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Chemical Research Odyssey: From High School Foundations to University Frontiers

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Abstract: Practicing research in high school is essential for preparing future university students, fostering critical thinking, and situating scientific knowledge within a broader context. However, such training remains rare in upper secondary education. Over the past 10 years, we have developed a research programme tailored for high school students, in which they create colorimetric sensors for analytes of societal importance using the simple strategy of indicator displacement assay (IDA). This initiative has led not only to publications, including in international journals, but also to awards and recognition at the Fall meeting of the Swiss Chemical Society (SCS), benefiting both our students and the broader scientific community. Each year, our students have presented their research at the SCS, gaining valuable experience in scientific communication. Moreover, the concept has extended beyond high school: the expertise gained in this program has directly contributed to initiating a PhD in the field of sensing. Taken together, these outcomes illustrate that such a visionary programme has great potential to be further developed and implemented in high schools. It therefore should be supported by institutions to promote excellence in science and chemistry. We hope that this article will inspire the scientific community to recognize and promote the importance of early research training in fostering excellence in science and chemistry.

Keywords: Chemical education · Indicator displacement assays · Research · Sensor

Dr. Thibaud Rossel, Balmer prize 2018 (left) with Pierre-Etienne Zürcher former rector of the GBJB, ©SCS.

Dr. Thibaud Rossel studied biology at the University of Neuchâtel, where he obtained a master's degree in 2006. He then pursued a PhD in chemistry at the University of Basel under the supervision of Prof. Thomas R. Ward. Since 2013, he has been a teacher at Gymnase de Bienne et du Jura Bernois (GBJB), where he received the Balmer Prize in 2018 and the EPFL Learn Award in 2019. Concurrently, he serves also as a senior research associate at the University of Neuchâtel in the group of Prof. Dr. Bruno Therrien, promoting scientific collaborations between gymnasiums and universities, and co-supervising a PhD thesis. His primary interests are at the intersection of teaching and research in chemical biology, utilizing machine learning.

1. Introduction

Ten years ago, we launched a chemistry research programme in chemistry at the Gymnase de Bienne et du Jura Bernois. The initiative stemmed from the observation that authentic research was rarely integrated into secondary education, despite the fact that future students would inevitably have to perform research during their master's or doctoral thesis. The programme was therefore designed with several objectives in mind. First, it seeks to move beyond the mere repetition of established knowledge and instead push students to explore the boundaries of science. Second, it avoids portraying science as a binary discipline, emphasising instead its complexity and nuances. Third, it aims to foster creativity and analytical thinking through direct engagement with contemporary scientific practice. Finally, it aspires to connect science with societal challenges in fields such as medicine, agriculture, and food security.

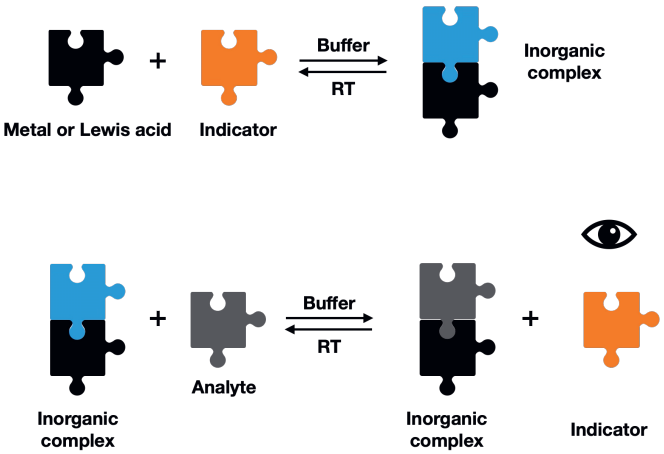

Fig. 1. Principle of the indicator displacement assay: a) a metal is added to an indicator forming a coloured coordination complex; b) An analyte is added to the metallic complex and triggers a ligand exchange thus liberating the indicator (optical signal).

With this vision, we were convinced that meaningful research, could be achieved with modest resources while yielding significant and relevant results. A thorough review of the literature lead us to select the indicator displacement assay (IDA), originally introduced by Anslyn, Sessler, and colleagues.[1–3] IDAs present nu-

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merous advantages: they operate in water, they are non-toxic, they require low micromolar concentrations, and rely on inexpensive indicators. This feature makes them particularly well-suited for research with societal relevance, allowing investigations into real matrices and analytes of importance such as glyphosate, phosphate, arsenate, *etc.*[4–8] Fig. 1 illustrates the principle of the IDA. In its simplest form, a Lewis acid (*e.g.* a metal salt) is dissolved in a buffer and combined with a colourimetric indicator. The resulting coloured inorganic complex can then undergo ligand exchange upon exposure to an analyte.[1,2] When binding occurs, the analyte displaces the indicator producing an optical signal.

This straightforward reaction enables the creation of extensive libraries for analytes detection (see Figs. 2 and 3).

In recognition of this concept and our efforts to introduce authentic chemical research at the high school level, we were awarded the Balmer Prize in 2018.

1.1 *Metal-Based Simple Indicator Displacement Assay*

With our students, we employed this strategy for the naked-eye detection of glyphosate in water. The students were tasked with constructing a library of inorganic complexes and testing them for detection of glyphosate with the naked-eye.[10] We combined indicators such as pyrocatechol violet (PCV) and calcein blue (CB) with various metal salts to create a matrix of inorganic complexes. This matrix was then tested against a collection of anions, with a particular focus on glyphosate.

We were surprised to observe that glyphosate is an excellent ligand for all the metals tested. Additionally, we found that manganese exhibited the least interference among the tested metals against the collection of anions (see Fig. 3). We presented this research as a poster at the SCS Fall Meeting (Fig. 4). Our findings have been adopted by the University of Zürich for further development in Felix Zelder's group, demonstrating the relevance of our work.[7] Furthermore, our research was presented at the EPFL Learn Day, where it received third prize in the competition (EPFL Learn Award 2019).

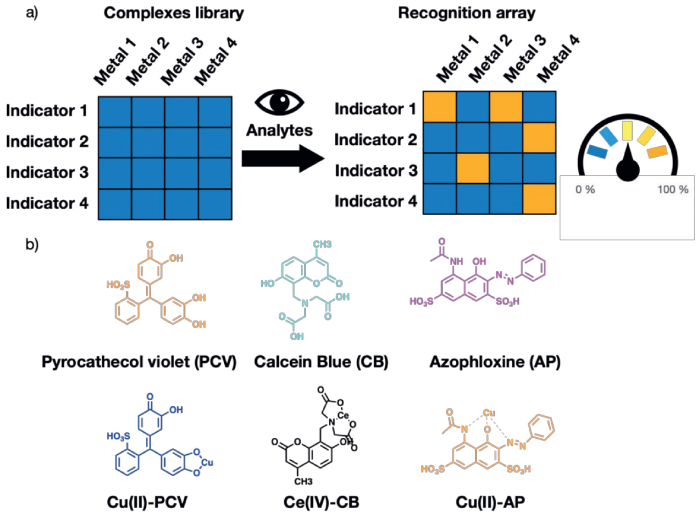

Fig. 2. Matrix of inorganic complexes tested for the naked-eye detection of various anions, particularly glyphosate. In blue, no reaction occurs; in yellow, a reaction occurs (recognition).

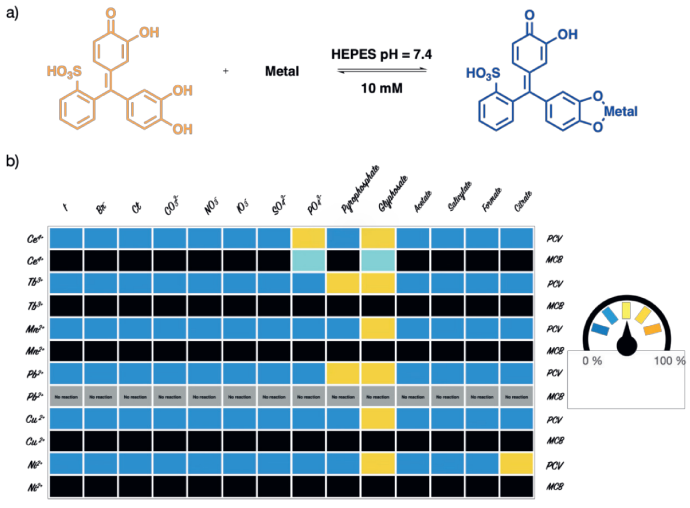

Fig. 3. a) Principle of the preparation of a library of inorganic complexes tested for the indicator displacement assay in the presence of analytes; b) Some used and reported ligands and inorganic complexes for the indicator displacement assay.[1,2]

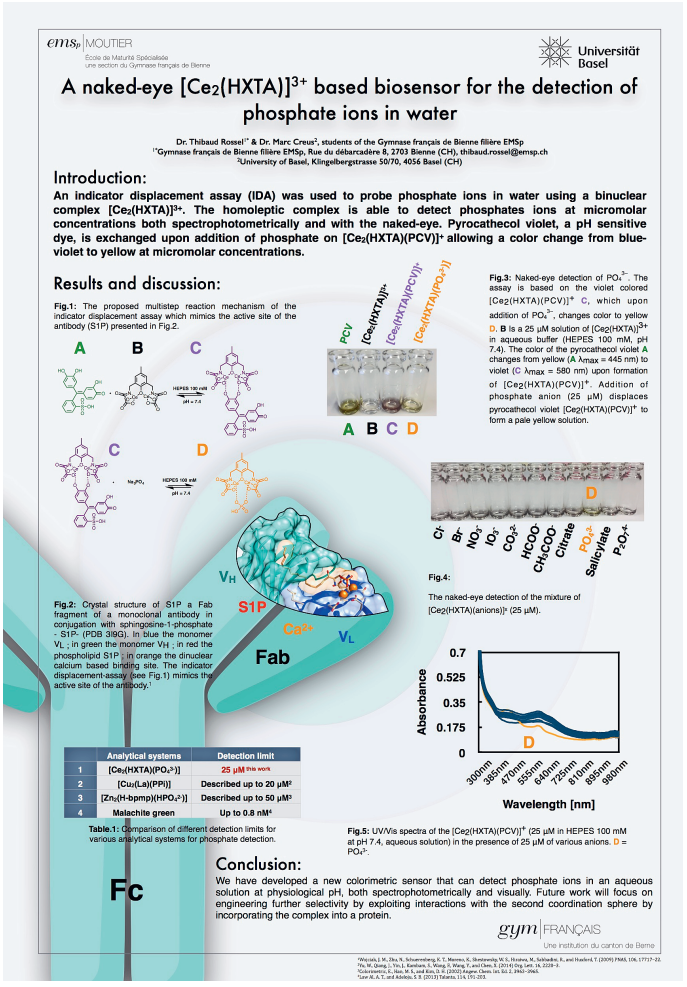

Fig. 4. Award winning poster presented at the SCS Fall Meeting 2016.

1.2 *Simple Fluorescent IDA*

Fluorescence is key to improving the detection limits of sensors. With this in mind, we investigated the possibility of forming inorganic complexes capable of releasing a fluorescent indicator upon analyte recognition.[11] Together with the students, we formed lanthanide-based inorganic complexes using calcein blue (CB) as a fluorescent ligand and reporter (see Fig. 5).

This strategy led to the discovery of $[Ce(IV)(CB)]^{2+}$, a pink sensor for the specific naked-eye recognition of phosphate. Interestingly, the complex is selective for phosphate over pyrophosphate and operates *via* an extrusion mechanism, resulting in the formation of cerium phosphate precipitation. This system can be used to probe phosphate in environmental samples, is easy to as-

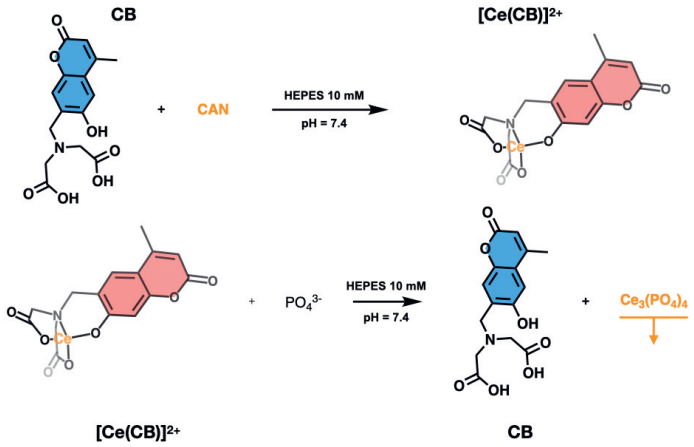

Fig. 5. Principle of the indicator displacement assay using Ce(IV) and CB for the specific recognition of phosphate.

semble, and represents the first description of a Ce(IV) mononuclear complex for naked-eye phosphate recognition. Ce(IV) complexes are generally underexplored in the host-guest chemistry field (see Fig. 6).

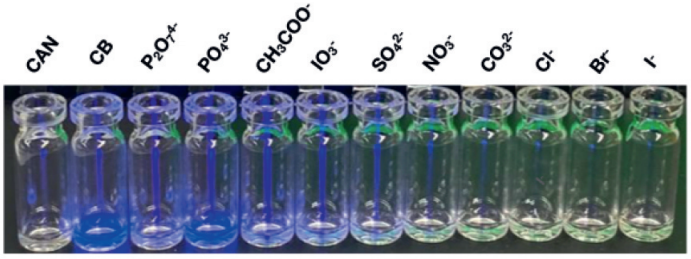

Fig. 6. Naked-eye fluorescent detection of phosphate using [Ce(IV)(CB)]$^{2+}$ in HEPES pH=7.4.

1.3 *Metal-Based Complexes for IDA*

Encouraged by our simple Ce(IV)-based strategy, we expanded the concept of indicator displacement assays by investigating dinuclear lanthanide complexes as receptors.[12] Cerium(IV), for instance, is rarely reported as a receptor for phosphorylated molecules, particularly in dinuclear complexes. The synergistic effect of metals in close proximity may enhance the recognition of challenging molecules. Phosphate, as a particularly difficult anion to recognise, was chosen as the primary target for the development of our receptors. In this context, students combined a well-characterised ligand reported by Larry Que Jr. (HXTA) with cerium ammonium nitrate (CAN) to form a pink dinuclear complex (see Fig. 7).[13] This inorganic complex, conjugated with a colourimetric indicator, facilitates a specific indicator displacement assay for the naked-eye detection of phosphate in water. The complex boasts the highest affinity constant reported in the literature to date and is selective for phosphate over pyrophosphate, which is notoriously difficult to achieve (see Fig. 8). Our research was highlighted in the Swiss Science Concentrate in *CHIMIA*.[14]

1.4 *Boolean Logic Gates*

Boolean logic gate sensors are systems where two different analytes generate two distinct signals. With our students, we investigated the potential of using $[Ni(PCV)]_{2+}$ complexes for the naked-eye detection of pyrophosphate or thiolated molecules (see Fig. 9).[15] When pyrophosphate is added to the complex, an indicator displacement assay occurs; conversely, when a thiol is introduced to the sensor, a 1,4-Michael addition takes place on the

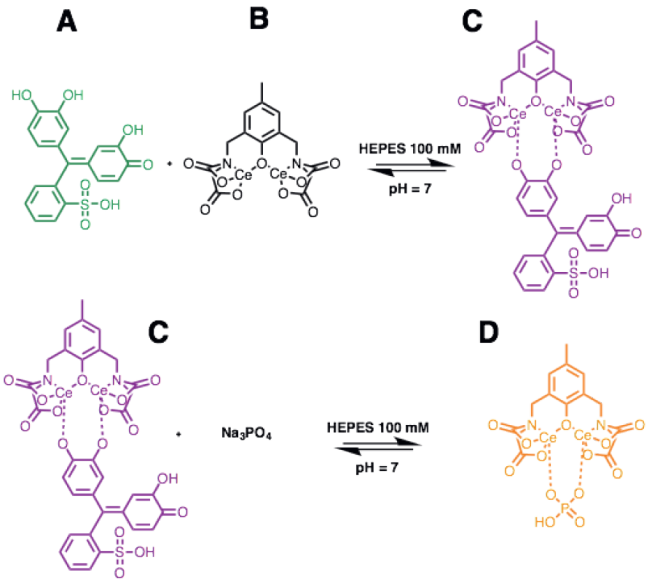

Fig. 7. Principle of the indicator displacement assay using Ce(IV) as a dinuclear complex for selective phosphate recognition.

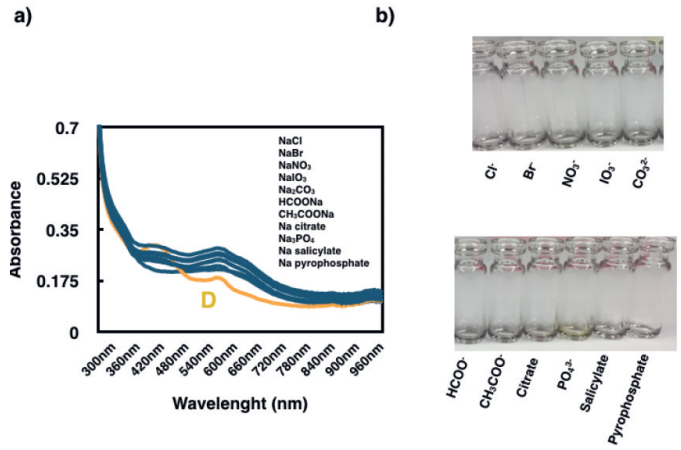

Fig. 8. a) Absorbance spectra of $[Ce_2(HXTA)(PCV)]^+$ in the presence of various anions; b) Visual recognition of phosphate over other anions with $[Ce_2(HXTA)(PCV)]^+$.

PCV, altering the colour of the sensor. To our knowledge, this represents the first description of a sensor for glutathione using PCV, which is extensively employed in chemosensors (see Fig. 10).

1.5 *Polymers*

Next, we investigated the possibility of encapsulating inorganic complexes within polymers for the naked-eye detection of analytes. Since $[Ce(PCV)]^{2+}$ was a promising candidate for phosphate detection (see Fig. 11), we attempted to encapsulate it in gelatin. In Figs. 11 and 12, we report our results, which were presented in poster form at the SCS Fall Meeting (Fig. 13). The polymer is able to selectively extract phosphate from water when other anions fail to cause recognition.

1.6 *Pyrophosphate Detection*

Next, we aimed to introduce selectivity into the sensing process by leveraging the *cis-trans* isomerisation of azobenzene.[16] We introduced azophloxine as an indicator and attempted to combine it with various metals to form inorganic complexes for the naked-eye detection of pyrophosphate (see Fig. 14). Screening of various transition metals revealed that only copper reacted di-

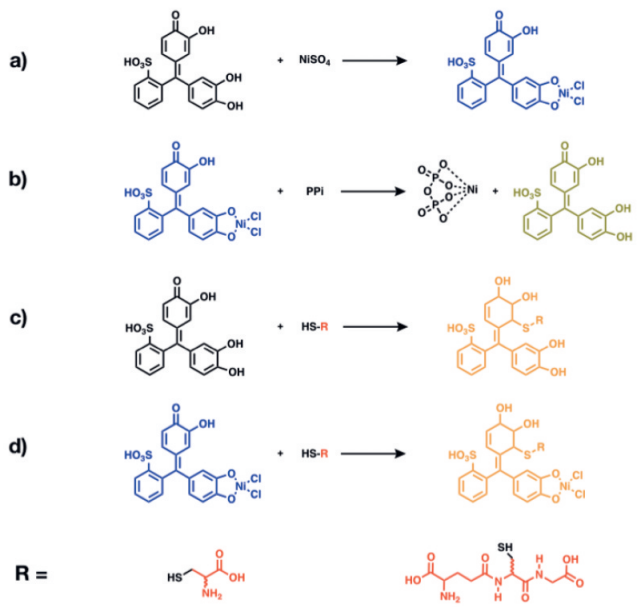

Fig. 9. a) Principle of the Boolean logic gate in the presence of $[Ni(PCV)]^{2+}$ sensing pyrophosphate (PPi) or glutathione (GSH). (Unreacted PCV in black, exchanged PCV in green).

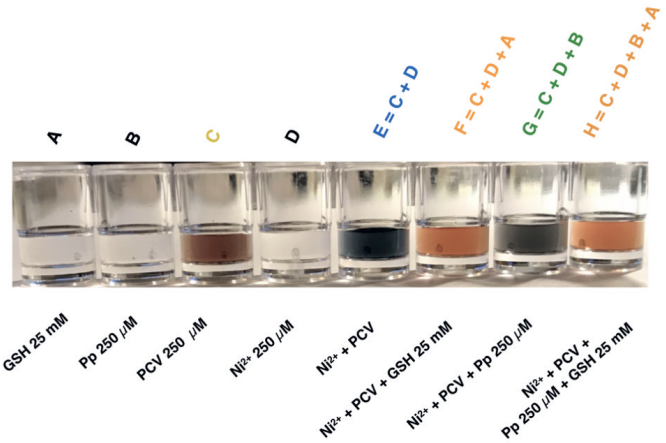

Fig. 10. Visual results of the Boolean logic gate (Pp = pyrophosphate).

rectly with azophloxine. Testing various anions against the copper complex indicated that only pyrophosphate yielded an indicator displacement assay. However, isomerisation of the complex with heat and light to switch the sensing reaction was unsuccessful. Nevertheless, [Cu(AP)] remains an excellent sensor for the naked-eye detection of pyrophosphate (see Fig. 15).

1.7 *Screening Strategy*

Screening matrices of analytes can be time-consuming, and preparing solutions at precise concentrations is a daunting task. In a gymnasium lab with students, it can be challenging to allocate sufficient time and resources to produce significant libraries for screening. This challenge is not only true for research at the gymnasium level but also for chemistry research in general. Consequently, we introduced a new screening strategy.[17] We deliberately constituted libraries of analytes with imprecise weighing, maintaining a concentration of 300 equivalents compared to the tested sensor ([Cu(AP)], where AP = Azophloxine). Additionally, to assess the discrimination abilities of our sensor, we selected two categories of analytes for testing: amino acids and sugars (see

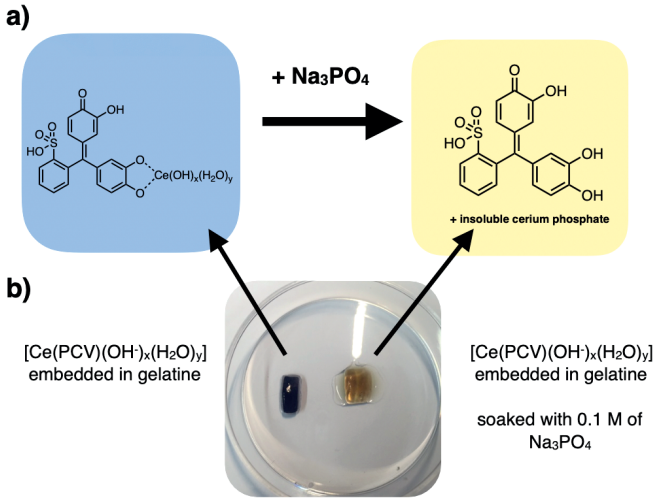

Fig. 11. a) Principle of the encapsulated inorganic complex in gelatin; b) a macroscopic view of the violet polymer changing color upon exposure to a 0.1 M solution of sodium phosphate.

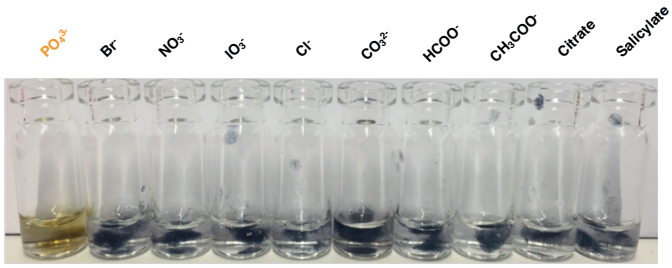

Fig. 12. Polymer in the presence of different anions; only phosphate generates an indicator displacement assay.

Figs. 16 and 17). We screened our sensor [Cu(AP] with an excess of analyte and analysed the results. In Figs. 16 and 17, we can observe that all amino acids are sensed when none of the sugars are recognized. We then diluted the stock solution of analytes 10 x and 100 x times and screened our sensors again. In Figs. 16 and 17, we observe that the same trend is followed. It suggests that if a reaction occurs with an excess of analyte (300 *eq.*), the abilities of the sensor should be investigated with further dilution of the analyte. If no reaction occurs, the analyte can be discarded since in principle no recognition would occurs at lower concentrations. This process therefore saves time. Finally, solutions with precise concentrations of analytes can be built to confirm the approximate results of the screening.

1.8 *Boronic Acid-Based Bioconjugates*

Next, in collaboration with a gymnasium student undertaking a two-month placement, we aimed to develop sensors with exquisite selectivity using second coordination sphere recognition.[19] We incorporated boronic acids into the deep cavity of a protein to exploit the second coordination sphere for recognition (Fig. 18). We coordinated a colorimetric indicator to the active site, which, upon binding with an analyte, changes color. The addition of an analyte generates an indicator displacement assay upon recognition, thereby replacing the indicator that is ejected as the analyte enters the pocket (Fig. 19). The second coordination sphere surrounding the active moiety allows selective recognition of the analyte, utilising synergistic weak interactions. Boronic acids are known to coordinate with sugars (especially D-fructose) as well as catechols, such as neurotransmitters. We therefore screened a small library of sugars and catechol-based neurotransmitters. Our screening demonstrated that dopamine was specifically rec-

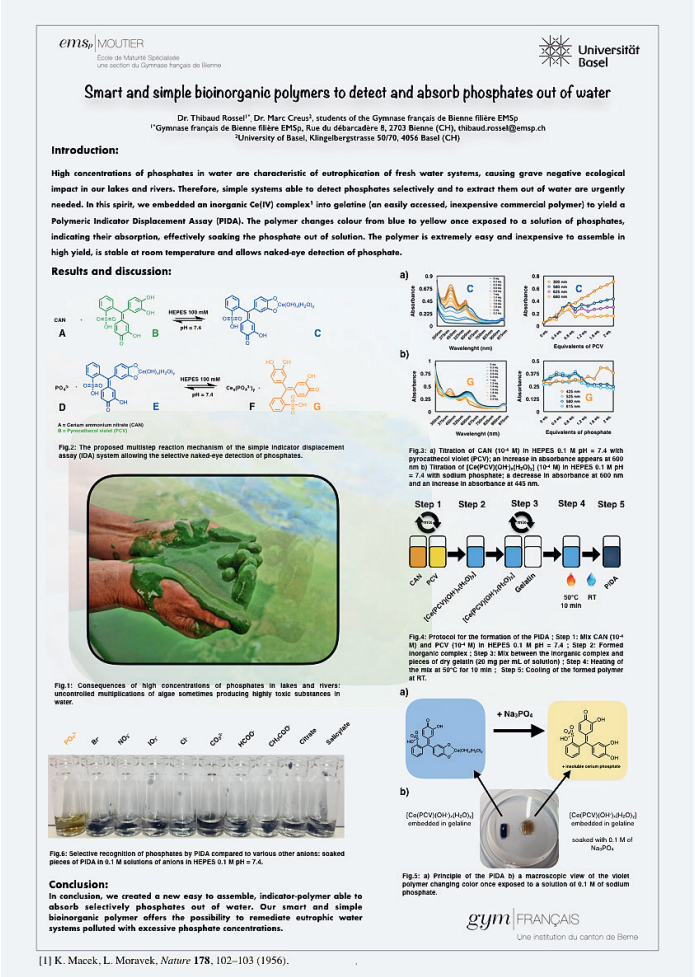

Fig. 13. Poster presented at the SCS Fall Meeting 2018.

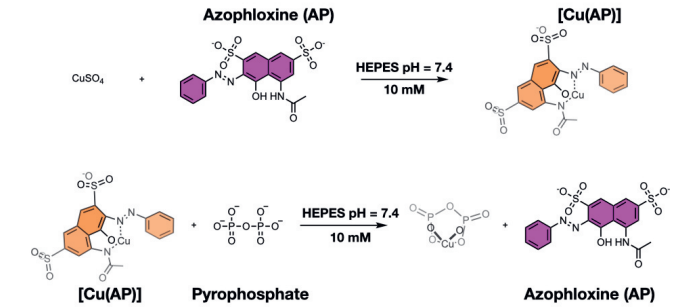

Fig. 14. The proposed multi-step reaction mechanism presenting the indicator displacement assay based on azophloxine (AP) added to copper sulfate, forming [Cu(AP)] at 250 µM in HEPES pH = 7.4 for the naked-eye detection of pyrophosphate.

ognised over D-fructose within the active site of the bioconjugate compared to the free boronic acid, thereby illustrating the discrimination capabilities of the second coordination sphere (Fig. 20). In the next step, we attempted to crystallize the boronic acid moiety within hCAII (Fig. 21). We successfully obtained a crystal structure that was investigated using docking to understand coordination of the dopamine within the active site (See Fig 22).

2. Extending Our Concept to Universities

Following a solid accumulation of knowledge, we wanted to extend our concept to universities. We initiated a PhD thesis in the field of sensing within the group of Prof. Dr. Bruno Therrien, focusing on metal coordination cages. We envisioned incorporat-

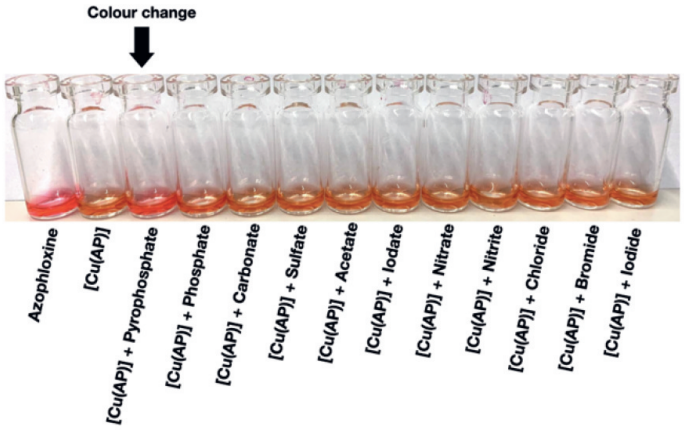

Fig. 15. Screening of [Cu(AP)] (250 µM, HEPES 10 mM pH = 7.4) in the presence of various anions (5 eq.).

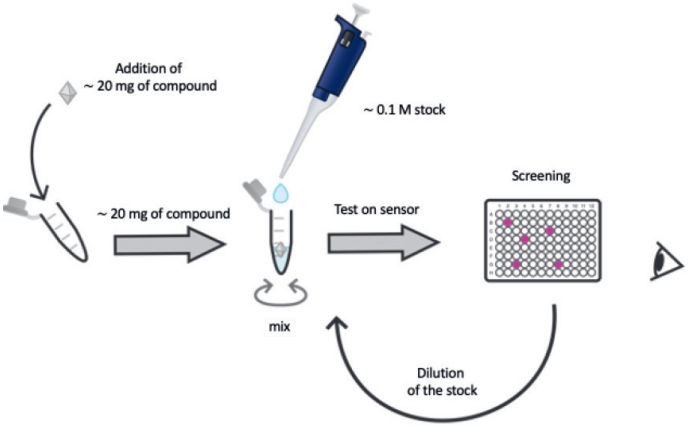

Fig. 16. Description of the screening and selectivity strategy procedure.

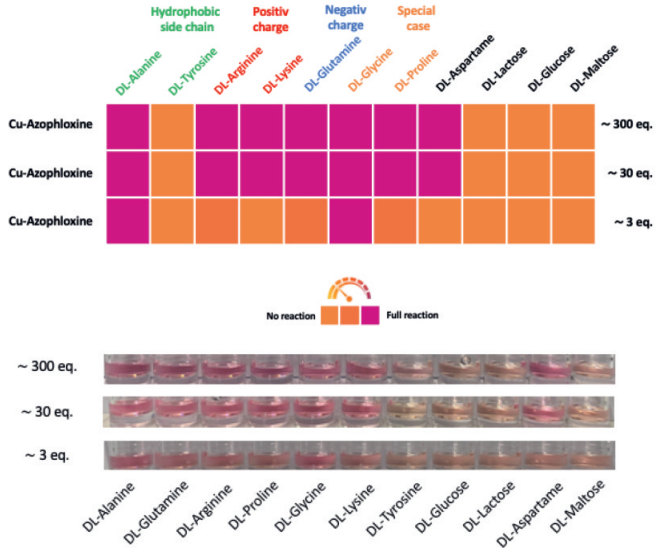

Fig. 17. Results of the screening strategy.

ing fluorophores into inorganic cages for indicator displacement assays with challenging analytes (see Figs. 23–25).[19] Drawing from our previous project based on proteins, we learned to introduce a second coordination sphere in our cages using boronic acids to enhance affinity and selectivity. Additionally, we incorporated machine learning to discriminate analytes of our choice, namely

saccharides. We were pleasantly surprised to achieve high affinities for saccharides with our systems hosting various fluorophores, such as fluorescein, eosyne Y and erythrosine B. This enabled us to create a library of sensors and extend our concept to other libraries of analytes. After one year of research, we successfully published a preliminary article and were selected by the editor for the cover of the journal. We presented a poster at the SCS Fall Meeting 2024 thus demonstrating that the knowledge accumulated in high school is invaluable for extending our concept to universities.

3. Conclusions

Uniquely, research in chemistry has been conducted at the gymnasium level over an extended period of ten years. During this time, a substantial amount of data has been accumulated and published, demonstrating that it is possible to transform the mission of secondary education towards improved research training. Students not only gain insights into the nature of research but also confront its inherent challenges. For mentors, this presents an opportunity to engage in research that interests them and to maximise its potential. Ultimately, the accumulated data can be transferred to universities for doctoral theses, thereby bridging the gap between gymnasium and university education. We are therefore convinced that this pioneering programme enhances the overall learning experience for students.

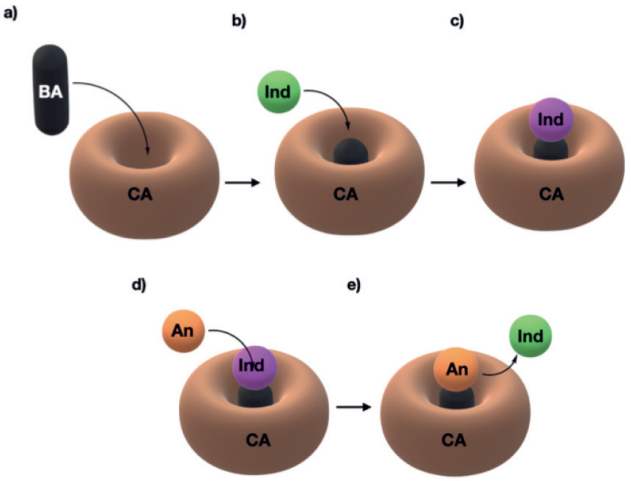

Fig. 18. Principle of the indicator displacement assay inside a protein: a) A boronic acid is incorporated in hCAII; b) An indicator is added to the active site; c) Upon coordination, a change in color occurs; d) and e) Addition of an analyte allows an indicator displacement assay.

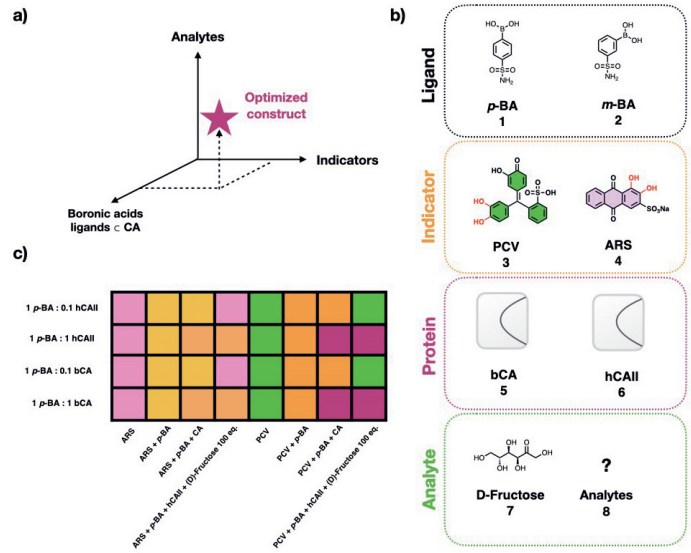

Fig. 19. a) and b) The mix of various sulfonamide-based boronic acids in conjunction with indicators and proteins allows the constitution of a library ready to be screened with analytes and the discovery of hits; c) results of the screening, with the best results highlighted in pink.

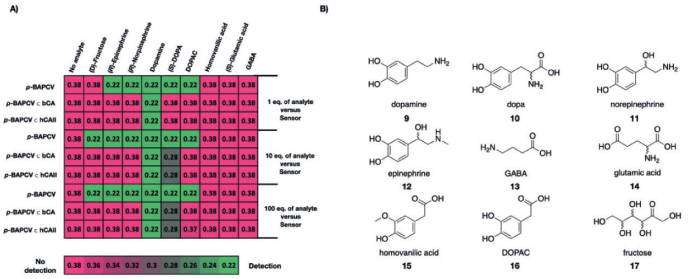

Fig. 20. a) and b) Results of the screening.

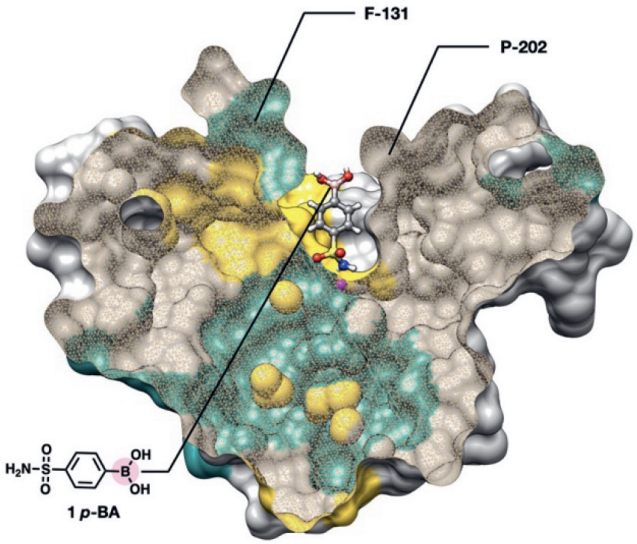

Fig. 21. a) and b) Results of the screening.

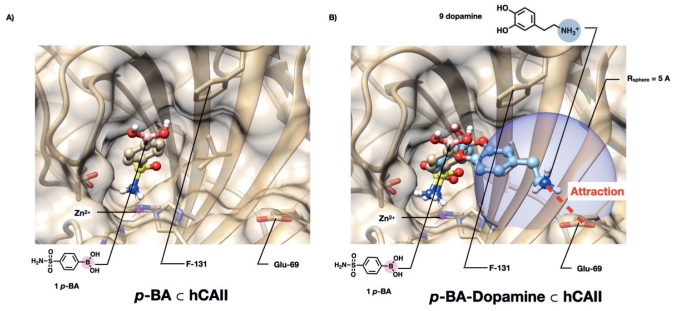

Fig. 22. a) Crystal structure of p-BA in hCAII; b) Docking of dopamine inside p-BA⊂ hCAII.

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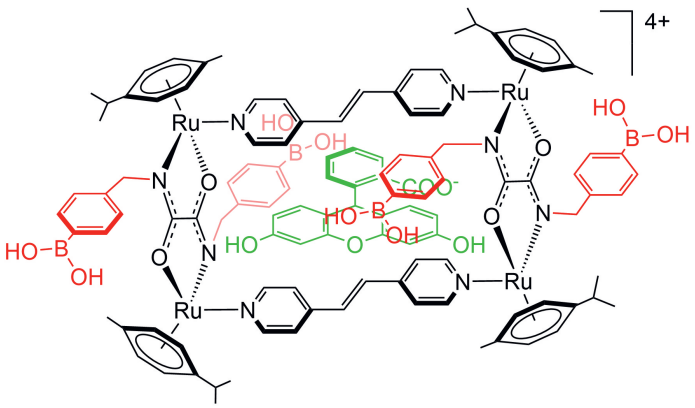
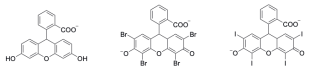


Fig. 23. Inorganic coordination cage (MR1) hosting a fluorophore (fluorescein) for the IDA fluorescent recognition of analytes in water. Fig. from ref. [19].



	analyte	A fluoresceinᴄMR1	B eosin YᴄMR1	C erythrosin BᴄMR1
1	D-fructose	17.2 ± 4.7 μM	50.9 ± 4.4 μM	79.7 ± 6.7 μM
2	D-glucose	50.6 ± 2.5 μM	n.d	30.6 ± 1.4 μM
3	D-galactose	37.0 ± 4.1 μM	n.d	61.4 ± 9.2 μM
4	D-ribose	24.3 ± 2.0 μM	63.8 ± 4.8 μM	64.6 ± 4.3 μM
5	sodium triphosphate	48.9 ± 3.8 μM	61.4 ± 9.3 μM	40.6 ± 2.2 μM
6	D-ribose-5-phosphate	24.3 ± 2.0 μM	110.5 ± 7.8 μM	50.1 ± 5.1 μM
7	adenosine triphosphate	53.9 ± 11.3 μM	62.1 ± 3.7 μM	66.4 ± 4.7 μM

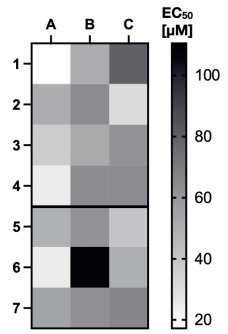


Fig. 24. EC_{50} of different saccharides detected by an IDA in the presence of MR1 hosting different fluorophores. Fig. from ref. [19].

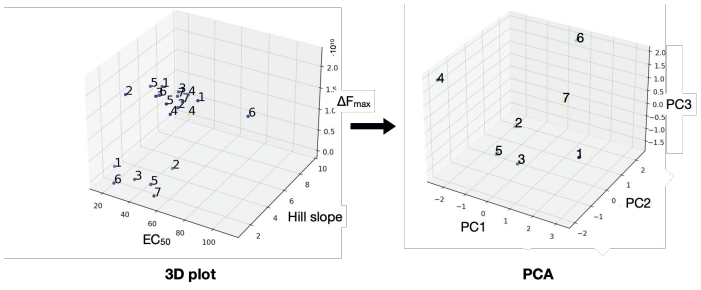


Fig. 25. PCA of MR1 in conjunction with 3 flurophores for the sensing of analytes. Fig. from ref. [19].

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