# Luminescent Lanthanide Probes for Cations and Anions: Promises, Compromises, and Caveats

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**Abstract**

The long luminescence lifetimes and sharp emission bands of luminescent lanthanide complexes have long been recognized as invaluable strengths for sensing and imaging in complex aqueous biological or environmental media. Herein we discuss the recent developments of these probes for sensing metal ions and, increasingly, anions. Underappreciated in the field, buffers and metal hydrolysis influence the response of many responsive lanthanide probes. The inherent complexities arising from these interactions is further discussed.

## Introduction

Luminescent lanthanide probes, including those emitting in the visible ($Eu^{III}$, $Tb^{III}$, $Dy^{III}$, and $Sm^{III}$) and the infra-red ranges ($Er^{III}$, $Nd^{III}$, and $Yb^{III}$) have long been recognized for their potential for sensing metal cations and anions in biological or environmental samples. This potential arises primarily from the uniquely narrow emission bands and very long luminescence lifetimes of the lanthanide-centered emission. In particular, the forbidden nature of the transitions and the resulting ms lifetimes readily enable gating of background autofluorescence, which is particularly beneficial for measurements in complex aqueous media where endogenous fluorophores can create significant background. The parameters that affect both their sensitized luminescence intensity and lifetimes are well-understood and are highly dependent, among other parameters, on the energy level of the excited states of the antenna relative to that of the lanthanide ion, the distance separating the antenna from the lanthanide ion, and the number of coordinated water molecules [1]. These dependencies give inorganic and supramolecular chemists a series of

now well-honed tools to design rationally luminescent lanthanide probes for a wide variety of analytes (Figure 1). We refer the readers to excellent reviews detailing the various approaches to the design of luminescent probes [2-9], and instead will focus on the direction of the field with respect to both cation and anion sensing with research published in the last few years. Of note, this opinion focuses on molecular probes only. MOFs[10] and proteins[11, 12] have also found applications for ion sensing, particularly in the field of environmental chemistry.

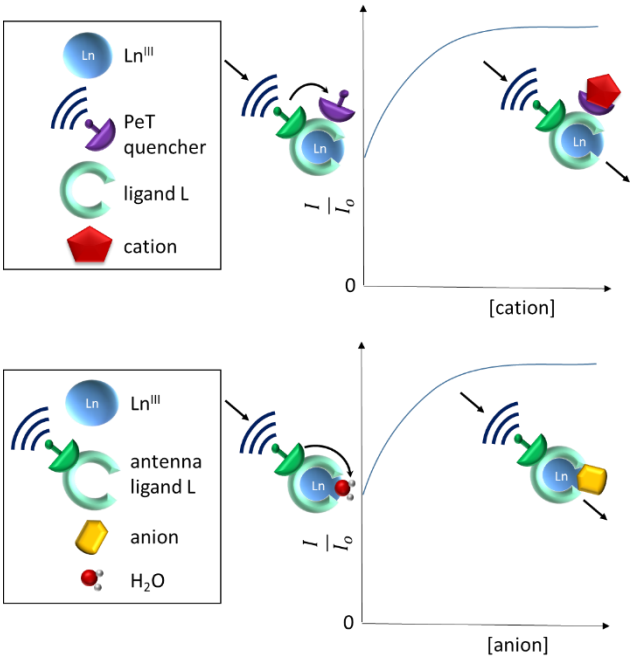


**Figure 1.** Most common approach to the design of responsive lanthanide-based luminescent probes for ions. Probes for cations generally incorporate a quencher that decreases the luminescence of the emitting lanthanide by photoelectron transfer (PeT). Coordination of a metal to the PeT quencher eliminates this decay pathway and restores the luminescence of the lanthanide (top). Probes for anions generally incorporate one or more open coordination sites that are filled with water molecules, which quench lanthanide luminescence due to energy transfer to the 4$^{th}$ vibrational overtone of $H_2O$. Coordination on an anion occurs via displacement of the water molecules, which restores the luminescence of the lanthanide (bottom).

## Luminescent probes for cations

Due to their significant biological role, most efforts on sensing cations with luminescent lanthanide complexes has focused on first row transition metals, specifically copper and zinc. For

the most part, the design of probes for these metals follows well-developed principles that have been honed previously with non lanthanide-based probes. Angelovski, for instance, developed a $Eu^{III}$-based probe for $Zn^{II}$ that employs a di(2-picolyl)amine group (**1**, Figure 2) [13]. Coordination of $Zn^{II}$ by the amine eliminates the photoelectron transfer-quenching pathway, resulting in an increase in europium-centered luminescence intensity. The probe also binds $Cu^{II}$, which prevents its response to $Zn^{II}$. This lack of selectivity is predictable given the similar coordination chemistry of those two metal ions. Indeed, the higher affinity of the probe for $Cu^{II}$ over $Zn^{II}$ follows the Irving-Williams series. Ullah observed similar response with a similar probe (**2**, Figure 2) [14].

Wu employed the same recognition motif—di(2-picolyl)amine—to instead detect $Cu^{II}$ with a similar turn-off and a surprising perfect selectivity over $Zn^{II}$ (**3**, Figure 2) [15]. Since $H_2S$ binds loosely bound copper, the $Cu^{II}$-bound probe also responds to hydrogen sulfide. Of note, the lack of a plateau observed in both the $Cu^{II}$ and $H_2S$ titrations suggest a more complicated system than the formation of a 1:1 probe:analyte assembly, possibly with dissociation of the lanthanide complex. Tuck followed a similar approach to detect $H_2S$ with a $Cu^{II}$:$Eu^{III}$ complex (**4**, Figure 2) [16]. As in the prior case, hydrogen sulfide sequesters $Cu^{II}$ to form CuS, thereby restoring the luminescence of $Eu^{III}$. Tuck's system is advantageously both well-defined and reversible.

Other recognition motifs have also been used to recognize copper and zinc. Tuck recently employed a supramolecular approach to develop a turn-on zinc probe (**5**, Figure 2) [17]. In this case the $Zn^{II}$ ion coordinates both the cyclen moiety and the lumazine antenna, gluing the sensitizer close to the $Tb^{III}$, which results in a substantial increase in the latter's luminescence (Figure 2). As for most other probe, Tuck's complex is not selective for $Zn^{II}$ over $Cu^{II}$ or $Cd^{II}$.

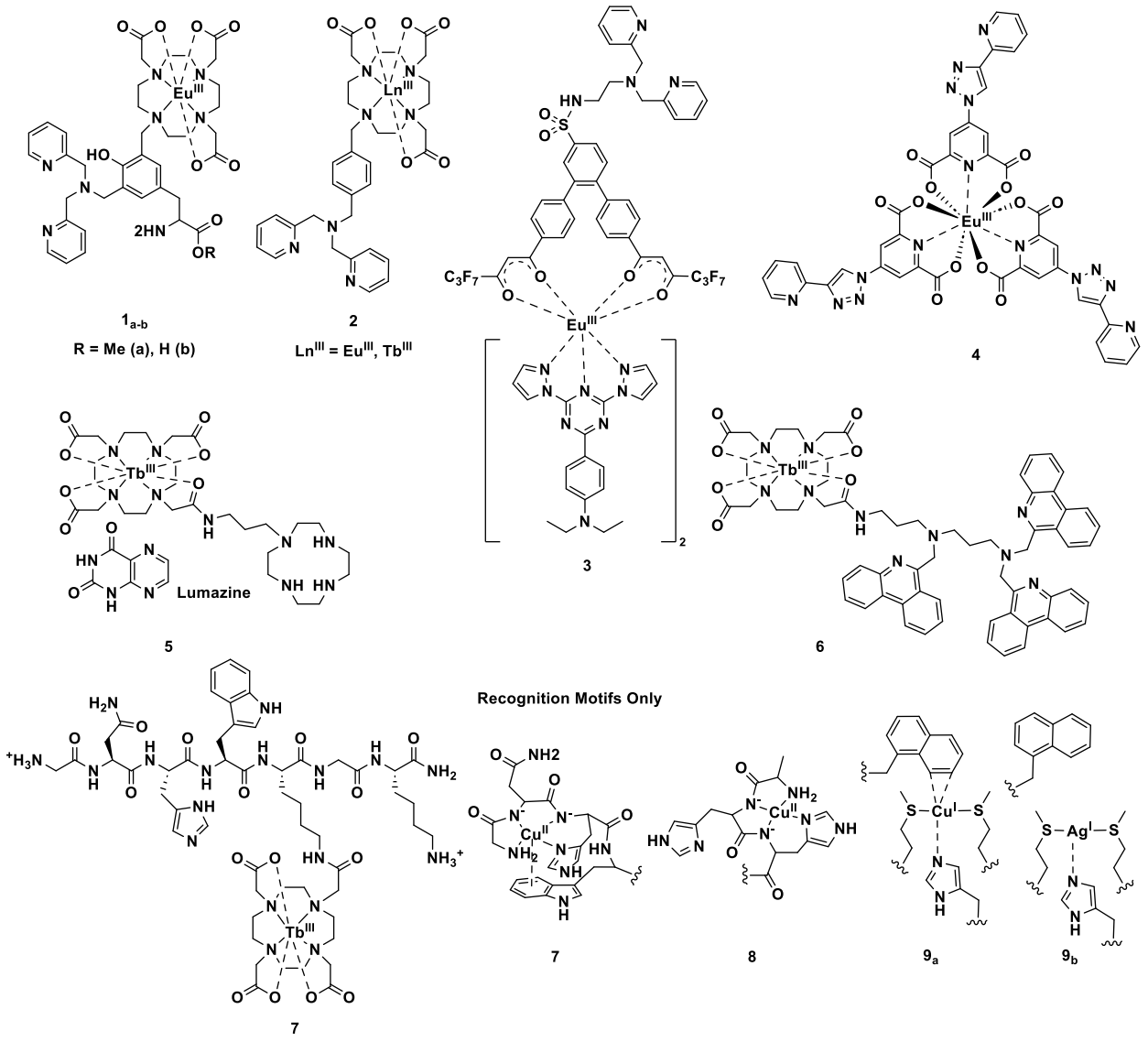


**Figure 2.** Luminescent lanthanide-based probes for biologically relevant cations.

Selectivity for copper over zinc can be achieved in water with molecular probes bearing different recognition motifs. Our group has recently achieved this via the use of phenanthridine antennas that coordinate copper (**6,** Figure 2) [18]. Copper coordination increases the distance between the antenna and the $Tb^{III}$, which results in a decrease of the lanthanide-centered emission but not the fluorescence of the phenanthridine. This dual response enables ratiometric detection. The unique selectivity for copper over zinc is not observed with other lanthanide-based copper or zinc probes.

Given their biological relevance, several groups have exploited Nature's recognition motifs in the design of luminescent lanthanide-based probes. This is most often accomplished by

conjugating a peptide known to bind copper with a desired affinity to a lanthanide complex. Raibaut, for instance, conjugated the ATCUN peptide to a macrocyclic $Tb^{III}$ complex (**7**, Figure 2). The 4N binding motif of the peptide favors coordination of square planar $Cu^{II}$ over $Zn^{II}$, which is tetrahedral, and other physiologically relevant metal ions. Advantageously, coordination of $Cu^{II}$ by Trp affects the latter's ability to sensitize $Tb^{III}$, which results in a significant turn-off of the lanthanide-centered emission [19]. The peptide was later optimized to increase the response rate of the probe as well as its stability in acidic pH (**8**, Figure 2) [20]. Sénèque latter demonstrated that a different peptide enables coordination of $Cu^{I}$ (as opposed to $Cu^{II}$) as well as differentiation with $Ag^{I}$ (Figure 2). This probe was subsequently rendered ratiometric by conjugating both a responsive $Eu^{III}$ and a non-responsive $Tb^{III}$ complex on the same peptide (**9**, Figure 2) [21]. These studies demonstrated the power of using Nature's already optimized motifs to develop luminescent probes uniquely adapted for biomedical applications.

**Luminescent probes for anions**

Lanthanides are oxophilic Lewis acids with high affinity for basic oxoanions. Since their luminescence intensity and lifetimes have a strong dependence on their number of inner-sphere water molecules, they are uniquely suited for the detection of basic oxoanions such as organic and inorganic phosphate, carbonates, and carboxylates, which typically bind lanthanides via displacement of weakly coordinated water molecules [22]. Importantly, the selectivity of lanthanide complexes for anions is primarily dependent on the basicity of the anion [23]. This trend enabled our group to design luminescent $Eu^{III}$ probes that are highly selective for inorganic phosphate over less basic anions such as bicarbonate, carboxylates and halides (**10**, Figure 3) [24]. Given the electrostatic nature of lanthanide coordination, the affinity of a lanthanide probe for an ion—be it a metal ion or an anion—is highly dependent on the charge of the complex. The affinity of our $Eu^{III}$-HOPO complexes for phosphate increases 200 fold by addition of a single positive charge nearby (**11**, Figure 3) [25]. A single negative charge, on the other hand, is sufficient to prevent any anion coordination. Importantly, this electrostatic effect does not influence the selectivity of the probe [25]. Sorensen recently reached the same conclusions with luminescent probes for a positively charged 7-dentate DO2A complex with a benzyl podand (**12**, Figure 3), in which affinity increased with positive charge while leaving selectivity unhindered [26].

Attaching well-positioned appendages on a lanthanide probe that has different lipophilicity or that can hydrogen-bond or π-stack with an anion can increase selectivity of a probe for a desired oxoanion. This strategy was employed by Butler to distinguish between nucleotides as needed to monitor enzymatic reactions. For instance, coordinating a sterically bulky 8-(benzyloxy)quinoline pendant arm to a macrocyclic complex limits the number of open coordination site on the europium ion of **13** (Figure 3) to one, which inhibits axial coordination of polyphosphates. Addition of a boronic acid aids in the selectivity of the probe by providing multisite recognition of AMP over ADP and ATP [27]. The accuracy in the predisposition of these groups is crucial. In this case, the ortho and para substitution of the phenylboronic acid motif yielded worse results than the meta one [28].

Similar interactions can also be beneficial with small substrates such as bicarbonates. Sorensen, for instance, used lipophilicity to control the affinity of carboxylates and carbonate to lanthanide complexes [29]. Incorporating the receptor in nanoparticles such as the nanooptode, can significantly enhance the response to anions [30]. Extending this approach to cations should enable sensitive detection of copper or zinc.

Since affinity for anions is governed by their basicity, it follows that both the affinity of luminescent lanthanide probes for anions and their selectivity are highly dependent on pH [23, 31]. At slightly basic pH, cyanide is deprotonated. Although it is generally considered a soft ligand, it is also basic and can coordinate appropriate $Eu^{III}$ such as $Eu^{III}$-Lys-HOPO (**11a**, Figure 3) by displacement of water molecules, resulting in a significant increase in luminescence intensity [32]. This response is not observed at neutral pH, conditions under which HCN is protonated. This study highlight the potential of lanthanide probes to sense softer anions that are nonetheless good bases. Luminescent lanthanide probes are not limited to hard anions.

It should be noted that although lanthanide ions have very weak affinity for $Cl^-$ in water, lanthanide receptors can nonetheless bind this halide *if* their structure has been designed to predispose them to do so. A rare example is the recent dinuclear lanthanide complexes of Faulkner (**14** in Figure 3) which are unusual due to their ability to chelate $Cl^-$ in water at concentration and under conditions that are biologically relevant (serum [$Cl^-$] ~ 100 mM).[33]

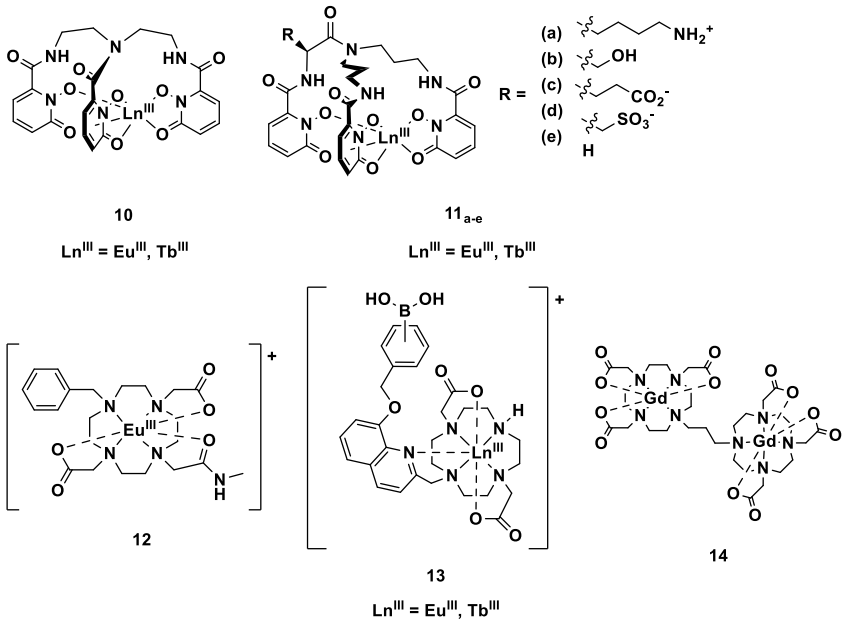


**Figure 3.** Luminescent lanthanide-based probes for biologically relevant anions.

## A note about metal hydrolysis

Because of their biological and environmental relevance, luminescent probes for metal ions—lanthanide-based or otherwise—are best tested in water. Probes that are only effective in organic solvents such as acetonitrile or dimethylsulfoxide should not be assumed to function similarly inside a cell, which is an aqueous environment. Parameters such as solvation and precipitation are likely to affect their response inside the cell. Even low concentrations of DMSO can strongly compromise the structure of cell membranes and dehydrate its surface [34].

Additional care should be taken when evaluating luminescent probes for transition metal ions in water. All physiologically relevant transition metal ions hydrolyze (Table 1). Although often ignored in probe validation experiments, the affinity of a probe for a metal ion is always a factor of the hydrolysis state of the latter. Zinc(II) is ca 50% hydrolyzed to $Zn(OH)_2$ at pH 8. At the physiological pH of 7.4, aqueous solutions of uncomplexed copper(II) contain significant proportion of $[Cu(OH)]^+$. Iron(III) hydrolyzes readily and precipitates at neutral pH as hydroxides. The solubility of iron(III) at neutral pH is a measly $1.1\times10^{-29}$ M. Yet, it remains common malpractice to evaluate the affinity of luminescent probes for iron(III) or the selectivity of copper and zinc probes over iron in μM aqueous solutions of $Fe^{III}$ (aq) (often from $FeCl_3$), i.e. conditions that defy well-established thermodynamics. As explained in detail by Burdette, for example [35],

results obtained under such conditions are meaningless. Affinity and selectivity of luminescent probes for iron(III) can only be determined at neutral pH by competition with water-soluble weaker iron(III) coordination complexes [35].

**Table 1.** Hydrolysis constants of physiologically-relevant first row transition metals [36].

| Metal | Salt | Hydrolysis Constants ($\log\beta_n$) |
|---|---|---|
| Mn(II) | $Mn(OH)^+$ | -10.59 ± 0.10 |
| | $Mn(OH)_2$ | -22.20 ± 0.20 |
| | $Mn(OH)_3^-$ | -34.80 ± 0.30 |
| | $Mn(OH)_4^{2-}$ | -48.31 ± 0.40 |
| Fe(II) | $Fe(OH)^+$ | -9.51 ± 0.10 |
| | $Fe(OH)_2$ | -20.38 ± 0.10 |
| | $Fe(OH)_3^-$ | -32.61 ± 0.20 |
| Fe(III) | $Fe(OH)^{2+}$ | -2.18 ± 0.05 |
| | $Fe(OH)_2^+$ | -5.66 ± 0.10 |
| | $Fe(OH)_3$ | -12.24 ± 0.20 |
| | $Fe(OH)_4^-$ | -21.25 ± 0.20 |
| Cu(I) | Cu(OH) | -7.84 ± 0.20 |
| | $Cu(OH)_2^-$ | -18.22 ± 0.20 |
| Cu(II) | $Cu(OH)^+$ | -7.97 ± 0.09 |
| | $Cu(OH)_2$ | -16.23 ± 0.15 |
| | $Cu(OH)_3^-$ | -26.60 ± 0.10 |
| | $Cu(OH)_4^{2-}$ | -39.74 ± 0.14 |
| Zn(II) | $Zn(OH)^+$ | -8.96 ± 0.10 |
| | $Zn(OH)_2$ | -17.84 ± 0.10 |
| | $Zn(OH)_3^-$ | -27.97 ± 0.10 |
| | $Zn(OH)_4^{2-}$ | -39.98 ± 0.10 |
| Co(III) | $Co(OH)^{2+}$ | -1.90 ± 0.10* |
| Ni(II) | $Ni(OH)^+$ | -9.86 ± 0.10 |
| | $Ni(OH)_2$ | -21.16 ± 0.10 |

Conditions: Zero net total ionic strength, 25°C, aqueous conditions. *Done in the presence of 1.0 M $LiClO_4$

**The not-so-Good's buffers**

A note should also be added to emphasize the roles of buffers. Any luminescent probe with an intended application for either biomedical or environmental applications must function in water. Except for a few organelles, the pH of interest is at or near neutral. Since most cations and anions are either acids or bases, respectively, the pH must be kept constant during measurements to ensure that the change in luminescence observed is indeed due to ion coordination and not to change in protonation state or hydrolysis of the probe. This is most often achieved via the use of buffer, such as phosphate, bicarbonate and the ubiquitous Good's buffers. Phosphate and bicarbonate, as we have noted above, are excellent ligands for lanthanide and will readily coordinate any terbium(III) or europium(III) complexes with open coordination sites. This affinity must be taken into consideration when applying luminescent lanthanide probes for ions for cellular imaging and blood/serum measurements. Phosphate and bicarbonate are present in the cytoplasm or serum at concentrations significantly higher than that of other anions or cations of interest (0.97-1.45 mM and 23-29 mM in serum for phosphate and bicarbonate, respectively).[37] Their presence will undoubtedly influence the response of the probe in cellular and blood studies, often negatively. Therefore, it is recommended that a probe intended for cellular applications first be tested in a media that resembles as much as possible that of the cytoplasm.

Phosphate also has high affinity for many biologically or environmentally-relevant transition metal ions, most notably zinc. The solubility products, $K_{sp}$, of several metal phosphate and hydrogen phosphate salts are given in Table 2. At pH 6.85, the solubility of $Zn^{2+}$ does not exceed $2.88 \times 10^{-6}$ M in the presence of phosphate [38, 39]. It is clear from these data that PBS (11.8 mM $P_i$) not just buffers the pH of a solution; it also affects the solubility of metal ions and thus the range of their concentration that can be tested. In so doing, the buffer has a substantial effect on the apparent selectivity of any luminescent probes for metal ions [40, 41]. The high selectivity of many copper probes over zinc measured in PBS does not necessarily originate solely from the probe but is instead significantly affected by the conditions in which the probe is tested. The distinction between a selective response due to the probe versus one influenced by the media is rarely appreciated, despite its significance.

**Table 2.** Solubility products of physiologically relevant transition metal ions with phosphate

| Salt | $K_{sp}$ |
|---|---|
| $FePO_4$ | $1.3 \times 10^{-22}$ |
| $FePO_4 \times 2H_2O$ | $9.91 \times 10^{-16}$ |
| $Co_3(PO_4)_2$ | $2.05 \times 10^{-35}$ |
| $Ni_3(PO_4)_2$ | $4.74 \times 10^{-32}$ |
| $Cu_3(PO_4)_2$ | $1.40 \times 10^{-37}$ |
| $Zn_3(PO_4)_2$ | $9.0 \times 10^{-33}$ |
| $Mg_3(PO_4)_2$ | $1.04 \times 10^{-24}$ |
| $Ca_3(PO_4)_2$ | $2.07 \times 10^{-33}$ |

Good's buffers refer to the organic buffers introduced by Good in the 1970's and 1980's that have become ubiquitous in analytical chemistry and chemical biology [42-44]. They include MES, HEPES, PIPES and other non-toxic organic weak acids whose safety profile and p$K_a$'s render them attractive for buffering aqueous solutions at or near physiological pH. All contain at least one amine that has inherent affinity for metal ions of comparable hardness, notably copper. These affinities are relatively weak, but they are not zero, not necessarily negligible, and not equal for all metal ions. Xiao recently published their affinity constants of Good's buffers for divalent metal ions of physiological relevance [45]. Yet, in most studies in which they are used, the buffer is considered to be a benign spectator ion, and its affinity for the targeted metal ions is rarely considered in the determination of the affinity or selectivity of the probe.

An increasing number of publications comment on the effect that these buffers and their affinity for metal ions have on the affinity and selectivity of luminescent probes. Rorabacher, for instance, first reported on the emission of a Cu(II)HEPES complex and on the interaction of Cu(II) ions with various Good's hydroxylalkyl buffers [46]. These conclusions extend to lanthanides complexes and luminescent probes. Drobot recently analyzed these weak interactions between Good's buffers and $Eu^{III}$ [47]. The affinity of $Eu^{III}$ for buffers decreases in order of MOPS>HEPES>PIPES>MES>TRIS. TRIS buffer is the only buffer with negligible affinity for lanthanide ions. While these constants are not high, buffers are typically present in much higher concentration ranges: such that 10 mM buffer concentration can result in in up to 80% bound $Eu^{III}$.

The ramifications of the choice of buffer on the apparent selectivity of probes, lanthanide or otherwise, can be illustrated with **15** and **16** (Figure 4), two nearly identical responsive $Gd^{III}$-based MRI contrast agent. The first was reported by Chang to be selective for copper(II) over zinc(II) *in PBS*, conditions that affect the concentration of zinc(II) in solution [48]. Meade shortly after reported that **15** was instead selective for zinc(II) over copper in 100 mM HEPES at 60 MHz and 37°C [41]. The conflicting results of these studies serve as a reminder that the selectivity of a probe for a metal ion is not always fully attributable to the probe itself and can be highly affected by the media. This is also true for lanthanide-based probes for anions. For instance, our phosphate receptors bind cyanide at basic pH. Apparent selectivity for cyanide over phosphate can be engineered by adding a source of $Ca^{2+}$, which precipitates phosphate as its calcium salt. In the absence of calcium, though, there is no selectivity for $CN^-$ over $HPO_4^{2-}$ [32].

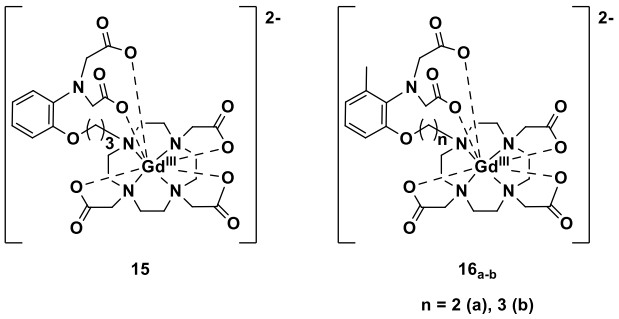


**Figure 4.** Similar $Gd^{III}$-based MRI contrast agents shown to have selective binding of copper *in PBS* (left) and zinc *in HEPES* (right), respectively. Note the presence of an extra methyl in **15**.

## Conclusion

Luminescent lanthanide probes have numerous advantages, the most important of which is their long luminescence lifetimes that readily enable accurate measurements in complex aqueous media by eliminating the interfering autofluorescence background. The principles guiding their response are now well-honed, and the influence of peripheral groups to tune the properties of the complex as desired is also well appreciated. The field now has in its hand a large array of probes for both cations and anions that should fulfill most of the needs of biological and environmental imaging. There are, however, some considerations that remain underappreciated. Chief of these are the influence of the media on the observed response and selectivity of the probe. We urge readers to consider those not only in the design, but also in the evaluation and application of the growing and powerful class of probes.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.


## Acknowledgments

The authors thank the support of National Institutes of Health provided by R01 DK124333 and the National Science Foundation provided by 2203624.


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