

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/277599278>

# Development of a method for detecting trace metals in aqueous solutions based on the coordination chemistry of hexahydrotriazines

ARTICLE *in* THE ANALYST · JUNE 2015

Impact Factor: 4.11 · DOI: 10.1039/c5an00099h · Source: PubMed

CITATION

1

READS

47

## 8 AUTHORS, INCLUDING:



**Rudy J. Wojtecki**

IBM - Almadan Research Center

12 PUBLICATIONS 327 CITATIONS

SEE PROFILE



**Alexander Yuen**

Universidad del País Vasco / Euskal Herriko...

4 PUBLICATIONS 3 CITATIONS

SEE PROFILE



**Gavin O Jones**

IBM

31 PUBLICATIONS 938 CITATIONS

SEE PROFILE



**Hans W Horn**

IBM

55 PUBLICATIONS 8,840 CITATIONS

SEE PROFILE



Cite this: DOI: 10.1039/c5an00099h

## Development of a method for detecting trace metals in aqueous solutions based on the coordination chemistry of hexahydrotriazines†

Rudy J. Wojtecki, Alexander Y. Yuen, Thomas G. Zimmerman, Gavin O. Jones, Hans W. Horn, Dylan J. Boday, James L. Hedrick and Jeannette M. García\*

The detection of trace amounts (<10 ppb) of heavy metals in aqueous solutions is described using 1,3,5-hexahydro-1,3,5-triazines (HTs) as chemical indicators and a low cost fluorimeter-based detection system. This method takes advantage of the inherent properties of HTs to coordinate strongly with metal ions in solution, a fundamental property that was studied using a combination of analytical tools (UV-Vis titrations,  $^1\text{H}$ -NMR titrations and computational modeling). Based on these fundamental studies that show significant changes in the HT UV signature when a metal ion is present, HT compounds were used to prepare indicator strips that resulted in significant fluorescence changes when a metal was present. A portable and economical approach was adopted to test the concept of utilizing HTs to detect heavy metals using a fluorimeter system that consisted of a low-pressure mercury lamp, a photo-detector, a monolithic photodiode and an amplifier, which produces a voltage proportional to the magnitude of the visible fluorescence emission. Readings of the prepared HT test strips were evaluated by exposure to two different heavy metals at the safe threshold concentration described by the U.S. Environmental Protection Agency (EPA) for  $\text{Cr}^{3+}$  and  $\text{Ag}^{2+}$  ( $100\ \mu\text{g L}^{-1}$  and 6.25, respectively). This method of detection could be used to the presence of either metal at these threshold concentrations.

Received 16th January 2015,  
Accepted 10th May 2015

DOI: 10.1039/c5an00099h

www.rsc.org/analyst

## Introduction

Contamination of water sources by heavy metals brought about by human influence from industrial discharge, urban runoff, and sewage effluents is a concern for both developing and developed countries.<sup>1a</sup> Although governments regulate limits of heavy metal concentrations for safe drinking water, it is also well-known that chronic exposure to heavy metals below these thresholds can cause adverse health effects. As people are becoming increasingly conscious and aware of these environmental concerns there is not only interest in more stringent regulations to ensure water safety but also the demand for rapid, portable and economical methods to detect the presence of trace heavy metals from water. Herein, we will describe efforts to fundamentally understand the coordination chemistry of 1,3,5-hexahydro-1,3,5-triazines (HTs) and their utilization to detect trace amounts of heavy metals in aqueous solutions.

The HT motif has recently attracted significant attention in its application for thermosetting materials.<sup>1b</sup> The unique reactivity of this functional group provides access to attractive material properties such as chemical recyclability and self-healing, that are generally elusive for highly-crosslinked thermosetting materials. While the polymeric materials based on this repeating unit have only recently been developed, many accounts of the respective small molecules – HTs – have been reported in the literature.<sup>2</sup> There are a wide spectrum of applications for HTs (realized and potential) such as national defense (hexahydro-1,3,5-trinitro-1,3,5-triazine – RDX<sup>3</sup>), insecticides (1,3,5-hexahydrotriazine-2-*N*-nitroimines<sup>4</sup>) polymerization catalysis (*N*-alkylated 1,3,5-hexahydrotriazines<sup>5</sup>), flame retardants<sup>6</sup> and antifungals<sup>7</sup> to name a few.

While the synthesis of HTs has been extensively reported, significantly less attention has been focused on the co-ordination chemistry of this class of ligands. Structurally, HTs contain a six-membered ring containing three nitrogen atoms, similar to many terdentate ligands (terpyridine,<sup>8</sup> 2,6-bisbenzimidazole pyridine,<sup>9</sup> amide pincer<sup>10</sup>) in their high local concentration of lone pairs of electrons and can be anticipated to provide a region for the strong association of cationic metals. Indeed, there have been detailed reports of the ability of HTs to associate with a number of mono- and multivalent metal

IBM Almaden Research Center, 650 Harry Road, San Jose, California 95120, USA.

E-mail: jmgarcia@us.ibm.com

†Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, IR, GC/MS) and Cartesian coordinates of optimized structures. See DOI: 10.1039/c5an00099h

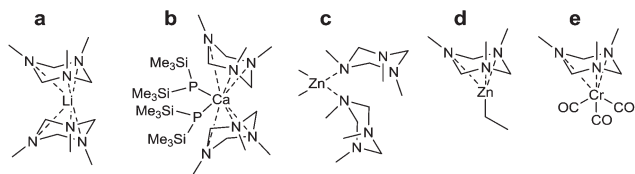


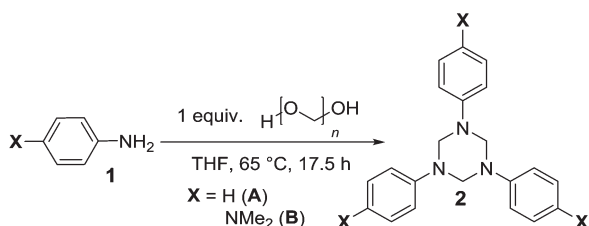
Fig. 1 Selection of HT complexes with (a)  $\text{Li}^+$ , (b)  $\text{Ca}^{2+}$ , (c, d)  $\text{Zn}^{2+}$  and (e)  $\text{Cr}^{3+}$  ions previously reported.

ions such as lithium, calcium, zinc<sup>11</sup> and chromium (Fig. 1).<sup>12</sup> However, reports of the formation of organometallic complexes using HTs have largely focused on descriptions of the complexes in the solid state and with a limited number of substituents.<sup>5</sup> The literature is scant with descriptions of such complexes in solution, though Zeigan and colleagues had briefly described, in their method of preparing single crystals of HT, the slow decomposition of the complex in a dichloromethane (DCM) solution.<sup>5</sup> In addition, using 2D-NOESY (nuclear Overhauser enhancement spectroscopy) they also showed that the HT became chemically different by ligand coordination to zinc.

Interested in broadening the repertoire and fundamental understanding of the coordination chemistry of HTs in solution, here we present several fundamental studies of organometallic complexes formed between aromatic substituted HTs and a range of metal salts in solution using both nuclear magnetic resonance ( $^1\text{H}$ -NMR) and UV-Vis titrations. In addition, these empirical studies were complemented by molecular modelling to provide a more nuanced understanding of not only the spatial arrangements of the complexes but the energies associated with their formation. These fundamental studies also provided the basis for a new application of these organometallic complexes for the detection of heavy metals in aqueous solution (we are unaware of any previous reported methods for metal detection using HTs). Taking advantage of the facile 1-step synthesis of the HT from commercial starting materials and a fluorometer-based method for the detection of metals using HTs, this approach may provide an additional low-cost method for the detection of heavy metals in solution.

## Design & synthesis of HTs

A large spectrum of chemically diverse HTs can be produced through a facile 1-step synthesis that simply requires a primary



Scheme 1 Facile 1-step synthesis to access aromatic HTs.

amine and paraformaldehyde heated in an appropriate solvent (Scheme 1). With interest, in part, directed towards the use of this HT for UV-Vis characterization, we focused our synthetic efforts on two HTs containing aromatic chromophores (2A–B).

## Solution studies of HT complexes

The interaction between HTs and various metals of different atomic radii, oxidation states and “hard” or “soft” properties were studied. These metal ions were selected to approximate metal binding behavior in applications in which heavy metals with varying oxidation states, hardness and atomic radii ( $\text{Cd}(\text{II})$ ,  $\text{Pb}(\text{II}, \text{IV})$ ,  $\text{Hg}(\text{I}, \text{II})$ , and  $\text{As}(\text{III}, \text{V})$ ) are present in contaminated water.<sup>13</sup> Metal binding studies were performed between metal triflates and **2B** including  $\text{LiOTf}$ ,  $\text{Ca}(\text{OTf})_2$ ,  $\text{Eu}(\text{OTf})_3$ ,  $\text{Zn}(\text{OTf})_2$ , and  $\text{AgOTf}$ .  $^1\text{H}$  NMR and UV-Vis studies of HTs bound to metal ions showed different reactivities with “soft” ions compared to “hard” ions (see the ESI† for details). In order to rule out possible binding at the  $-\text{NMe}_2$  group of **2B**, UV-Vis titrations of the unsubstituted **2A** were performed.

### UV-Vis studies of HT complexes

The addition of  $\text{LiOTf}$  to a 25  $\mu\text{M}$  solution of **2A** resulted in an increase in the ligand absorbance at 251 nm and 285 nm (Fig. 2). Interestingly, no isosbestic points were observed during these titration experiments. The plot of the absorbance at 251 nm vs. the ratio of the metal to ligand ( $\text{M}:\text{L}$ ) revealed a significant change in absorbance at an  $\text{M}:\text{L}$  ratio of *ca.* 0.5, suggesting that the two  $\text{LiOTf}$  ions bind to **2A**, a result consistent with previous literature reports.<sup>11</sup> When titrations were carried out with **2A** and a variety of other metal salts, the  $\lambda_{\text{max}}$  shifted after the introduction of metal ions, even at  $\text{M}:\text{L}$  ratios as low as 0.12. A shift in the  $\lambda_{\text{max}}$  may correspond to a chemical

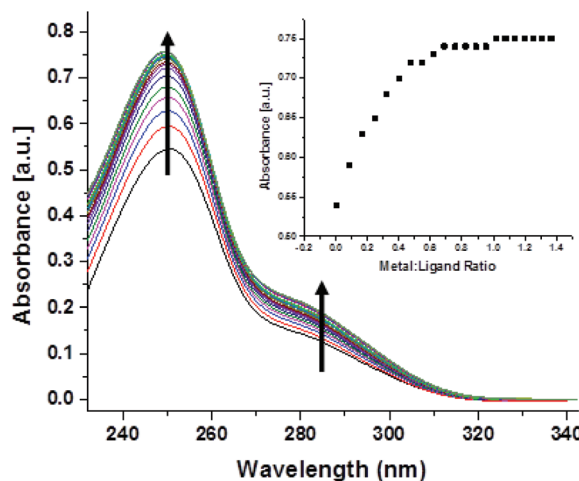


Fig. 2 UV-Vis titration of  $\text{LiOTf}$  with **2A** (25  $\mu\text{M}$ ). Inset: plot of absorbance at  $\lambda = 251$  nm vs. molar ratio of  $\text{LiOTf}$  to ligand.

change of **2A** in the presence of each of these metal salts and this was explored by the use of  $^1\text{H-NMR}$  titrations. NMR titrations reveal peak shifts characteristic of metal-binding consistent with UV-Vis titrations (Fig. S6†). Furthermore, based on these NMR titrations it was revealed that HT **2B** would undergo degradation from soft or borderline Lewis acid metal cations ( $\text{Ag(I)}$ ,  $\text{Zn(II)}$ , and  $\text{Eu(III)}$  salts). The degradation products, a complex mixture involving aniline **1B** and other species, turned NMR samples of **2B** from colourless to strongly coloured samples (Fig. S30†).

In addition to the fundamental characterization of the association of HT with metal salts, in more concentrated forms visible color changes were observed. For instance, the addition of  $\text{Zn(OTf)}_2$  to a solution of HT **2B** led to the formation of a yellow color. Thus, we were motivated to observe the absorbance spectra of these metal : HT solutions at longer wavelengths (Fig. 3). The absorbance spectra at wavelengths above 340 nm produced peaks that are distinct to the metal complexes. For instance, at a wavelength of ca. 550 nm a broad peak was observed in the sample solution of **2B** + 1.0 equiv. of  $\text{AgOTf}$  consistent with a charge transfer type of metal-ligand interaction (Fig. 3). The solution of **2B** + 1.0 equiv. of  $\text{Zn(OTf)}_2$  also produced distinct peaks at higher wavelengths and a characteristic shoulder at ca. 400 nm was observed. In the case of other metal containing solutions, the presence of distinguishing peaks at higher wavelengths was difficult to observe and shoulders may not be as pronounced as in the case of  $\text{Zn(OTf)}_2$ . In addition, titrations with  $\text{Zn(OTf)}_2$  produced a shift in  $\lambda_{\text{max}}$  as well as an increase in absorbance. This was the only metal in which an increase in absorbance was noted. Observation of unique absorption spectra dramatically different from the parent ligand at various wavelengths may, however, provide a method for detecting and determining the presence of metal ions in solution and thus inspired such an investigation.

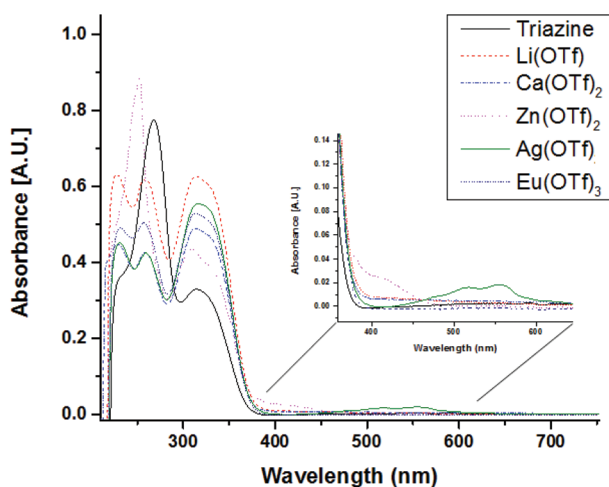


Fig. 3 UV-Vis absorbance spectra of HT **2B** and **2B** + 1 equiv.  $\text{Li}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Ag}^+$  and  $\text{Eu}^{3+}$  ions (all spectra have a conc. of **2B** at 25  $\mu\text{M}$ ). Inset: expanded section of absorbance spectra.

## Computational modelling of HT complexes

To complement these studies and to determine trends in the complexation of metal ions to HT, we performed computational studies with the dispersion-corrected B3LYP-D3 density functional method (see the ESI† for details) on the binding of group I and group II metal chlorides  $\text{LiCl}$ ,  $\text{NaCl}$ ,  $\text{KCl}$  and  $\text{MgCl}_2$ , as well as  $\text{ZnCl}_2$  and  $\text{AgCl}$  to **2A** in MeCN solvent (Table 1).

These studies reveal that all of the metal chlorides bind strongly to the HT with binding free energies ranging from  $-21$  to  $-51$   $\text{kcal mol}^{-1}$ . Binding free energies decrease moving down the periodic table with, for example,  $\text{LiCl}$  being more strongly bound to the HT than  $\text{NaCl}$ , which is, in turn more strongly bound than  $\text{KCl}$ . Moreover, binding free energies increase moving across the periodic table with  $\text{LiCl}$  being less strongly bound to **2A** than  $\text{MgCl}_2$ . These results are qualitatively consistent with Pearson's HSAB theory with harder Lewis acidic metal chlorides being more strongly bound to the hard Lewis basic heterocyclic amine core of the HT.<sup>14</sup> Interestingly, the calculations reveal that  $\text{ZnCl}_2$  and  $\text{AgCl}$  might be as strongly bound to the HT if not for the experimentally observed degradation.

## HT based detector: design & performance

The motivation for studying the coordination chemistry of HTs is exploiting a metal ion induced change in their UV signature to develop an economical means of detecting heavy metals in aqueous solution. As our introduction suggests our interest in detection is primarily limited and would primarily be utilized as a means of testing metal concentrations for safe drinking water. The scope of developing an economical method of metal detection is therefore limited to a narrow range of field measurements limiting the variation in pH (to at or near 7) and temperatures above freezing and below 50  $^{\circ}\text{C}$ . This range of temperature and pH is well within the stability of the HT molecule, which only shows degradation at low pH ( $<2$ ) and temperatures above 250  $^{\circ}\text{C}$  (based on thermogravimetric analysis, Fig. S5†).<sup>1</sup> The use of HTs is therefore, well suited for this targeted application.

Table 1 Binding free energies ( $\Delta G_{\text{bind}}$ ), in  $\text{kcal mol}^{-1}$ , for the complexation of  $\text{ZnCl}_2$ ,  $\text{AgCl}$  and group I and II metal chlorides ( $\text{MCl}_n$ ) with **2A**

$\text{MCl}_n$	$\Delta G_{\text{bind}}$ ( $\text{kcal mol}^{-1}$ )
$\text{LiCl}$	$-28.1$
$\text{NaCl}$	$-25.5$
$\text{KCl}$	$-21.4$
$\text{MgCl}_2$	$-50.7$
$\text{CaCl}_2$	$-50.7$
$\text{ZnCl}_2$	$-39.7$
$\text{AgCl}$	$-34.6$

Commercial methods for the detection of trace chemicals in aqueous solutions often utilize colorimeters and fluorometers. In these methods of detection, generally, an aqueous sample to be tested is placed in a cuvette, followed by the addition of a chemical reagent whose fluorescence/colorimetric signature changes upon the presence of a trace chemical of interest. The resulting solution is then placed in an optical path for measurement. However, a lower cost alternative can instead use a detecting agent adhered to a substrate such as paper- or silica-based devices, which increases the convenience and portability of field measurements for water quality and simplifies sample collection and measurement.

## Detector characteristics

This more portable and economical approach was adopted to test the concept of utilizing HTs to detect trace amounts of heavy metals. We developed a detection system that implements a compact fluorometer. The fluorometer was built using a UV LED light source (UVTOP255TO39 Sensor Electronic Technology) with a central wavelength of  $255\text{ nm} \pm 10\text{ nm}$  providing  $300\text{ }\mu\text{W}$  of optical power and a photodetector (OPT101 Texas Instruments) producing a voltage proportional to the magnitude of the visible fluorescence emission (Fig. 4). The photodetector output voltage is digitized (ATmega328P microprocessor, Atmel) at 10 bits with a sample rate of 125 kHz. The conversion uses a 1.1 internal voltage reference resulting in a  $1.074\text{ mV}$  sensitivity.

The prepared test strip (Sample) is placed between the UV light source and a photo-detector, and 100 sequential readings are captured and averaged to reduce noise and achieve sub-bit resolution. The photodetector has negligible sensitivity at  $254\text{ nm}$  ( $<1\%$ ) so no UV blocking filter is required and enables an in-line measurement, simplifying construction. The measured electrical noise is  $0.22\text{ mV}$  peak-to-peak with a dark (light fully blocked) voltage of  $5.5\text{ mV}$ . The signal-to-noise ratio for a typical measurement is of the order of 19 dB ( $17.6\text{ mV}$  signal for a silver metal concentration of  $12.5\text{ }\mu\text{g L}^{-1}$ ).

Sample readings are measured using an indicator strip consisting of silica impregnated with a fluorescent indicator adhered to strips of poly(ethylene terephthalate) (PET). The

strip is mechanically pulled across the optical path of the LED and the photodetector by using a geared electric motor at a rate of  $1.4\text{ mm}$  per second while the photodetector voltage is digitized and collected on a computer. The silica matrix provides a chemically inert hydrophilic surface for the HT 2B indicator. Several methods were explored to coat the silica matrix with an indicator including drop casting, dip coating and spray coating. Spray coating visually appears to provide the most uniform distribution of the indicator and the metal sample to the test strips, and was used to prepare all strips reported here.

During repeatability experiments it was observed that subsequent readings of a strip, performed by mechanically pulling the strip across the UV optical path, would produce an exposure phenomenon. The strip would exhibit a visible dark band tracing along the length of the strip, corresponding to the contact of the UV illumination on the strip. The exposed area would have a lower transmission, decreasing 4% on the first pass and 8.8% on the second pass, as illustrated in Fig. S49.†

Test strips were spray coated with HT 2B from a dilute solution (conc.  $10\text{ mM}$ ) from an organic solvent such as dichloromethane. Referring to Fig. 5b, the absence of flat plateaus in the UV light absorption of the sprayed segments reveals the variability of the coating method. Spin coating is often used in industry to deposit uniformly thin films and should produce better uniformity than our spray coating method.<sup>15</sup> Other sources of signal variation are changes in silica coating, thickness and tiny scratches that remove portions of the silica gel matrix. While these variations in the silica coating may be of little consequence for the strips intended use of thin layer chromatography, these imperfections produce dramatic (*e.g.* 20%) variations in the detected signal and therefore must be controlled before commercial use. These developments, however, are outside the scope of this paper, which seeks to establish a proof of concept method for the use of HTs for the detection of heavy metals.

## Detector performance

For a proof of concept detection system, we explored the limits of detection based on safety thresholds for several heavy metals prescribed by the U.S. Environmental Protection Agency (EPA). To test the effectiveness of this detection system the indicator strips were exposed to two metals, AgOTf and  $\text{Cr}(\text{acac})_3$ , at and above the safe threshold concentrations in water set forth by the EPA ( $6.25\text{ }\mu\text{g L}^{-1}$  and  $100\text{ }\mu\text{g L}^{-1}$ , respectively). The test strips were spray coated with these metal solutions, dried, then inserted into the fluorometer to obtain a reading. A plot of transmission intensity *vs.* strip position first encounters an area unexposed to UV light, establishing a zero transmission baseline, followed by a deposited indicator mixed with a metal solution, resulting in a transmission intensity responsive to silver metal concentration (Fig. 5a). The plot indicates that AgOTf can be readily detected at concentrations

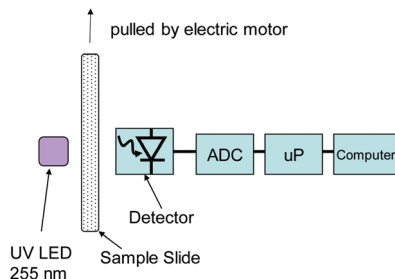
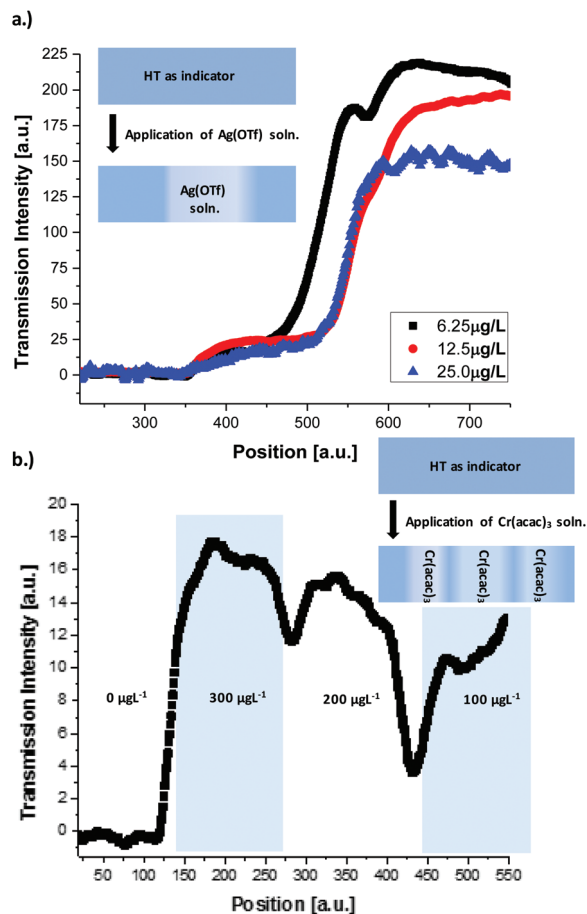


Fig. 4 Schematic representation of the fluorometer based detection system.





**Fig. 5** Transmission vs. position of test strips containing **2B** exposed to a trace amount of heavy metals, measured using fluorometer detection. (a) Results from test strips exposed to varying concentrations of AgOTf. Inset schematic illustrates area exposed to a metal solution. (b) Test strip exposed to Cr(acac)<sub>3</sub> with inset highlighting how a test strip was exposed to different concentrations of a metal solution.

as low as  $6.25 \mu\text{g L}^{-1}$  ( $0.024 \mu\text{M}$ ), with detectable difference at the three concentrations tested. The response is dependent on the metal being detected. Increasing concentrations of AgOTf lead to a decrease in transmission intensity. In the case of Cr(acac)<sub>3</sub> the inverse trend is observed. Increasing concentrations of Cr(acac)<sub>3</sub> lead to an increase in transmission intensity (Fig. 5b). It is believed that this behaviour results from a difference in the coordination chemistry of the two metals with **2B**. Further investigations will pursue the influence of coordination chemistry on detector response. In any case, it is clear that **2B** is sensitive enough to be used as a method of detecting trace amounts of metals in aqueous solutions.

With a proof of concept device sensitive enough to produce readings at EPA safe drinking water thresholds we sought to optimize the device performance by exploring the effect of the light source. In a comparison study of signal quality using a low-pressure mercury lamp vs. a light emitting diode (LED), the mercury lamp tends to display a noisy baseline with significant fluctuations as a result of the light source flickering at a constant rate. However, the use of a LED light source led to a

significant improvement in signal quality and this baseline noise is, in large part, eliminated (Fig. S42†). Using the LED light source blank indicator strips were tested and produced a largely stable baseline, though over the length of the test strip (containing silica and an indicator) show a small decrease in transmission from *ca.* 21 to 18% (Fig. S43†). When using the LED source and test strips exposed to a low concentration of AgOTf ( $6.25 \mu\text{g L}^{-1}$ ) a signal was observed using this device, though the signal is only 1–2× the baseline signal (Fig. S44†).

Two of the most significant aspects of detection are, of course, reproducibility and detection limit. Therefore, we sought to explore the reproducibility of detecting a heavy metal at the lowest concentration possible for our device. Therefore we selected silver as the EPA's concentration for safe drinking water is  $6.25 \mu\text{g L}^{-1}$ . Several test strips were prepared using the safe threshold silver concentration of  $6.25 \mu\text{g L}^{-1}$ . The test strips were then dried and measured in a consistent manner with the previous results. At this low concentration we observed decreasing transmission intensity at the areas exposed to Ag<sup>2+</sup>. While the intensity of this signal is not as dramatic as the use of the low-pressure mercury light source, the results are reproducible and given the signal strength (only 1–2× the baseline) suggest reliable readings would not be achievable at lower concentrations. Three concurrent runs of the same test strips lead to the same type of signal generated with no observable decrease in signal intensity (Fig. S44 & S45†). Furthermore, doubling and tripling the concentration of Ag<sup>2+</sup> led to an increase in signal intensity (Fig. S46 & S48†); this raw data also highlights the reproducibility of the signals generated by this detection method with only minor disparities in the position, primarily due to slight differences in the areas spray coated with the Ag<sup>2+</sup> sample.

## Conclusion

In conclusion, the coordination chemistry of HTs has been explored by <sup>1</sup>H-NMR and UV-Vis titrations and we found that in organic solvents HTs strongly coordinate with a variety of metal ions, a conclusion supported by computational modelling. However, it appears that soft Lewis acid cations lead to the degradation of HTs in solution as evidenced by <sup>1</sup>H-NMR titrations while complexes formed with hard cations remained stable during observation. Furthermore, the unique UV absorbance traces motivated the exploration of these HTs as a method of detecting trace quantities of heavy metals using low cost components. It was demonstrated that quantities described as the threshold levels for safe water quality, as prescribed by the EPA, could be detected using a HT-based method. This method can be used to gather reproducible data with a limit of detection at or near the EPA threshold for silver ions ( $6.25 \mu\text{g L}^{-1}$ ). Given the identified stability of HTs to mono and divalent cations (Li<sup>+</sup> and Ca<sup>2+</sup>), future work will explore the use of this detection method to selectively detect transition metals in a solution containing a mixture of ionic species.

## Acknowledgements

The authors gratefully acknowledge Andy Tek for thermal analysis and Gijs ter Hurme for helpful discussions.

## Notes and references

- (a) S. Morais, F. Garcia e Costa and M. de Lourdes Pereira, *Heavy Metals and Human Health, Environmental Health – Emerging Issues and Practice*, ed. J. Oosthuizen, InTech, 2012, ISBN: 978-953-307-854-0; (b) J. M. García, G. O. Jones, K. Virwani, B. D. McCloskey, D. J. Boday, G. M. ter. Huurne, H. W. Horn, D. J. Coady, A. M. Bintaleb, A. M. S. Alabdulrahman, F. Alsewailam, H. A. A. Almegren and J. L. Hedrick, *Science*, 2014, **344**, 732.
- E. M. Smolin and L. Rapoport, *s-Triazines and derivatives*, Interscience, New York, 1959, pp. 473–544.
- B. T. Oh, C. L. Just and P. J. J. Alvarez, *Environ. Sci. Technol.*, 2001, **35**, 4341–4346.
- C. Sun, J. Zhu, H. Wang, J. Jin, J. Xing and D. Yang, *Eur. J. Med. Chem.*, 2011, **46**, 11–20.
- M. Haufe, R. D. Köhn, R. Weimann, G. Seifert and D. Zeigan, *J. Organomet. Chem.*, 1996, **520**, 121–129.
- E. Weil, *US Patent*, 3,849,409, 1974.
- A. Dandia, K. Arya, M. Sati and P. Sarawgi, *J. Fluor. Chem.*, 2009, **125**, 1273.
- M. A. R. Meier, B. G. G. Lohmeijer and U. S. Schubert, *J. Mass Spectrom.*, 2003, **38**, 510–516.
- B. M. McKenzie, A. K. Miller, R. J. Wojtecki, J. C. Johnson, K. A. Burke, K. A. Tzeng, P. T. Mather and S. J. Rowan, *Tetrahedron*, 2008, **64**, 8488–8495.
- H. Hofmeier and U. S. Schubert, *Chem. Soc. Rev.*, 2004, **33**, 373–399.
- G. Seifert, *Synthesis and Coordination Chemistry of Triazacyclohexanes and Orthoamides*, Doctoral Thesis, Technical University of Berlin, Germany, 1999.
- M. V. Baker, D. H. Brown, B. W. Skelton and A. H. White, *J. Chem. Soc., Dalton Trans.*, 1999, 1483–1490.
- (a) L. Järup, *Br. Med. Bull.*, 2003, **68**, 167; (b) D. Mohan, A. Sarswat, Y. S. Ok and C. U. Pittman Jr., *Bioresour. Technol.*, 2014, **160**, 191.
- R. G. Pearson, *J. Chem. Educ.*, 1968, **45**, 581–586.
- <https://www.spincoating.com/en/applications/spin-coating-theory/68/>.