of the parent compound **6** in CH_2Cl_2 (λ_{max} values at 406, 508, 542, 590, and 644 nm);[35] of note is that the longest wavelength transition is essentially unchanged. The metallochlorin-like spectra of the PEGylated platinum(II) complexes are, except for smaller shifts, likewise as previously described for the platinum porpholactone complexes, respectively (Figures 1B).[36] The spectra of the novel gallium complexed are also as expected,[48-50] and resemble those of the zinc complex (*cf.* Figure 1C and Figure 2A), that itself is as described previously.[36]

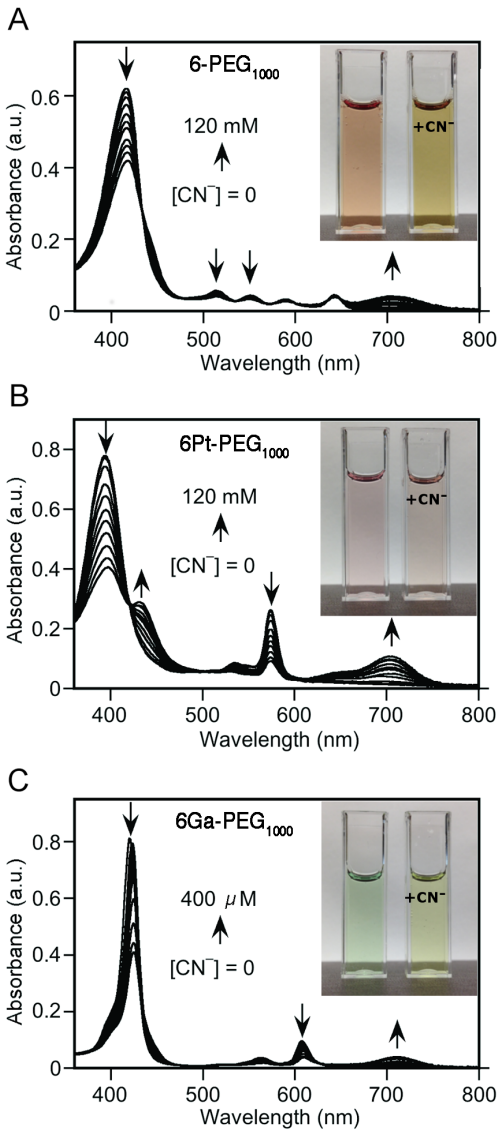


Fig. 1. Spectrophotometric CN^- titration of the PEGylated porpholactones investigated, all in an aqueous pH 7 phosphate buffer and CN^- in the form of an aqueous NaCN solution; any dilution effects < 2%. A: **6-PEG$_{1000}$** (6.06×10^{-6} M). B: **6Pt-PEG$_{1000}$** (3.97×10^{-6}M). C: **6GaCl-PEG$_{1000}$** (5.10×10^{-6} M). Dye concentrations in the images of the cuvettes ~5×10^{-5} M.

Colorimetric Cyanide Sensing

Free Base, Pt-, and Ga-Complexes. Free base porpholactone **6-PEG$_{1000}$**, as well as the two metal complexes **6Pt-PEG$_{1000}$**, **6Zn-PEG$_{1000}$**, and **6GaCl-PEG$_{1000}$** showed an optical response upon addition of cyanide (in the form of an aqueous solution of NaCN), but their response profiles vary from each other (Figures 1A through 1C; the zinc complex is discussed below, Figure 2). Addition of cyanide to unmetallated **6-PEG$_{1000}$** caused a color change from purple-orange to yellow-brown (Figure 1A). The pink color of **6Pt-PEG$_{1000}$** switched to light pink with an orange tinge upon cyanide addition (Figure 1B). The addition of cyanide led to a decrease of the Soret band, the regular metallo-chlorin-type side bands diminished in intensity, and a single new, broad, and much red-shifted band appeared (λ_{max} = 703 nm). In μM dye solutions, the color changes require at ambient temperature several minutes to fully develop for the platinum **6Pt-PEG$_{1000}$** (not shown) and gallium **6GaCl-PEG$_{1000}$** complexes (Figure 3).

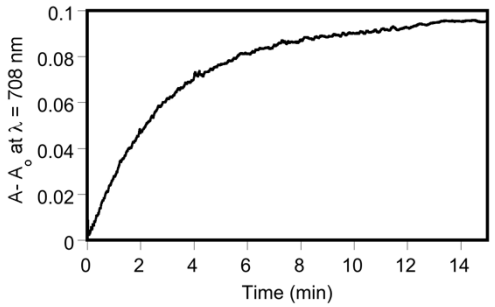
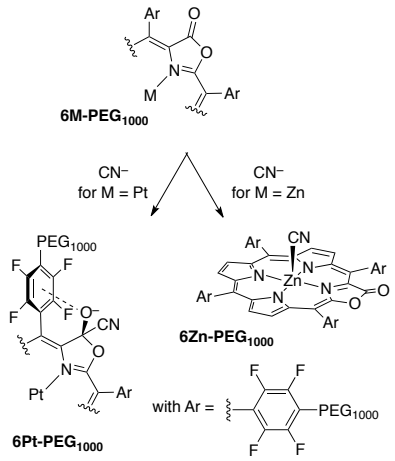


Fig. 3. Rate of optical response at λ = 708 nm of **6Ga-PEG$_{1000}$** (7.9×10^{-6} M in pH 7 phosphate buffer, 20 °C) upon addition of 133 mM CN^-.

The optical response to cyanide is qualitatively equivalent, albeit slower, to that observed for **6Pt** (and other metal complexes) when exposed to pH values above 11.5.[26, 44] Thus, we interpret the cyanide-induced shift of the optical spectrum correspondingly, namely as a nucleophilic attack of CN^- onto the lactone. This converts the sp^2-hybridized lactone carbonyl to an sp^3-hybridized cyanohydrin-like β-carbon (Scheme 3). Chemical reduction of the lactone moiety also leads to large optical changes in the resulting chromophore.[37, 41] The anionic charge of the cyanohydrin-like addition species is likely stabilized by interaction with the adjacent pentafluorophenyl moiety. The design of multiple other cyanide sensors also relied on the ability of cyanide to attack carbonyl groups[5-13] (or vinylogous carbonyl groups[14] or carbonyl derivatives[15]). Some of the resulting cyanohydrin adducts were also stabilized through intramolecular interactions, mainly hydrogen bonds.[5, 8, 11]



Scheme 3. Proposed cyanide sensing mechanism of **6Pt-PEG$_{1000}$** and **6Zn-PEG$_{1000}$**.

Free base porpholactone **6-PEG$_{1000}$** showed a qualitatively similar response (Figure 1A) to the corresponding platinum complex **6Pt-PEG$_{1000}$** that we therefore also explain with a

nucleophilic CN^- attack onto the lactone. This is interesting as exposure of free base porpholactone **6** to more basic–though less nucleophilic–hydroxide ions merely deprotonated the inner nitrogen(s).[26] The response of the platinum complex **6Pt-PEG$_{1000}$** toward cyanide under identical [CN^-] is significantly stronger than that of the free base **6-PEG$_{1000}$** (cf. Fig. 1A and 1B), a finding that does not surprise. The presence of a dication of a strongly electronegative element in the center of the porphyrin is expected to increase the susceptibility of the ligand to nucleophilic attack.[44] At pH 7, we determined a detection limit for CN^- using **6Pt-PEG$_{1000}$** of 4.0 mM; at a higher pH of 8.0, of 0.9 mM (all detection limits and K_d values are summarized in Table 1). Cyanide is the conjugated base of the weak acid HCN (with a pK_a value of 9.2). Thus, the higher pH value increases the effective cyanide concentration. Free base base **6-PEG$_{1000}$** possesses a detection limit of 1.5 mM.

Table 1. Cyanide sensing data

	Cyanide Detection Limit		
	concentration	mass fraction	K_d
6-PEG$_{1000}$[a]	1.5 mM	40 ppm	87 mM
6Pt-PEG$_{1000}$			
at pH 7.0	4.0 mM	100 ppm	210 mM
at pH 8.0	0.9 mM	47 ppm	99 mM
6Ga-PEG$_{1000}$[a]	240 μM	6 ppm	9.7 mM
in Nafion membrane[a]	5 mM	130 ppm	n/d
6Zn-PEG$_{1000}$[a]	2.0 mM	50 ppm	14 mM
8Zn-PEG$_{1000}$[a]	3.4 mM	90 ppm	45 mM

a at pH 7.0 *b* Determined as $3\sigma/m$, with σ = standard deviation, and m = slope of the response at the lower linear limit, $\Delta A/\Delta[CN^-]$[59]

The green color of **6Ga-PEG$_{1000}$** switched to yellow upon cyanide addition. The response profile of the gallium complex **6Ga-PEG$_{1000}$** to cyanide is similar to that of the platinum complex **6Pt-PEG$_{1000}$** and thus also suggestive of a nucleophilic attack onto the lactone (Figure 1C). Surprisingly, however, the response is significantly more sensitive compared to the platinum complex, with a detection limit of 240 μM CN^-. The increased sensitivity is possibly a reflection of the higher charge of the central metal. We could not find any indication that the hard gallium(III) center has any affinity for cyanide as an axial ligand (in comparison, see for the sensing mechanism of the zinc complexes described previously,[29, 31-33] and below).

The addition of cyanide to the lactone moiety could be demonstrated to be, as expected, reversible (see also below for the demonstration of reversibility of the dye embedded into a membrane). Thus, addition of molar excess Zn(II) chloride to a solution of **6Ga-PEG$_{1000}$** and cyanide in pH 7 buffer removes the cyanide from the lactone-cyanohydrin equilibrium by precipitation as $Zn(CN)_2$. Consequently, the native UV-vis spectrum of the sensor is restored (after the removal of the precipitate by filtration; see ESI).

Zn-Complexes. The optical response of the zinc complex **6Zn-PEG$_{1000}$** to cyanide differs fundamentally from that of the free base, platinum, and gallium complexes. Addition of cyanide causes the green color of the metallochlorin-type spectrum to take on a yellowish tone and only a modest (~10 nm) bathochromic shifts of the Soret and Q bands is observed (Figure 2A). This response is comparable of the shifts of the metalloporphyrin spectra of the metalloporphyrin [*meso*-tetrakis(pentafluorophenyl)porphyrinato]zinc(II) **(8Zn)** lacking the lactone functionality (Figure 2B; water-soluble zinc porphyrin **8Zn-PEG$_{1000}$** was prepared from zinc porphyrin **7Zn** analogous to the water-soluble porpholactones (Scheme 4)) and other zinc porphyrin-based sensors,[29, 31-33] although the visible color change from purple to yellow is more significant. It thus can be attributed to axial ligation of the cyanide to the central metal (Scheme 3). The formation of square pyramidal complexes for the zinc porphyrinoids is well known.[60] Evidently, the association constant for this process is significantly higher than for the nucleophilic attack of cyanide to the lactone moiety of **6Zn-PEG$_{1000}$**, for which we find no evidence.

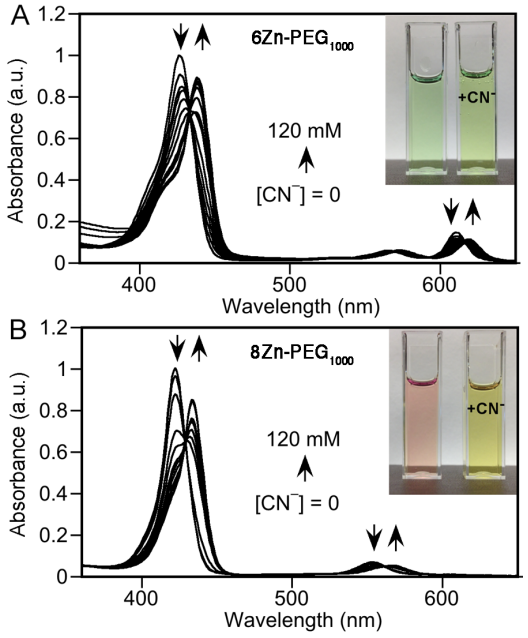
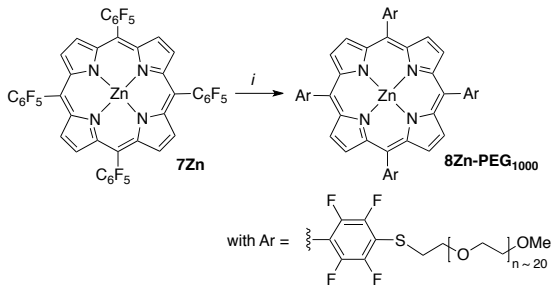


Fig. 2. Spectrophotometric CN^- titration of the PEGylated zinc complexes investigated, all in H_2O and CN^- in the form of an aqueous NaCN solution; any dilution effects < 2%. A: **6Zn-PEG$_{1000}$** (4.48×10^{-6} M). B: **8Zn-PEG$_{1000}$** (5.10×10^{-6} M). Dye concentrations in the images of the cuvettes ~5×10^{-5} M.



Scheme 4. Formation of [porpholactonato]Zn(II) **8Zn-PEG$_{1000}$**. *Reaction Conditions:* (i) H-PEG$_{1000}$, DMF, NEt_3 (2:1), reflux.

The response of the zinc complexes is much faster than that of the other dyes and completed upon mixing. The sensitivity of

the zinc lactone complex for CN^- is high, with a detection limit of 2.0 mM, i.e., in the same order of magnitude as the platinum complex, and lower than for the parent zinc porphyrin **8Zn-PEG$_{1000}$** (3.4 mM). We attribute this to the generally decreased Lewis basicity of the oxidized porpholactone compared to the porphyrin;[26] this renders the coordinated metal ion to be a better Lewis acid,[61] with a corresponding higher binding affinity for cyanide (with a K_d of 14 mM for porpholactone complex **6Zn-PEG$_{1000}$** compared to 45 mM for the porphyrin complex **8Zn-PEG$_{1000}$**).

Selectivity of Cyanide Sensing in Aqueous Solutions

In the pH range between 5 and 9, the selectivity of the response for cyanide in water is excellent. At solutions buffered at pH 7 (phosphate buffer) or in water at ambient conditions, no other commonly occurring anion (F^-, Cl^-, Br^-, I^-, AcO^-, ClO_4^-, NO_3^-, NO_2^-, $H_2PO_4^-$, N_3^-, SCN^-, or OCN^-), applied as their Na^+ or K^+ salts elicited a colorimetric response with **6Ga-PEG$_{1000}$**, even in the presence of large (50 molar equiv) to exceedingly large (2.5×10^5-fold molar equiv) excess of the anions (Figure 4). The gallium complex was also suitable to sense mM quantities of CN^- in the presence of 2 M Cl^- ions (30-fold molar excess, in the form of NaCl or KCl). Alas, at pH values well below 2, the free base porphyrin will become protonated and change its UV-vis spectrum;[26] at pH values above 10, the platinum complex can act, as described previously, as a high pH sensor.[26] The ability of the sensor to selectively detect cyanide even in high ionic strength solutions over a broad pH range may make this sensor particularly useful.

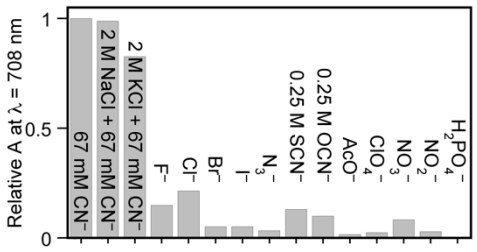


Fig. 4. Relative absorbance intensity response at λ = 712 nm of **6Ga-PEG$_{1000}$** (5.10×10^{-6} M) in pH 7 buffer or water upon the addition of various anions (50 equiv, unless noted otherwise).

Fluorimetric Cyanide Sensing

Fluorimetric sensing modes are generally more sensitive than comparable colorimetric modes.[63] The porpholactone zinc complex **6Zn-PEG$_{1000}$** is, like most zinc porphyrins, highly fluorescent but this compound was deemed not to possess a large enough signal separation to be an attractive cyanide sensor (Figure 2A). Porphyrin platinum complexes are strongly luminescent but this luminescence is partial oxygen pressure-dependent.[47, 64] We thus also did not consider this compound to be a practical fluorimetric sensor for cyanide. Gallium porphyrin complexes are chemically robust with respect to the metal oxidation state and their resistance toward demetalation.[65] And, like all closed-shell metalloporphyrins, they are fluorescent. These characteristics provided the impetus to prepare and study the gallium(III) complex **6Ga** and its PEGylated derivatives **6Ga-MET** and **6Ga-PEG$_{1000}$** in the first place.

Indeed, the porpholactone gallium complex **6Ga-PEG$_{1000}$** in water is fluorescent. The two-band emission spectrum (λ_{max} = 610 nm) is metallochlorin-like (Figure 5), with a relatively low fluorescence yield ϕ of 0.8%. Addition of cyanide reduces, as expected, the fluorescence intensity by this fluorescent species. In turn, the fluorescence of the cyanide adduct increases (at λ_{max} = 745 nm; note the weak emission in the main graph of Figure 5, amplified in the insert). Most damaging to the potential utility of **6Ga-PEG$_{1000}$** as a switch-on fluorescence cyanide sensor is that fact, however, that the absolute fluorescence intensity of the cyanohydrin anion species (*cf.* Scheme 3) is very weak (less than 1% of the intensity of **6Ga-PEG$_{1000}$**, with an estimated ϕ of less than 0.01%). We suspect that the electron-rich cyanohydrin anion species leads to fluorescence quenching through a PET mechanism.[66]

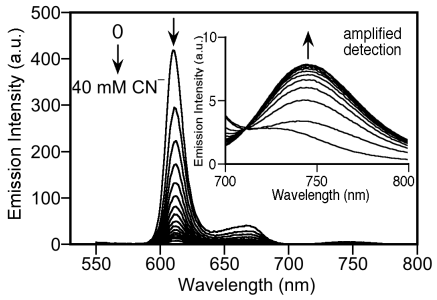


Fig. 5. Fluorescence emission titration of **6Ga-PEG$_{1000}$** (5.10×10^{-7} M) in H_2O with 0-40 mM aq. NaCN; $\lambda_{ex} = \lambda_{Soret}$ = 418 nm. Insert: Emission intensity in the region between 700 and 800 nm recorded with amplified sensitivity.

An Optode Membrane for Optical Cyanide-sensing

Optical solid chemosensors (optodes) are based on a substrate-specific change of the absorbance or luminescence of a solid into which a sensor dye is chemically or physically immobilized. Optodes overcome several limitations of solution-based sensing methods. For instance, they are suitable to continuously monitor solution streams and readily allow remote sensing.[67, 68] The requirements for an ideal optode are well established and include a strong color change, rapid respone time, reversibility, and long-term stability.[67, 68] As we will demonstrate, the optode material prepared largely fulfills these requirements.

Water-soluble porphyrins (generally, *meso*-tetrakis(4-sulfonatophenyl)-substituted derivatives) have been incorporated into Nafion® (a sulfonated polytetrafluoro-ethylene polymer) before.[69] We opted for the incorporation of the most cyanide-sensitive dye, the PEG-derivatized gallium porpholactone complex **6Ga-PEG$_{1000}$**, into a Nafion® membrane. The dye was added to the precursor Nafion® solutions from which the membranes were fabricated (as Nafion®–0.018 mm (0.7 mil) PTFE film–Nafion® sandwich of overall minimum thickness of 0.025 mm (~1-2 mil)) according

to the literature.[70] The Nafion® matrix was chosen for its transparency, high chemical and thermal stability, strength, hydrophilicity, and known ion conduction properties.[70]

Unlike other examples of porphyrins embedded into Nafion® membranes,[69] **6Ga-PEG$_{1000}$** does not display any altered optical absorption spectra as compared to the compound in aqueous solution (Figure 6; cf. to Figure 1C). This indicates that it does not form aggregate structures and further highlights the excellent solubilization properties of the PEG chains. Addition of cyanide to a pH 7 buffer solution in which the membrane is mechanically suspended elicits an optical response much similar to that of the dye in solution, with a reduced–but still respectable–sensitivity (detection limit = 5 mM CN^-, 130 ppm). We rationalize the abated sensitivity of the dye to its location within an anionic polymer matrix. The reduced sensitivity of this sensor may be of utility in the determination of high cyanide concentrations frequently used in industry.

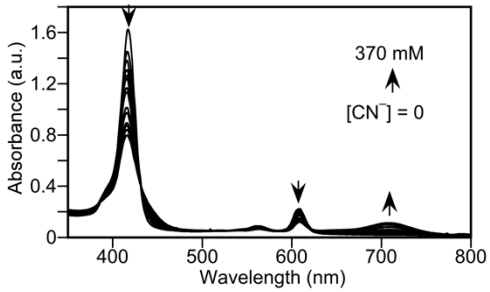


Fig. 6. Spectrophotometric CN^- titration of the PEGylated porpholactone **6Ga-PEG$_{1000}$** in Nafion® membrane in pH 7 phosphate buffer and CN^- in the form of an aqueous NaCN solution.

Importantly, the optode material showed a reversible response. Upon exchanging the cyanide solution with cyanide-free pH 7 buffer, the optical reponse reverted nearly completely within 40 min (Figure 7). The intensity fluctuations observed from one cyanide signal maximum to the next are attributed to slight position changes of the flexible membrane in the solution (for the setup, see ESI). Nonetheless, some increase of the baseline signal was noted. The membrane remained stable and transparent even after days in aqueous solutions.

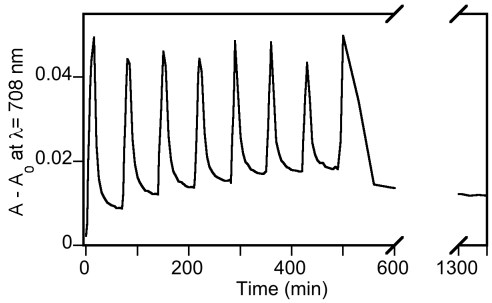


Fig. 7. UV-vis signal of the **6Ga-PEG$_{1000}$**-containing Nafion® membrane upon repeated exposure to 0.5 M NaCN (in pH 7 buffer) for 10 min, followed by pH 7 buffer for 60 min each.

Conclusions

We have shown that a class of pyrrole-modified porphyrins carrying a lactone functionality at the chromophore periphery can be utilized as an optical cyanide sensors, albeit these sensors possess only modest sensitivities. The sensing mechanism relies on a nucleophilic attack of the cyanide onto the lactone moiety. The induced change in the hybridization of the carbonyl carbon that is electronically strongly coupled to the chromophore elicits the expression of a dramatically (~100 nm) red-shifted new band and a reduction of the Soret band intensity upon cyanide addition, thus enabling the ratiometric sensing of cyanide. Further, the pentafluorophenyl-substituted derivatives utilized allowed the conversion to freely water-soluble derivatives through PEGylation, thus allowing the cyanide sensing in purely aqueous solutions. We also demonstrated the influence of the presence and nature of the central metal on the sensing profile.

From a practical colorimetric assay point of view, the platinum and gallium complexes are the best sensors. The more costly platinum complex **6Pt-PEG$_{1000}$** possesses a larger colorimetric response (i.e. larger relative increase of the intensity of the band at 703 nm), while the less costly gallium complex **6Ga-PEG$_{1000}$** possesses the highest sensitivity. The ~100 nm peak separation between the spectra of the 'off' and 'on' stages of both sensors are similar and equally attractive, making these sensors suitable for ratiometric sensing methods, and distinguish these sensors from their zinc analogue and most other known cyanide sensors.[1, 28-33] Valid direct cyanide sensing performance comparisons to other cyanide sensors are difficult. Most were not tested in aqueous solutions or operated at lower pH values to enhance the cyanide concentrations.[62]

The gallium(III) complex is also a fluorescence switch-on sensor for cyanide but the signal is very weak. Only weakly fluorescent in water in its native form, its cyanide adduct is further quenched.

Beyond the introduction of a highly selective sensor for cyanide in water suitable to detecting high μM to single digit mM cyanide concentrations, the value of this work lies in the demonstration that the functionalities of suitably pyrrole-modified porphyrinoids can be readily utilized for analyte capture and signal transmission to the porphyrinic chromophore.[26, 27] Once rarities, porpholactones (and closely related derivatives)[27, 43] are now readily accessible.[26, 37, 38] We hope that this third example in which a porpholactone or porpholactone derivative was utilized as a chemosensor (or chemodosimeter), the demonstration of their robustness and strong light absorption qualities, and their ability to be converted to water-soluble derivatives, will inspired further work on the intriguing class of pyrrole-modified porphyrins.

Experimental Section

All solvents and reagents (Aldrich, Acros) were used as received. For the materials used in the fabrication of the membranes, see below. Flash column silica gel (premium

grade, 60 Å, 32-63 μm) was provided by Sorbent Technologies, Atlanta, GA. Porpholactone **6** and metalloporpholactones **6Zn** and **6Pt** were prepared as described previously.[26, 36, 44] ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 instrument in the solvents indicated. UV-vis spectra were recorded on a Cary 50 and fluorescence spectra on a Cary Eclipse spectrophotometer, both Varian Inc. The fluorescence quantum yield (ϕ) of **6Ga-PEG$_{1000}$** was determined relative to that of *meso*-tetraphenylporphyrin (ϕ = 0.11 in benzene,[71] calculated to be 0.08 in CH_2Cl_2); $\lambda_{excitiation} = \lambda_{Soret}$. High and low resolution mass spectra were provided by the Mass Spectrometry Facilities at the Department of Chemistry, University of Connecticut.

***meso*-Tetrakis(4-[2-(2-methoxyethoxy)ethane]thioxy-2,3,5,6-tetrafluorophenyl)porpholactone (6-MET).**

Free base porpholactone **6** (20 mg, 2.0 × 10^{-5} mol) was dissolved in DMF:NEt_3 (2:1, 10.5 mL). 2-(2-Methoxyethoxy)-ethanethiol (4 equiv, 11 μL) was added and the solution heated to reflux for 1 h. The resulting solution was evaporated to dryness by rotary evaporation and purified by column chromatography (silica gel, CH_2Cl_2/5% MeOH) to provide **6-MET** in near-quantitative yield (29 mg). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.98-8.97 (m, 1H), 8.92 (d, *J* = 5.4 Hz, 2H), 8.85-8.84 (m, 1H), 8.85-8.80 (m, 1H), 8.72 (t, *J* = 4.7 Hz, 1H), 8.64 (d, *J* = 4.7 Hz, 1H), 3.93-3.86 (m, 7H), 3.77 (dd, *J* = 8.2, 4.5 Hz, 1H), 3.70-3.66 (m, 7H), 3.54 (td, *J* = 5.9, 3.3 Hz, 8H), 3.46-3.41 (m, 9H), 3.31-3.30 (m, 14H), 3.10 (t, *J* = 3.0 Hz, 1H), 3.07-3.02 (m, 2H), 2.89 (q, *J* = 5.7 Hz, 1H), -1.73 (s, 1H), -2.03 (s, 1H) ppm. UV-vis λ_{max} (CH_2Cl_2) (log ε): 408 (5.10), 502 (3.75), 538 (3.60), 596 (3.55), 634 (3.60) nm. HR-MS (ESI+) calc'd. for $C_{63}H_{53}F_{16}N_4O_{10}S_4$ $[MH]^+$: 1457.2389, obs. 1457.2427.

***meso*-Tetrakis(4-PEG$_{1000}$thioxytetra-2,3,5,6-fluorophenyl)-porpholactone (6-PEG$_{1000}$).**

Synthesized using **6** (50 mg, 5.0 × 10^{-5} mol) and poly(ethylene glycol) methyl ether thiol (average M_n = 1,000) (~4 equiv, 202 mg) as described for the synthesis of **6-MET**. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.96-8.93 (m, 1H), 8.90-8.87 (m, 2H), 8.83-8.78 (m, 1H), 8.69-8.68 (m, 1H), 8.62-8.60 (m, 1H), 3.94-3.37 (m, >400 H), -1.77 (s, 1H), -2.08 (s, 1H) ppm. UV-vis λ_{max} (H_2O) (Rel. Int.): 417 (1.0), 514 (0.07), 552 (0.05), 589 (0.04), 643 (0.05) nm. HR-MS (ESI+ ionization, 0.5% formic acid in CH_3CN, with Q-TOF detection): clusters of peaks corresponding to different degrees of protonation, all indicative of the quadruple addition of PEG$_{1000}$-S-chains (with n = 18-21).

***[meso*-Tetrakis(4-[2-(2-methoxyethoxy)ethane]thioxytetra-2,3,5,6-fluorophenyl)porpholactonato]platinum(II) (6Pt-MET)**

Prepared from **6Pt** (25 mg, 2.1 × 10^{-5} mol) dissolved in DMF:Et_3N (2:1, 10.5 mL). 2-(2-Methoxyethoxy)ethane (4 equiv, 12 μL,) was added and the solution was heated to reflux for 3 h. The resulting solution was evaporated to dryness by rotary evaporation and purified by column chromatography (silica, CH_2Cl_2/3% MeOH) to provide **6Pt-MET** in near-quantitative yield (31 mg). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.78 (t, *J* = 2.5 Hz, 2H), 8.75 (s, 4H), 3.97-3.90 (m, 8H), 3.76-3.75 (m, 7H), 3.66-3.65 (m, 7H), 3.59-3.56 (m, 1H), 3.48-3.41 (m, 20H), 2.92 (t, *J* = 6.8 Hz, 1H) ppm. UV-vis (CH_2Cl_2) (log ε): 396 (5.25), 533 (4.20), 573 (4.79) nm. HR-MS (ESI+) calc'd. for $C_{63}H_{50}F_{16}N_4O_{10}S_4Pt$ $[M+H_2O]^+$: 1667.1908, obs. 1667.3102.

[*meso*-Tetrakis(4-PEG$_{1000}$thioxy-2,3,5,6-tetrafluorophenyl)-porpholactonato]platinum(II) (6Pt-PEG$_{1000}$)

Prepared from **6Pt** (50 mg, 4.2 × 10^{-5} mol), poly(ethylene glycol) methyl ether thiol (average M_n = 1,000) (~4 equiv, 169 mg) in DMF:Et_3N (2:1; 19.5 mL) as described for the synthesis of **6Pt-MET**. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.76-8.66 (m, 6H) 3.91-3.35 (m, >400 H) ppm. UV-vis (H_2O) (log ε): 396 (5.3), 534 (4.2), 573 (4.8) nm. HR-MS (ESI+ ionization, 0.5% formic acid in CH_3CN, with Q-TOF detection): clusters of peaks corresponding to different degrees of protonation, all indicative of the quadruple addition of PEG$_{1000}$-S-chains (with n = 18-21).

[*meso*-Tetrakis(4-PEG$_{1000}$thioxytetra-2,3-5,6-fluorophenyl)-porpholactonato]zinc(II) (6Zn-PEG$_{1000}$)

Prepared from **6Zn** (30 mg, 2.8 × 10^{-5} mol), poly(ethylene glycol) methyl ether thiol (average M_n ~ 1,000) (~4 equiv, 114 mg) in DMF:Et_3N (2:1, 10.5 mL) as described for the synthesis of **6Pt-MET**. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.78-8.75 (m, 1H), 8.72-8.67 (m, 3H), 8.66-8.58 (m, 2H) 3.72-3.32 (m, >400 H), ppm. UV-vis λ_{max} (H_2O) (log ε): 424 (5.4), 563 (4.0), 609 (4.4) nm. HR-MS (ESI+ ionization, 0.5% formic acid in CH_3CN, with Q-TOF detection): clusters of peaks of corresponding to different degrees of protonation, all indicative of the quadruple addition of PEG$_{1000}$-S-chains (with n = 18-21).

[*meso*-Tetrakis(4-PEG$_{1000}$thioxytetra-2,3-5,6-fluorophenyl)-porphyrinato]zinc(II) (8Zn-PEG$_{1000}$)

Prepared from **7Zn**[72] (30 mg, 6.05 × 10^{-6} mol), poly(ethylene glycol) methyl ether thiol (average M_n ~ 1,000) (~4 equiv, 120 mg) in DMF:Et_3N (2:1, 10 mL) as described for the synthesis of **6Pt-MET**. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.96 (br s, 1H), 3.95 (t, J = 6.4 Hz, 1H), 3.75 (overlapping t, 2H) 3.6-3.4 (m, 47 H; 44 H is theoretical value) ppm. UV-vis λ_{max} (H_2O) (log ε): 422 (5.4), 554 (4.3) nm. HR-MS (ESI+ ionization, in CH_3CN, with Q-TOF detection): clusters of peaks of corresponding to different degrees of protonation, all indicative of the quadruple addition of PEG$_{1000}$-S-chains (with n = 18-21).

Chloro-[*meso*-tetrakis(pentafluorophenyl)porpholactonato]-gallium(III) (6Ga)

In a 10 mL thick-walled tube containing a stir bar were placed free base *meso*-tetrakis(pentafluorophenyl)porpholactone **6** (50 mg, 5.04 × 10^{-4} mol), $GaCl_3$ (44 mg, 5 equiv), $NaOAc{\cdot}3H_2O$ (45 mg, 3.14 × 10^{-4} mol) and acetic acid (5 mL). The vessel was sealed with a septum and placed in a microwave cavity (CEM Discover Scientific Microwave). Using an initial

microwave power of 200 W, the reaction mixture was heated to 180°C and held at that temperature for 20 min, then cooled to 25°C. The reaction mixture was evaporated to dryness using rotary evaporation and the resulting crude product was purified by column chromatography (silica, CH_2Cl_2/50% hexane) to give **6Ga** (22 mg) in 40% yield, with 55% recovery of **6**. R_f (silica, CH_2Cl_2/50% hexane) = 0.39. UV-vis λ_{max} (CH_2Cl_2) (log ε): 418 (5.25), 564 (3.80), 611 (4.42) nm. IR: υ = 1782.6 (C=O) cm. Fluorescence (CH_2Cl_2, λ_{ex} = 418) (Rel. Int.) 614 (1.0), 673 (0.09) nm, ϕ = 0.008. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 9.00 (t, *J* = 5.3 Hz, 1H), 8.93 (dq, *J* = 16, 4.3 Hz, 3H), 8.90 (dt, *J* = 8.9, 4.6 Hz, 2H), 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, δ): 170.9, 168.9, 163.2, 154.1, 153.1, 150.9, 150.5, 150.0, 147.2, 147.1, 145.1, 144.2, 141.7, 139.7, 139.53, 139.51, 137.2, 137.1, 137.0, 136.9, 134.8, 133.0, 132.9, 131.8, 131.2, 131.1, 130.1, 129.1, 126.3, 114.3, 111.0, 110.4, 106.6, 104.4, 86.9, 66.5, 66.4, 64.6, 56.1, 53.7, 32.2, 31.1, 29.9, 24.0, 22.8, 20.5, 14.4 ppm. HR-MS (ESI+ of MH^+, 100% CH_3CN, TOF) *m/z* for $C_{43}H_6F_{20}GaN_4O_2$, $[M\text{-}Cl]^+$: calc'd. 1058.9427, obs. 1058.9401; for $C_{43}H_8F_{20}GaN_4O_3$, $[M\text{-}Cl+H_2O]^+$: calc'd. 1076.9533, obs. 1076.9499.

Chloro-[*meso*-tetrakis(4-[2-(2-methoxyethoxy)ethane]thioxy-tetra-2,3,5,6-fluorophenyl)porpholactonato]gallium(II) (2Ga-MET)

Prepared from complex **6Ga** (22 mg, 2.0×10^{-5} mol) dissolved in DMF:Et_3N (2:1, 10.5 mL), 2-(2-ethoxyethoxy)ethanethiol (4 equiv, 11 μL,) as described for the preparation of **6Pt-MET**. Chromatography (silica gel, CH_2Cl_2/3% MeOH) provided **6Ga-MET** in near-quantitative yield (29 mg). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 9.04-8.84 (m, 6H), 3.99-3.90 (m, 8H), 3.78-3.75 (m, 7H), 3.65 (d, *J* = 3.2 Hz, 7H), 3.49-3.39 (m, 22H) ppm. UV-vis λ_{max} (CH_2Cl_2) (log ε): 408 (5.20), 560 (3.60), 607 (4.30) nm. HR-MS (ESI+) calc'd. for $C_{63}H_{50}ClF_{16}GaN_4O_{10}S_4$, $[M\text{-}Cl]^+$: 1523.1405, obs. 1523.1370.

Chloro-[*meso*-tetrakis(4-PEG$_{1000}$thioxytetra-2,3,5,6-fluoro-phenyl)porpholactonato]gallium(III) (6Ga-PEG$_{1000}$)

This compound was prepared from the gallium complex **6Ga** (20 mg, 1.8×10^{-5} mol), poly(ethylene glycol) methyl ether thiol (average M_n 1,000) (4 equiv, 73 mg) in DMF:Et_3N (2:1, 10.5 mL) as described for the synthesis of **6Pt-PEG$_{1000}$**. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 9.01-8.79 (m, 6H) 3.75-3.38 (m, 400 H) ppm. UV-vis λ_{max} (H_2O) (log ε): 419 (5.4), 563 (4.0), 611 (4.5) nm. Fluorescence (CH_2Cl_2, λ_{ex} = 418) 745 nm, ϕ = $< 1.0 \times 10^{-3}$. 008. HR-MS (ESI+ ionization, 0.5% formic acid in CH_3CN, with Q-TOF detection): clusters of peaks of corresponding to different degrees of protonation, all indicative of the quadruple addition of PEG$_{1000}$-S-chains (with n = 18-21).

UV-Vis and Fluorescence Spectroscopic Titrations

All titrations were carried out in standard 1 cm path length methacrylate cuvettes (Fisher) in H_2O or the buffers indicated at ambient temperature. The PEGylated dyes **6-PEG$_{1000}$**, **6Pt-PEG$_{1000}$** and **6Zn-PEG$_{1000}$** were dissolved in H_2O and diluted to 10^{-6} M concentrations. At pH 7, 5.0 M sodium cyanide (NaCN) stock solution in H_2O was used as the source of CN^-. The absorbance was measured as aliquots of the aqueous CN^- solution were added by micropipette to 3 mL of the sensor dye solutions (the absolute quantity of the additions ranged typically below 100 μL). The concentration of **6Ga-PEG$_{1000}$** in the UV-vis titrations as well as in the fluorescence measurements was 5.10×10^{-6} M and a 1.0×10^{-2} M sodium cyanide stock solution was used as the source of CN^-. All spectra are uncorrected.

Two 1.5 cm diameter stainless steel washers were braised parallel to each other to the ends of a pair of stainless steel curved tweezers. A ~1.6 cm diameter piece of the sensor membrane was held taught between the washers and the tweezers were held clamped shut using a metal clip. The washers holding the membrane were submersed in a 5 × 5 × 1 cm glass cuvette containing the desired aqueous solutions, with the 1 cm path length of the cuvette perpendicular to the washer, and the hole in the washer carefully placed into the center of the beam of the UV-vis spectrometer.

Sensing Membrane

The Nafion® membranes were prepared as Nafion®-PTFE-Nafion® sandwiches using Tetratex PTFE Film (0.7 mil) and using Nafion® solutions (Ion Power, Inc., 5% DuPont™ D521 Nafion® solution in H_2O/^{i}PrOH, EtOH) according to methods adopted from the literature.[70]

The dye **6Ga-PEG$_{1000}$** (4 mg, 7.9×10^{-7} mol) was dissolved in 13 g (~14 mL) of the commercial Nafion® solution and the solution was magnetically stirred at ambient temperature for ~15 min. Then 11 mL of EtOH and 3 mL of DMF were added and once again stirred for ~15 min. In a fume hood, a large stone tile was precisely leveled and a box was fitted over it that allowed a nitrogen stream to flow through it (and to block the light). A sheet of PTFE film was stretched tightly onto a 5 × 5 clean glass plate with polished edges; excess film was rolled up to make sure none is underneath the plate. The glass was placed on the leveled tile (Teflon® film up) and ~10 drops of EtOH were spread evenly over the entire film while preventing any spills over the edges. This clarifies the otherwise white film and defines the area onto which the Nafion film will spread. The EtOH was allowed to evaporate (and the membrane turned opaque again). Half of the dye-Nafion® solution prepared above (~14 mL) was then added onto the film drop-wise and spread evenly (we used a smooth broad metal spatula). The plate was allowed to dry overnight under a stream of nitrogen in the chamber constructed. The second half of the solution was capped and left stirring. Once the first load of the Nafion solution had dried (after about 12-15 h), the membrane was lifted off the glass plate and flipped over. This was accomplished using the following process: ~20-25 drops of DI water were placed on the membrane surface and a second, clean 5 × 5 glass plate was placed on top. The plate was pushed down hard to distribute the water evenly between the glass and membrane surface; the purpose of the water is to help adhere the membrane to the second glass plate. The excess Teflon® film sticking out was then transferred from the edge of the first

plate to edge of the new plate. The plates were then pulled apart carefully while adding drops of DI water into the small gap forming between the old glass plate and the membrane (this may require the use of four hands). The membrane thus transferred was then stretched evenly along the new plate by hand to smooth out any wrinkles (nitrile gloves). The membrane was dried of any remaining DI water using a dust-free paper wipe. The second half of the solution was added onto the flipside of the membrane using the procedure described above, except that the EtOH priming stage was omitted. After 24 h drying time, the plate was moved into a vacuum oven and left to dry for 3 h at 150 °C and 25 torr. The membrane was pealed off carefully with the help of DI water between the membrane and the glass plate. After air drying, the membranes were, cut into smaller pieces, and used as is.

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Notes and references

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† Electronic Supplementary Information (ESI) available: A reproduction of key ^{1}H, ^{13}C NMR, IR, UV-vis, and fluorescence spectra of the novel compound described herein, including images of the setup and a membrane. See DOI: 10.1039/b000000x/

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