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A Tetranuclear Copper(II)/Calcium(II) Complex as Dual Chemosensor for Colorimetric and Fluorescent Detection of Non-Steroidal Anti-Inflammatory Drugs

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The tetranuclear $Cu^{2+}/Ca^{2+}/Ca2^{+}/Cu^{2+}$ complex based on Malten ligand has been investigated as a platform for anion binding. Simple organic carboxylates and non-steroidal anti-inflammatory drugs (NSAIDs) have been tested, revealing the ability of the platform to bind them. The receiving platform hosts at least two guests in solution although a third anion can be bound, as suggested by X-ray diffraction analysis. The addition of the anions is accompanied by a color change of the solution, making the system a colorimetric sensor for carboxylates (LOD values comprised between 3.6 and 20.7 ppm). A fluorescent system consisting of the 2-(3-oxido-6-oxoxanthen-9-yl)benzoate (fluorescein anion) linked to the tetranuclear platform has been also prepared and used in a chemosensing ensemble approach to signal the presence of the selected anions (Log *K* between 2.6 and 5.6 for the addition of two guests). The latter also works in a paper strip test, offering the chemosensor a possible practical application.

Introduction

The area of anion coordination chemistry is continuously expanding, representing a fascinating field of Supramolecular Chemistry.[1–5] Anion recognition in solution though is an arduous task, due to issues related to their large size, that requires suitable host cavities for inclusion, and other crucial properties such as multiple protonation equilibria, diverse geometries (spherical, linear, trigonal, tetrahedral, octahedral), high solvation energies. Especially in water, recognition of anions by synthetic receptors is a real challenge, since water can hydrate the receptor and the substrate through strong hydrogen bonds, competing for the hydrogen bonding sites of the receptor.[6–9] Nevertheless, sensing of anions is highly desirable, not only due to the crucial role anions play in life processes, but also because they are becoming a considerable source of pollution in wastewater. As an example, NSAIDs (non-steroidal anti-inflammatory drugs), that are weak acids featuring carboxylic groups and can be therefore present in water in their anionic forms, are among the emerging pollutants (EPs)[10–12] that enter the environment mainly with industrial, municipal, pharmaceutical and hospital wastewater.[13] This is not surprising considering the growing consumption of drugs by the population, along with the fact that NSAIDs represent the most commonly prescribed classes of medication for pain and inflammation and constitute approximately 5–10% of all medications prescribed each year,[14] with an estimated annual consumption of several hundred tons in developed countries.[11] The monitoring of surface waters, influent and effluent wastewaters and drinking waters revealed a low concentration of these compounds in surface water (ng dm^{-3} to mg dm^{-3}), nevertheless the continuous release and chronic exposure to these substances can result toxic to aquatic life and, finally, to human health.[10] NSAIDs are not fully metabolized in the human body and may be excreted either unchanged or as glucuronate conjugates, from which they can be eventually released during wastewater treatment, even more increasing the concentration of NSAIDs.[13]

In this view, the availability of efficient analytical tools for the detection, monitoring and sequestering of anions is highly desirable. Both colorimetric chemosensors for anions, that reveal the presence of the analyte with the naked eye, as well as fluorescent chemosensors, that offer advantages in terms of sensitivity, response time and cost, are of interest.[15–20]

Both free ligands[21–26] and metal complexes[27–29] could be employed as receptors for anions. As a consequence, both non-covalent intermolecular and coordination interactions could be invoked in their binding.[3] Metal-based receptors often offer advantages over purely organic hosts, with the metal ion acting both as an electrochemical or optical signaling unit as well as a binding site for the anion. The metal center also behaves as a structural element able to return a preorganized receptor. On the other hand, the presence of weakly bound ancillary ligands

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would make coordination sites available for the incoming anions, allowing for anion sensing.[30–32]

Among metal complexes, those featuring polynuclear motifs are particularly captivating, in that the cooperation of two or more metal ions in creating the active center offers the chance to achieve receptors able to form stable and selective adducts also by virtue of the tunable distance between the metal centers.[33–37] Few examples of hetero-tetranuclear complexes mixing transition and main group metal ions are reported in the literature,[38–47] even less are related to $(Cu^{2+}Ca^{2+})_2$ complexes.[48–51]

Recently we reported hetero-tetranuclear complexes incorporating both a transition metal ion (Cu^{2+}) and a main group cation (Ca^{2+}) assembled by the ligand Malten (**L**, N,N′-bis((3-hydroxy-4-pyron-2-yl)methyl)-N,N′-dimethylethylendiamine, Figure 1).[50,51] The latter belongs to a class of molecules containing two maltol (3-hydroxy-2-methyl-4-pyrone) units linked to a polyamine fragment and also exerts antineoplastic activity.[52–55] In the solid state complexes, the four $Cu^{2+}/Ca^{2+}/Ca^{2+}/Cu^{2+}$ metal ions arrange in a chain, bridged by oxygen atoms belonging to the Malten ligands. Briefly, the complexes form in aqueous solution by mixing **L** and Cu^{2+} in an equimolar ratio around pH 7 in the presence of a large excess of Ca^{2+}. The high stability constant guarantees the formation of the stable copper complex $[Cu(H_{-2}\mathbf{L})]$ as the first step, followed by the coordination of Ca^{2+} and the self-assembling of two $[Ca\{Cu(H_{-2}\mathbf{L})\}]^{2+}$ units.[50]

Interestingly, in the previous study the hetero-tetranuclear $[Ca\{Cu(H_{-2}\mathbf{L})\}]_2^{4+}$ complex has been used as a scaffold to bind simple inorganic anions, such as halides and oxyanions (perchlorate and nitrate), both in aqueous solution and in the solid state. The anions indeed do not act as ancillary counterions but help saturate the coordination sphere of the metal cations. The perchlorate anions locate in a bridge disposition between Cu^{2+} and Ca^{2+}; the addition of chloride and nitrate induces the displacement of ClO_4^- in favor of Cl^- and NO_3^-, that respectively coordinate to the copper ion, occupying the apex position of the square pyramid (Cl^-), and to the calcium ion in a bidentate fashion (NO_3^-). In other words, perchlorate is the weakest bound guest in aqueous solution and is easily replaced by halides and nitrate, even if it is always present in solution in the largest amount and is the ancillary counterion in all crystal structures. For this reason, the perchlorate complex has been chosen as the starting material for the studies. However, the tetranuclear complex exists in aqueous solution only in extreme experimental conditions, that is in the presence of a very large excess of Ca^{2+}, from which, unfortunately, it promptly precipitates. A not sufficient amount of calcium causes instead the presence in solution of the more stable hetero-trinuclear $[Ca\{Cu(H_{-2}\mathbf{L})_2\}]^{2+}$ species, where two $[Cu(H_{-2}\mathbf{L})]$ species are held together by a Ca^{2+} cation. For this reason, ethanol has been chosen as the solvent, since our studies demonstrated that the desired tetranuclear complex exists in such conditions in solution. The tetranuclear metallo-receptor basically turned out to be a host for halides, perchlorate and nitrate in solution (both water and ethanol): it showed selectivity among the tested guests and proved able to bind two anions mainly via the Cu^{2+} metal centers and, as a consequence, to signal the guest coordination through a color variation visible to the naked eye.[50]

Herein we wanted to extend the anion binding ability of the tetranuclear platform to simple organic carboxylates, and, considering the above reported considerations, going as far as to NSAIDs anions. Among NSAIDs, diclofenac, ketoprofen, naproxen and ibuprofen (Figure 2) are within the most representative and were chosen as model drugs in this work.

The absorption properties in the presence of such carboxylate guests were investigated and the obtained crystal structures are reported. Moreover, a chemosensing ensemble approach has been employed to transform the anion platform in a fluorescent probe for NSAIDs, making it a dual colorimetric/fluorescent chemosensor.

Results and Discussion

The ability of the heteronuclear platform to bind and sense carboxylate guests has been performed, as in the previous study,[50] using the perchlorate complex in ethanol solution as the starting point. The tetranuclear complex $[Ca\{Cu(H_{-2}\mathbf{L})(\mu\text{-}ClO_4)\}(H_2O)_2]_2 \cdot 2(ClO_4) \cdot (\mathbf{1}H_2O)$ has been pre-synthesized as previously described in aqueous solution, from which it precipitates as a pink solid.[50] After collection by filtration and drying, the complex was dissolved in ethanol to give a solution that is similar in color to the solid itself: this resemblance suggests the same assembly also in solution, confirmed by the invariance of the spectrum after the addition of an excess of ClO_4^- and by the crystal structure of the complex $[Ca\{Cu(H_{-2}\mathbf{L})(\mu\text{-}$

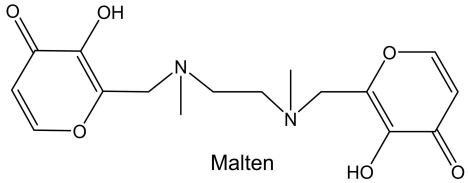

Figure 1. The ligand **L** (Malten).

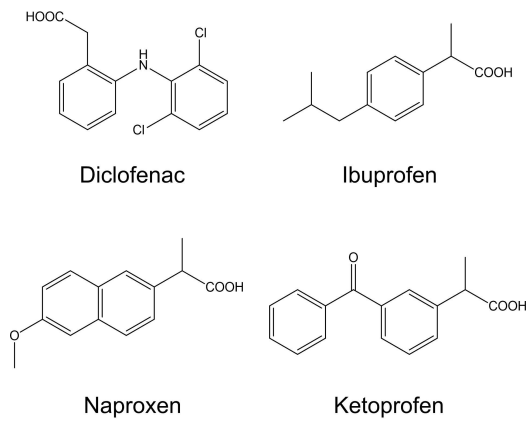

Figure 2. The NSAIDs studied in this paper.

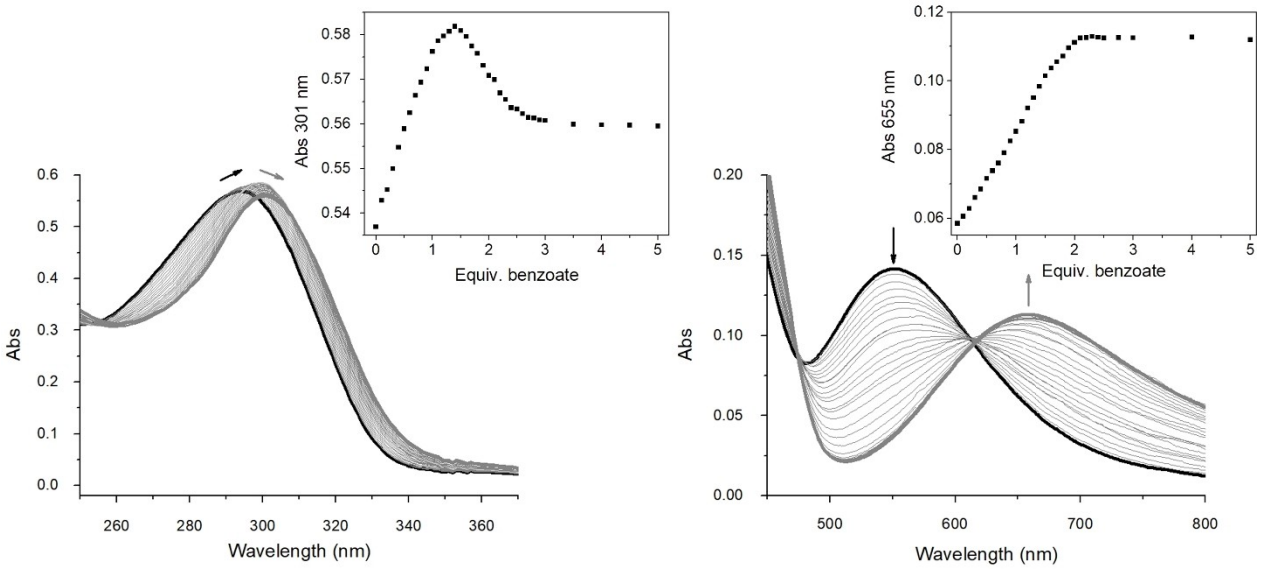

Figure 3. Changes in the UV (left) and Vis (right) spectra of an ethanolic solution of **1***EtOH* upon addition of increasing amounts of an aqueous solution of benzoate up to 5 equiv. (black line: (**1***EtOH*); grey line: (**1***EtOH*)-benzoate adduct). Inset: trend of the absorbance at 301 or 655 nm vs. equiv. of benzoate ([**1***EtOH*] = $5.5 \cdot 10^{-4}$ mol dm^{-3} (Vis), $1.83 \cdot 10^{-5}$ mol dm^{-3} (UV), EtOH, 25 °C).

ClO_4)}$(H_2O)_2]_2 \cdot 2(ClO_4) \cdot 2$EtOH (**1***EtOH*)[56] obtained from slow evaporation of an ethanol solution of the complex (Figure S1).

Interaction with simple carboxylate guests

UV-Vis absorption titrations were performed in order to investigate the spectrophotometrical behavior of **1***EtOH* towards different carboxylate guests (X). To assess the feasibility of the system to analyze aqueous samples, the carboxylate guests were added as aqueous solutions, revealing the stability of the tetranuclear complex in such a mixed ethanol/water environment.

In a typical titration, an increasing amount of the X anion up to 5 equiv. was added to an ethanolic solution of **1***EtOH*. Aqueous solutions of sodium or tetrabutylammonium salts of X were used to the purpose and the tetranuclear species was considered to be the only one existing in solution, so the addition of the X ion can be interpreted as the interaction with such a species. As previously reported, the UV-Vis spectrum of $[Ca\{Cu(H_{-2}\mathbf{L})\}]_2^{4+}$ in ethanol solution shows two main bands centered at λ_{max} 292 ($\varepsilon = 31100$ cm^{-1} mol^{-1} dm^3) and 550 ($\varepsilon = 257$ cm^{-1} mol^{-1} dm^3) nm, respectively attributed to the n→π* electronic transitions of deprotonated maltol moieties coordinated to both Cu^{2+} and Ca^{2+} and to the coordinated Cu^{2+} chromophore d-d electronic transitions.[57]

As a first step, simple carboxylate ions as acetate and benzoate have been tested to verify the ability of the platform to interact with such guests. The Vis range of the titrations are reported in Figures 3 (right) and S2 (right). Both anions similarly perturb the d-d Cu^{2+} transition, red shifting the band from 550 to 653 and 660 nm for acetate and benzoate, respectively, also lowering the absorbance by 20%. The variation can be thus ascribed to the coordination of acetate and benzoate to Cu^{2+} by straightforward replacement of ClO_4^-, as previously described for Cl^- and Br^-. The red shift of the band suggests the lowering of the d-d energy gap upon replacement of ClO_4^- with carboxylates. In both cases, the trend of the absorption at ≈650/660 nm vs. the equivalents of acetate and benzoate plateaued after 2 equiv. of anion added with respect to the tetranuclear complex, meaning that the two copper(II) ions in the platform are able to bind two anions in solution. It is possible to suggest that the carboxylate guests are bridged by Cu^{2+} and Ca^{2+}, as it occurs in the solid state. The displacement of the coordinated perchlorates upon the binding of the carboxylates is accompanied by a color change of the ethanolic solution from pink to green, which is clearly visible to the naked eye (Figure 4).

The binding of benzoate is confirmed by the crystal structure of complex $[Ca\{Cu(H_{-2}\mathbf{L})\}(OBz)_{1.5}]_2 \cdot (ClO_4) \cdot 0.5(H_2O) \cdot$EtOH (**2**) obtained in the solid state from slow evaporation of an ethanol solution containing the tetranuclear complex and the benzoate anion (Figure 5).

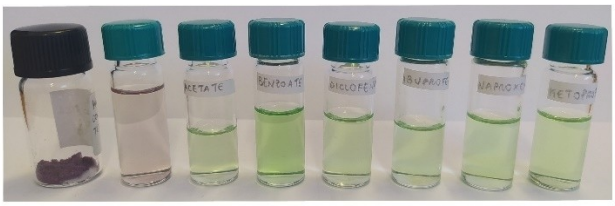

Figure 4. Samples of the tetranuclear complex in the solid state and in ethanol solution (pink); adducts formed in ethanol solution upon addition to the tetranuclear complex of 5 equiv. of (from left to right): acetate, benzoate (as tetrabutylammonium salts), diclofenac, ibuprofen, naproxen and ketoprofen (as sodium salts).

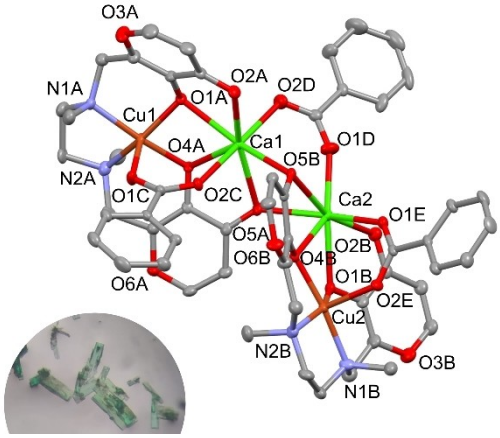

Figure 5. ORTEP-3 view of the asymmetric unit of $[Ca\{Cu(H_{-2}\mathbf{L})\}(OBz)_{1.5}]_2^+$ cation in **2** (ellipsoid probability: 30%). Hydrogen atoms have been omitted for the sake of clarity and labels have been added only for selected atoms. Bottom: picture of single crystals of **2**.

Table 1. Crystal data and refinement parameters of **2**.

	2
Formula	$[Ca\{Cu(H_{-2}\mathbf{L})\}(OBz)_{1.5}]_2\cdot(ClO_4)\cdot0.5(H_2O)\cdot EtOH$
MW	1393.74
T (K)	100
λ (Å)	1.54178
Crystal system, space group	monoclinic, $P2_1/c$
Unit cell dimensions (Å, °)	a = 9.3680(3) b = 25.9868(8); β = 95.272(2) c = 24.4282(8)
Volume ($Å^3$)	5921.8(3)
Z, dc (mg/cm^3)	4, 1.563
μ (mm^{-1})	3.553
F(000)	2876
Crystal size	0.23 × 0.21 × 0.18
Reflns collected / unique (Rint)	65707/10614 (0.1041)
2θ range (°)	4.98/136.55
Data / parameters	10614/792
Final R indices [$I > 2\sigma$]	R1 = 0.0733, wR2 = 0.2031
R indices (all data)	R1 = 0.0888, wR2 = 0.2270
GoF	1.039

Table 1 reports crystal data and refinement parameters for **2**. In the asymmetric unit of **2** one $[Ca\{Cu(H_{-2}\mathbf{L})\}(OBz)_{1.5}]_2^+$ cation, one perchlorate anion, one EtOH molecule and a half water molecule in disordered position are present. The structure of the $[Ca\{Cu(H_{-2}\mathbf{L})\}(OBz)_{1.5}]_2^+$ cation in **2** was compared with those of three similar complexes of formula $[Ca\{Cu(H_{-2}\mathbf{L})\}(H_2O)_2(\mu\text{–}ClO_4)]_2^{2+}$ from **1***H*$_2$*O*, $[Ca\{Cu(H_{-2}\mathbf{L})Cl\}(H_2O)_2]_2^{2+}$ and $[Ca\{Cu(H_{-2}\mathbf{L})(H_2O)\}(H_2O)(NO_3)]_2^{2+}$, respectively (CSD[58] refcodes: LOMHAY,[51] OWUJUO and OWUKAV[50]), that differ for the inorganic anion that completes the coordination sphere of the copper and calcium cations. In all the four complexes the $(H_{-2}\mathbf{L})^{2-}$ ligand takes a U-shaped conformation due to the coordination of the copper cation, as previously reported.[50]

While in **1***H*$_2$*O*, OWUJUO and OWUKAV the $[Cu(H_{-2}\mathbf{L})]$ unit almost lies on a plane (the two maltol rings of the ligand form an angle comprised in the 11–30° range, Figure 6), the angles between the ring planes observed in **2** are larger (54.1(2) and 43.0(2) for the a and b ligand within the complex, respectively), thus the ligand adopts a more folded overall conformation (Figure 6).

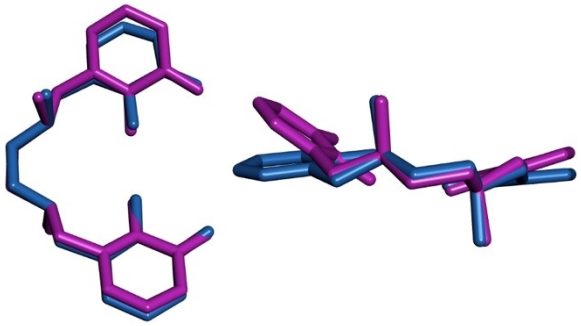

Figure 6. Top and side views of the superimposition of the $(H_{-2}\mathbf{L})^{2-}$ ligand in **2** (purple) and **1***H*$_2$*O* (blue).

As in **1***H*$_2$*O*, OWUJUO and OWUKAV, also in **2** the copper cations show a square pyramid coordination polyhedron. The Cu^{2+} ions are coordinated by the two nitrogen atoms and the two deprotonated oxygen atoms of the malten ligand and the coordination sphere is completed by an oxygen atom of a benzoate anion that occupies the apex position (Figure S3).

As observed in **1***H*$_2$*O*, the external ligand (i.e. perchlorate and benzoate anion in **1***H*$_2$*O* and **2**, respectively) and the oxygen atoms O1 and O4 of the malten molecule act as bridging ligands linking together the copper and calcium cations (O1a and O4a for Cu1/Ca1, O1b and O4b for Cu2/Ca2). The different distance between the two donor oxygen atoms in the coordinated anions (O···O = 2.237(6)/2.240(5) Å in **2** and 2.344(7) Å in **1***H*$_2$*O*) implies a shorter Cu···Ca distance in **2** with respect to **1***H*$_2$*O* (Cu···Ca = 3.320(1)/3.313(1) Å in **2** vs. 3.429(2) Å, respectively) and may explain the different conformation observed in **2** for the $[Cu(H_{-2}\mathbf{L})]$ unit.

Finally, the third benzoate anion, together with the oxygen atoms O5a and O5b bridges the two calcium cations. As a consequence, each Ca^{2+} is hepta-coordinated by four oxygen atoms of one $(H_{-2}\mathbf{L})^{2-}$ unit, one oxygen atom of the second $(H_{-2}\mathbf{L})^{2-}$ unit (O5) and two oxygen atoms of two different benzoate anions, with a distorted pentagonal bipyramid as the resulting coordination (as observed in OWUJUO).

Due to the presence of a benzoate anion bridging together the two Ca^{2+} cations, the overall shape of the $[Ca\{Cu(H_{-2}\mathbf{L})\}(OBz)_{1.5}]_2^+$ species in **2** is very different from that observed in the other three structures (Figure 7). Indeed, while in the latter the two $[Cu(H_{-2}\mathbf{L})]$ moieties (defined by the mean plane passing through the N1, N2, O1, O2, O4 and O5 donor atoms) are coplanar, in **2** the same two moieties are almost perpendicular (angle between the mean planes: 87.27(6)°).

The binding in solution of a third anion could not be ruled out, as suggested by both the crystal structure (see above) and the Vis measurements, since two calcium sites are still available for a carboxylate to be possibly bound in a bridge disposition between the two Ca^{2+} metal centers: evidently, the coordination of a guest to Ca^{2+} would not significantly perturb the Cu^{2+}

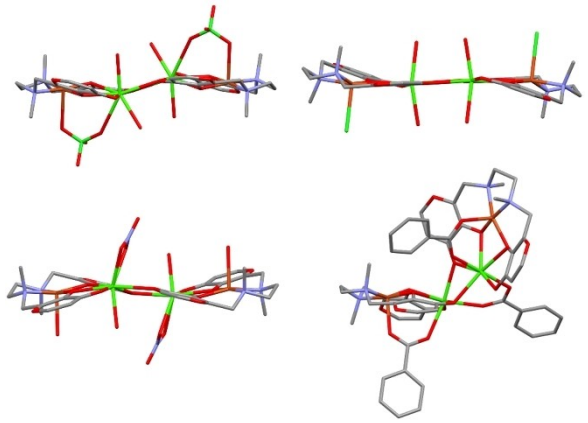

Figure 7. Stick representation of the tetranuclear cations in: top: **1***H*$_2$*O* (left), OWUJUO (right); bottom: OWUKAV (left), **2** (right).

-chromophore and would not be visible in the current analysis. In addition, working at higher concentrations allows to reach the saturation of the system sooner, as a consequence more diluted conditions could possibly give more information. To try to get more insights in this regard, similar measurements in the UV range in more diluted conditions were performed, to follow the behavior of the maltolate moieties coordinated to both Cu^{2+} and Ca^{2+} upon addition of the anions.

The trend of the absorption at 301 nm vs. the equivalents of benzoate indeed reached a plateau above the addition of two equivalents of anion, possibly suggesting the binding in solution of three guests (Figures 3, left and S2, left).

Interaction with NSAID guests

After ascertained that the tetranuclear platform is able to bind simple carboxylates, more complex systems containing carboxylate groups belonging to NSAIDs were tested. More in detail, sodium salts of diclofenac, ibuprofen, naproxen and ketoprofen dissolved in water were employed to perform UV-Vis absorption titrations as described above (from now on, the use of terms diclofenac, ibuprofen, naproxen and ketoprofen is intended as their anionic form from sodium salts). Unfortunately, no data can be derived from measurements in the UV range with diclofenac and ketoprofen, since these species show broad absorption bands that sum up with that of the tetranuclear complex (292 nm complex, 284 nm diclofenac, 254 nm ketoprofen).

In all cases, the addition of the guest provokes a red shift of the band of the tetranuclear complex and a lowering of the absorption, with a titration profile in the Vis range similar to that of benzoate (Figures S4–S7).

It has to be noticed that for all samples the spectra in the visible range are much more perturbed than those in the UV region by the coordination of carboxylates, with a larger red shift of the λ_{max} ($\geq$100 nm in the Vis range vs. $\approx$5 nm in the UV range) and a more pronounced absorption drop (drop between 20 and 30% in the Vis range vs. a drop between 3 and 15% in the UV range). The six tested anions can be divided into two families, with benzoate, ibuprofen, naproxen and ketoprofen shifting the band in the Vis region up to $\approx$660 nm, while acetate and diclofenac only reaching $\approx$650 nm (Figure 8). Anyway, all carboxylate guests shift the λ_{max} of the band of the Cu^{2+}-chromophore more than Cl^- does (642 nm)[50] and the binding of the anions can be followed with the naked eye (Figure 4).

For all carboxylates, in the whole UV-Vis region the trend of the absorption at the reached maximum vs. the equivalents of anion plateaued after 2 equivalents of anion added with respect to the tetranuclear complex, indicating that the latter can bind even species more complex than acetate and benzoate in solution and that it can bind two guests. However, the binding of a third anion could not be totally ruled out on the basis of these experiments.

It must be noted that, contrarily to the tested NSAIDs, the chloride guest did not affect the absorption of the tetranuclear complex in the UV region (neither did the other halides), meaning that the maltolate moiety coordinated to both Cu^{2+} and Ca^{2+} was not significantly perturbed by the presence of Cl^-.[50] However, the solid state analysis clearly showed a chloride occupying the apex position of the square pyramid around copper in place of the oxygen atom of the original perchlorate anion; likewise, it can be supposed that chloride is coordinated to Cu^{2+} in solution, too. The perturbation of the absorbance in the UV region observed in the present analysis may thus be due to a different influence of carboxylates on the geometry of the complex compared to chloride, due to their larger size, bidentate behavior and oxygen donor atoms, resulting in a perturbation of the coordinated maltolate moiety. In addition, the binding of a carboxylate to the calcium ion could impact the electrostatic interaction between Ca^{2+} and the maltolate group thus affecting the electronic transitions on the maltolate moiety, accordingly showing a shift in the spectrum.

The stability constants of the species formed within the X/[{Ca[Cu(H$_{-2}$**L**)]}$_2$(ClO$_4$)$_2$]$^{2+}$ systems are too high to be safely determined by spectrophotometric measurements.

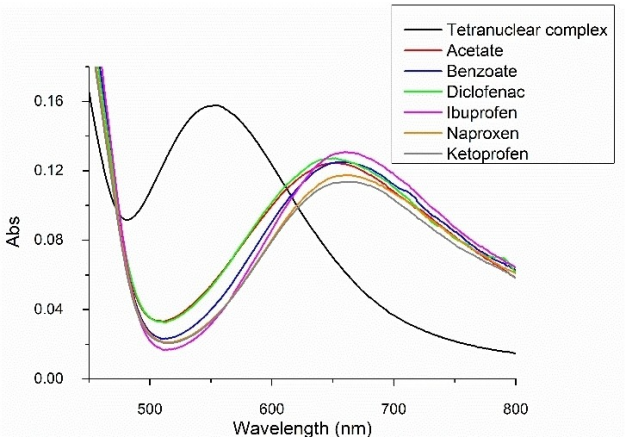

Figure 8. Superimposition of the spectra of tetranuclear complex-anionic guest adducts ([**1***EtOH*] = 5.5·10^{-4} mol dm^{-3}, EtOH, 25 °C).

This is not surprising if taking into account the high constant values found for the addition of halide guests ([{Ca[Cu(H_{-2}**L**)]}$_2$(ClO_4)$_2$]$^{2+}$ + X = [{Ca[Cu(H_{-2}**L**)]}$_2$(X)(ClO_4)]$^{2+}$ + ClO_4^-: Log K = 4.43 (X = Cl^-); 3.80 (X = Br^-); [{Ca[Cu(H_{-2}**L**)]}$_2$(X)(ClO_4)]$^{2+}$ + X = [{Ca[Cu(H_{-2}**L**)]}$_2$(X)$_2$)]$^{2+}$ + ClO_4^-: Log K = 4.39 (X = Cl^-); 3.54 (X = Br^-)).[50] This suggests that the Cu^{2+}/Ca^{2+}/Ca^{2+}/Cu^{2+} platform possesses a higher affinity for the carboxylate guests than for halides; probably, this can be attributed to the ability of the carboxylate guest to simultaneously bind the Cu^{2+} and Ca^{2+} ions in a bridge disposition, as suggested by the crystal structure of **2**.

The statistical analysis of the trend of absorption of the platform upon addition of carboxylate guests through the linear regression method[59] furnished limit of detection (LOD) values comprised between 3.6 and 20.7 ppm (Table S1, Figure S8).

The ability of the platform to bind carboxylates was also tested in the presence of a competing anion such as chloride. Titrations with acetate, benzoate and NSAIDs were performed in the presence of a 0.5 or $8{\cdot}10^{-3}$ mol dm^{-3} Cl^- solution, representative of the chloride content in sea- and fresh water, respectively. Both media containing chloride at different concentrations showed the band at ca. 640 nm due to the formation of the chloride complex (Figure S9, dashed lines), as previously reported.[50] The addition of carboxylates provoked the red-shift of the band at 640 nm in all cases except for diclofenac, suggesting the replacement of chloride anions with carboxylates in the coordination to the metal centers (Figure S9). As expected in competitive binding experiments, a higher amount of guest is needed to reach or at least to shift the starting band (640 nm) towards the same maxima observed in the absence of chloride, especially when a large excess of Cl^- is present (0.5 mol dm^{-3}) (see Table S2). For instance, in the case of naproxen, when working in a low Cl^- concentration a λ_{max} of 662 nm is reached upon the addition of 7 equivalents of guest, while a λ_{max} of 654 nm was reached with ten equivalents of guest in a high Cl^- concentration (Figure S10).

Among all anions tested, only the addition of diclofenac did not cause any shift of the band at both Cl^- concentrations, suggesting that it is not able to replace chloride in the coordination to the platform at these concentrations. In other words, five out of six carboxylates tested are able to bind the platform also in the presence of the competitive chloride guest, displacing it from the coordination to the Cu(II) ion, not only at a concentration simulating the drinking water but also at the higher concentration of the sea water. The higher affinity of carboxylates for the platform compared to chloride is likely due to the optimal distance between the Cu^{2+} and Ca^{2+} metal ions and to their nature, that allow for a bridge disposition of the carboxylate guests via their oxygen atoms. Given this higher affinity, the system can therefore signal the presence of NSAIDs even in the presence of a large excess of chloride.

Chemosensing ensemble approach

The colorimetric change in the solution is an easy and fast way to monitor the anion binding, indeed all guests induce a color variation from pink to green which is clearly visible to the naked eye. Unfortunately, since the colorimetric change depends on the coordinated Cu^{2+} chromophore, whose absorption coefficient is necessary low, the sensitivity is also low and scarce selectivity is observed within the series (Figure 4).

To overcome this issue, a useful fast, sensitive and low-cost technique able to signal the binding of a guest in solution such as fluorimetry could possibly be employed; unfortunately, the tetranuclear complex is not fluorescent itself, nor it becomes emissive upon coordination of the carboxylate guests (of which only naproxen is emissive in ethanol, with λ_{em} 354 nm). For this reason, a chemosensing ensemble approach has been exploited for the qualitative sensing of NSAIDs. The technique consists in the employment of a signaling ligand (a fluorophore) able to interact with the tetranuclear platform, whose emission is quenched as long as it is bound to the platform, while the fluorescence is switched-ON in the presence of a competitive ligand that displaces the fluorophore in the coordination. The interaction with the analyte would indeed replace that with the fluorophore, and once the latter is released in solution its emission gradually returns to the original state (Figure 9).

In the present analysis, fluorescein disodium (disodium 2-(3-oxido-6-oxoxanthen-9-yl)benzoate, FL) was chosen as the signaling ligand. The fluorophore has been chosen for its high quantum yield, the availability of –COOH/–OH groups suitable for the coordination to a metal center and the solubility in ethanol. To favor the existence of the dianionic form of FL (FL^{2-},

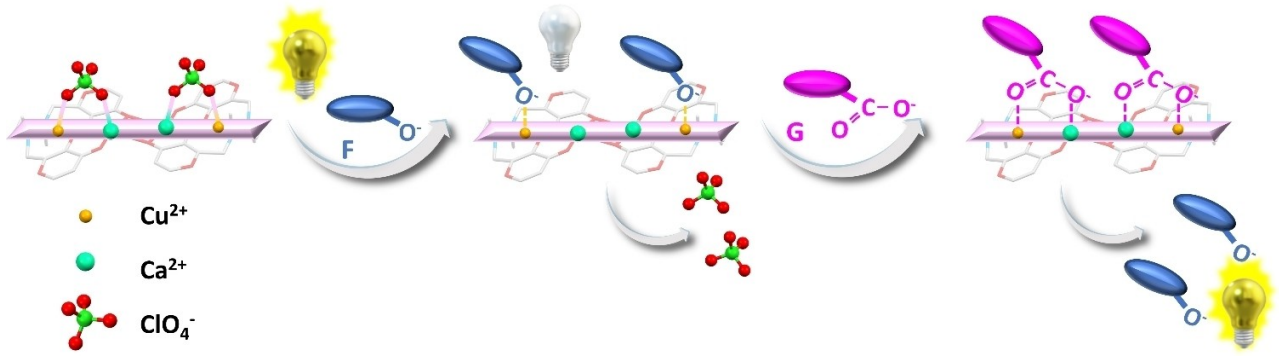

Figure 9. The chemosensing ensemble approach (F = Fluorophore; G = Guest).

Figure S11), that is the most emissive protonated species of this fluorophore, two equivalents of NMe_4OH were added to its ethanol solution. In this solvent, indeed, the acidity of FL is decreased with respect to water, due to lower number of donor atoms, dielectric constant and solvating power of ethanol.[60] The addition of the base raises both the absorption (λ_{max} 500 nm) and the emission intensity (λ_{ex} 500 nm, λ_{em} 520 nm) of the dianionic form (Figure S12). Finally, the working concentration of FL is as low as $2.26\,10^{-6}$ mol dm^{-3}, to ensure the presence of the molecule as a monomer, avoiding the risk of aggregation to form a dimer.[61–63]

The mixing of the tetranuclear complex and the FL solution in a 1:2 molar ratio efficiently quenches the fluorescence emission of FL down to 3% (Figure 10). On the other hand, the absorption of the dianionic form (λ_{max} 500 nm) greatly increases (Figure S13), suggesting that the addition of the complex favors the deprotonation of the monoanionic form, shifting the equilibrium towards the FL^{2-} species. It can be hypothesized that the acidity of the –OH of the carboxylic or, more probably, the phenol group of FL,[64] that interacts with the metal center replacing the perchlorate anion, is indeed increased by the Cu^{2+}-coordination. Taken together, these data suggest a coordination of the fluorescein moiety from the tetranuclear complex with a consequent quenching of the emission due to the paramagnetic effect of Cu^{2+}.

The addition of a carboxylate guest mainly affects the emission behavior of the system; the absorption is also perturbed, but only to a lesser extent. In the case of naproxen, the emission intensity at 520 nm gradually increases, reaching that of the free FL in solution upon the addition of 80 equivalents of the guest (Figure 10).

On the other hand, the absorption of the band of the dianionic form (λ_{max} 500 nm) undergoes a little decrease, whereas the absorption in the 410–455 nm region increases, with an isosbestic point at 466 nm (Figure S13). This points at a small shift of the equilibrium back to the monoanionic form of FL, suggesting that the fluorophore is slowly getting released from the complex and, being again free in solution, tends to go back to its more stable form in ethanol (HFL^-). This aspect is supported by the fact that additional carboxylate guest further increases the emission beyond that of the free FL in sole ethanol solution (in the presence of two equivalents of NMe_4OH): the additional carboxylate guest acts as a base on the free fluorophore, increasing the amount of the dianionic form and, as a consequence, the emission intensity. The absorption spectrum indeed shows that the FL^{2-} form (λ_{max} 500 nm), notwithstanding its small drop, continues to prevail over the HFL^- form. In other words, the guest "buffers" the equilibrium shift that would be observed in the absence of a compound having basic properties in solution. It must be highlighted that at the working concentrations, the absorption signal of the guest does not overlap with the absorption of FL.

These data point at an extremely stable adduct between FL and the tetranuclear complex, indeed its formation constant is too high to be reliably calculated from spectrophotometric data. As a consequence, many equivalents of guest are needed to completely restore the emission of the free fluorescein and the apparent formation constants of 1:1 adducts between the FL-tetranuclear platform complex and NSAID guests are generally low (Table S3).

The same behavior described for naproxen can be applied to all other carboxylate guests. Anyway, the chemosensing ensemble approach revealed a certain degree of selectivity between the tested anions. In all cases an excess of guest is needed to completely restore the fluorescence of FL (Figure 11, cyan line), though this amount greatly varies within the series of tested carboxylates. More in detail, naproxen and ketoprofen require the least number of equivalents (with respect to the complex) to restore FL emission (70–80 equiv., Figure 11,

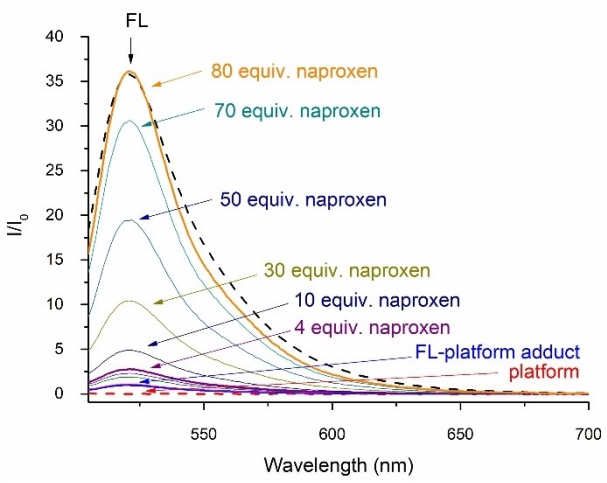

Figure 10. Chemosensing ensemble with naproxen. Black dashed line: FL; red dashed line: tetranuclear complex; blue solid line: tetranuclear complex-FL 1:2 adduct. Addition of naproxen to the adduct (equiv.): 0.1 (magenta), 1 (olive), 2 (violet), 4 (purple), 10 (navy), 30 (dark yellow), 50 (blue), 70 (dark cyan), 80 (orange). [**1***EtOH*] = $1.13\cdot10^{-6}$ mol dm^{-3}, [FL] = $2.26\cdot10^{-6}$ mol dm^{-3}, λ_{ex}: 500 nm, EtOH, 25 °C.

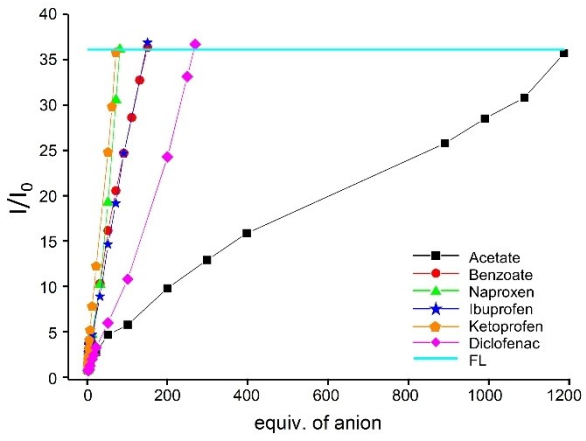

Figure 11. Comparison between trends of normalized emission at λ_{em} 520 nm upon addition of acetate (black squares), benzoate (red circles), ibuprofen (blue stars), naproxen (green triangles), ketoprofen (orange pentagons) and diclofenac (magenta diamonds) to the 1:2 tetranuclear complex-FL adduct in ethanol (λ_{ex}: 500 nm). The cyan line is the emission of free FL (+2 equiv. NMe_4OH). Equiv. of anions are calculated with respect to the complex.

orange pentagons and green triangles), followed by ibuprofen and benzoate (150 equiv., Figure 11, blue stars and red circles) and diclofenac (270 equiv., Figure 11, magenta diamonds). Finally, to achieve the complete fluorescence restoration more than 1000 equiv. of acetate (1200 equiv., Figure 11, black squares) are needed.

These results suggest naproxen and ketoprofen to be the best performing competitors of FL in ethanol, while acetate is the worse.

The sensitivity towards naproxen has been tested in the presence of a mixture of 20, 25 and 50 equiv. of all other carboxylates (acetate, benzoate, ibuprofen, diclofenac and ketoprofen) with respect to the tetranuclear complex. By exciting at 500 nm, a fluorescence emission increase at 520 nm was observed starting from 5 equiv. of naproxen, suggesting that the sensitivity towards such a guest is preserved also in the presence of interfering anions.

A possible role of the aromatic rings in NSAIDs and FL in the binding of anions could not be totally ruled out, however the obtained crystal structure with benzoate clearly shows the formation of only a coordination bond between the $-COO^-$ group of the anion and the metal centers. Moreover, a π–π stacking interaction between FL and the guests could be also excluded based on the fact that the emission of FL is restored upon the addition of the guest, suggesting the release of the fluorophore in solution following an exchange process. This would not be observed in case of the formation of a π–π stacking interaction.

The development of an easy and rapid qualitative procedure to assess the presence of carboxylates in solution could be of interest, due to their role as EPs. To this purpose, the chemosensing ensemble system was moved from the solution environment to a solid support by performing a paper strip test. The test allows in principle to rapidly and qualitatively signal the presence of carboxylate guests in a sample via a fluorescence signal.

To assess the feasibility of the system, the fluorescence emission of FL on the paper and the quenching ability of the tetranuclear complex on this support was first verified. To this aim, simple filter paper strips were immersed in an ethanolic solution of FL ($6.67\cdot10^{-5}$ mol dm^{-3}) for a few minutes; after complete drying, the emission of the FL deposited on the paper was verified and confirmed under a 360 nm UV lamp (F in Figure 12, left). A strip was then partially soaked in an ethanolic solution of the tetranuclear complex ($3.33\cdot10^{-5}$ mol dm^{-3}). Once dried, the immersed paper portion revealed the desired quenching of the emission under a 360 nm UV lamp compared to that of FL (Figure 12, left).

The chemosensing ensemble was thus tested by soaking a paper in a mixture of tetranuclear complex and FL (1 : 2 molar ratio) in ethanolic solution. Following complete drying, the paper showed, as expected, a diminished fluorescence emission compared to FL. Deposition of guest solutions with increasing concentrations was then performed (Figure 12, right), revealing that the emission of FL under a 360 nm UV lamp is enhanced in the case of acetate, naproxen, ibuprofen and ketoprofen, while

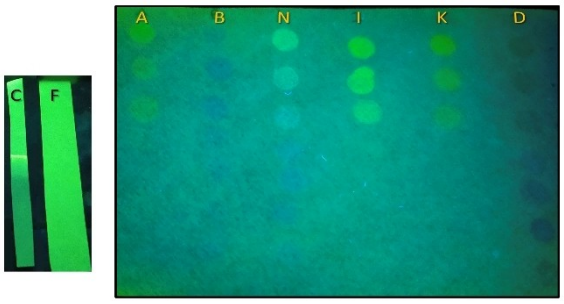

Figure 12. Paper strip test. Left: F: filter paper soaked in an ethanolic FL solution ($6.67\cdot10^{-5}$ mol dm^{-3}); C: same filter paper as F partially immersed in an ethanolic tetranuclear complex solution ($3.33\cdot10^{-5}$ mol dm^{-3}). Right: filter paper immersed in a 1 : 2 tetranuclear complex-FL solution in EtOH on which 1 ml of guest solution at growing concentrations (from bottom to top: $4.95\cdot10^{-4}$, $1.65\cdot10^{-3}$, $2.67\cdot10^{-3}$, $4.95\cdot10^{-3}$, $1.67\cdot10^{-2}$, $2.67\cdot10^{-2}$, $4.95\cdot10^{-2}$ mol dm^{-3}) was deposited. A = acetate, B = benzoate, N = naproxen, I = ibuprofen, K = ketoprofen, D = diclofenac. All paper strips were observed under a UV lamp at 360 nm.

benzoate and diclofenac seemed to show a quenching of fluorescence.

In these conditions, to appreciate the switch-ON of the fluorescence on the paper strip, concentrations as high as $\geq 4.95\cdot10^{-3}$ mol dm^{-3} (for ibuprofen) or $1.67\cdot10^{-2}$ mol dm^{-3} (for ketoprofen and acetate), corresponding to 150 or 500 fold the concentration of the complex, respectively, are needed.

In the case of naproxen, the blue emission at lower concentrations of the guest is probably related to the emission of naproxen itself; at higher concentrations, the emissions of both naproxen and FL are visible at this excitation wavelength, returning a light blue emission instead of yellow. Ibuprofen and naproxen returned the most intense signals, followed by ketoprofen and acetate. The paper strip test therefore proved successful in signaling the presence of carboxylates, more in particular of NSAIDs, showing a certain degree of selectivity within the tested anions.

Finally, since the aim of this work was the development of a system for an easy one-time detection of carboxylates and NSAIDs, only one assay was performed both in solution and on a paper support.

Conclusion

The binding ability of a $Cu^{2+}/Ca^{2+}/Ca^{2+}/Cu^{2+}$ hetero-tetranuclear complex containing the ligand Malten has been further investigated towards carboxylate guests, both in solution and solid state. The $Cu^{2+}/Ca^{2+}/Ca^{2+}/Cu^{2+}$ hetero-tetranuclear architecture has been confirmed in a crystal structure obtained from ethanol solution and the anion-exchange in solution between perchlorate and benzoate anions has been confirmed through X-ray diffraction of the obtained single crystals, showing the binding of three anions.

The spectrophotometric analysis in ethanol solutions revealed the ability of the tetranuclear platform to bind up to two carboxylate guests, added as aqueous solutions, ranging from

simple anions, such as acetate and benzoate, to more complex structures, such as NSAIDs (ibuprofen, naproxen, ketoprofen, diclofenac). The guests replace the coordinated perchlorate anions forming stable complexes and red-shifting the absorption band of more than 100 nm. The binding of a third anion, as suggested by the solid state analysis, could not be ruled out. Notably, the system works also in the presence of one of the most competitive anions present in the environment, such as chloride. The formation of the complexes goes along with the change of the color solution from pink to green, which makes the system a colorimetric sensor for carboxylate anions. The tetranuclear platform has been also tested towards the same guests by using a chemosensing ensemble approach, employing sodium fluorescein as the signaling fluorophore moiety in a low working concentration, so as to avoid the formation of dimers. The addition of the tetranuclear complex to an ethanolic solution of fluorescein in a 1:2 molar ratio efficiently quenches the emission of the fluorophore, that is then restored upon the addition of the guests. Taking into account that fluorescein forms an adduct with the tetranuclear platform with a very high formation constant value, naproxen and ketoprofen resulted the best competing binders, requiring the least number of equivalents to replace fluorescein. The chemosensing ensemble approach has been also tested on paper strips, to evaluate a practical application of the system, with naproxen, ketoprofen and ibuprofen returning the best result. Considering all data, the present system can be reasonably considered a dual colorimetric and fluorescent chemosensor for carboxylates.

Experimental Section

Synthesis: Compounds **L** (**L** = Malten) and complex normales - und bei · $[Ca\{Cu(H_{-2}\mathbf{L})(m\text{-}ClO_4)\}(H_2O)_2]_2\cdot 2(ClO_4)$ (**1***H*$_2$*O*)[51] were obtained following the synthetic procedures reported previously.[51,53]

$[Ca\{Cu(H_{-2}\mathbf{L})(\mu\text{-}ClO_4)\}(H_2O)_2]_2\cdot 2(ClO_4)\cdot 2EtOH$ (**1***EtOH*):[56] a sample of solid **1***H*$_2$*O* was dissolved in ethanol: purple single crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of such a solution.

$[Ca\{Cu(H_{-2}\mathbf{L})\}(OBz)_{1.5}]_2\cdot(ClO_4)\cdot 0.5(H_2O)\cdot EtOH$ (**2**): a sample of solid **1***H*$_2$*O* was dissolved in ethanol and an excess of NBu_4OBz (OBz = benzoate) was added, obtaining a green solution. Green crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of such a solution.

X-ray crystallography: Intensity data for compound $[Ca\{Cu(H_{-2}\mathbf{L})\}(OBz)_{1.5}]_2\cdot(ClO_4)\cdot 0.5(H_2O)\cdot EtOH$ (**2**) were collected with the Bruker APEX2 program[65] and reduced with the Bruker SAINT[66] one. The structure was solved using the SIR-2004 package[67] and refined by full-matrix least squares against F^2 using all data (SHELX2018/3[68]). All the non-hydrogen atoms, except for the oxygen one of the disordered water molecule, were anisotropically refined. All hydrogen atoms were set in calculated position and refined in accordance with the atoms to which they are bonded, except for those of the water molecule, that were not introduced in the refinement. The disorder of the water molecule was modelled introducing in the refinement two positions for the oxygen atom, each model having an occupancy factor of 0.25. Table 1 reports crystal data and refinement parameters for **2**. In Figure 5 the ORTEP-3 view of the $[Ca\{Cu(H_{-2}\mathbf{L})\}(OBz)_{1.5}]_2^+$ cation is shown. Geometrical calculations were performed by PARST97[69] and molecular plots were produced by the program Mercury (v2020.2.0)[70] and Discovery Studio Visualizer 2019.[71]

Deposition Number 2151003 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

UV-Vis experiments: UV-Vis absorption spectra were recorded in ethanol at 298 K on a Varian Cary-100 spectrophotometer equipped with a temperature control unit.

UV-Vis titrations of **1***EtOH* with NBu_4OAc, NBu_4OBz, NaIbuprofen, NaNaproxen, NaKetoprofen, NaDiclofenac were performed by adding to an ethanolic solution of **1***EtOH* an increasing amount of an aqueous solution of each salt up to 5 equivalents with respect to the complex. A concentration of $[\mathbf{1}EtOH] = 5.5\cdot10^{-4}$ mol dm^{-3} (Vis) and $1.83\cdot10^{-5}$ mol dm^{-3} (UV) was used for the measurements.

UV-Vis titrations of **1***EtOH* with the same anions were similarly performed also in the presence of 0.5 or $8\cdot10^{-3}$ mol dm^{-3} NBu_4Cl ($[\mathbf{1}EtOH] = 5.5\cdot10^{-4}$ mol dm^{-3}).

Chemosensing ensemble: Uncorrected emission spectra were obtained in ethanol with a Varian Cary Eclipse fluorescence spectrophotometer. Fluorescence emission titrations were performed by adding to an ethanolic solution containing **1***EtOH* and fluorescein (FL) (in the presence of 2 equiv. of NMe_4OH) in a 1:2 molar ratio an increasing amount of each carboxylate salt. Each titration was performed by adding an amount of carboxylate suitable to reach and overcome the emission of the sole fluorescein in solution (in the presence of 2 equiv. of NMe_4OH). The same samples were also analyzed at the same time on the Varian Cary-100 spectrophotometer. A concentration of $[\mathbf{1}EtOH] = 1.13\cdot10^{-6}$ mol dm^{-3} and $[FL] = 2.26\cdot10^{-6}$ mol dm^{-3} was used for the measurements. The spectrophotometric data were processed to calculate the apparent association constants. At least three sets of spectrophotometric titration curves for each anion/(**1***EtOH*-FL) system were performed. All sets of curves were treated either as single sets or as separate entities, for each system; no significant variations were found in the values of the determined constants. The HypSpec computer program was used to process the spectrophotometric data.[72]

Paper strip-based detection of Carboxylate guests: A preliminary test was performed by soaking two narrow filter papers in an ethanolic solution of fluorescein ($6.67\cdot10^{-5}$ mol dm^{-3}) for a few minutes. After complete drying, one of the two filter papers was partially immersed in an ethanolic solution containing the tetranuclear platform ($3.33\cdot10^{-5}$ mol dm^{-3}). The paper strips were observed under a UV lamp at 360 nm, showing the emission of the sole fluorescein-soaking and the quenching of the complex-soaking.

To perform the test, a filter paper of 11 × 8 cm was soaked for a few minutes in an ethanolic solution containing a 1:2 tetranuclear complex-fluorescein molar ratio. After complete drying, ethanol solutions at growing concentrations ($4.95\cdot10^{-4}$, $1.65\cdot10^{-3}$, $2.67\cdot10^{-3}$, $4.95\cdot10^{-3}$, $1.67\cdot10^{-2}$, $2.67\cdot10^{-2}$, $4.95\cdot10^{-2}$ mol dm^{-3}) of the 6 guest anions were deposited on the paper (drops of 1 μL each), that was then observed under a UV lamp at 360 nm.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: anti-inflammatory drugs · chemosensors · coordination chemistry · maltol ligands · tetranuclear complexes

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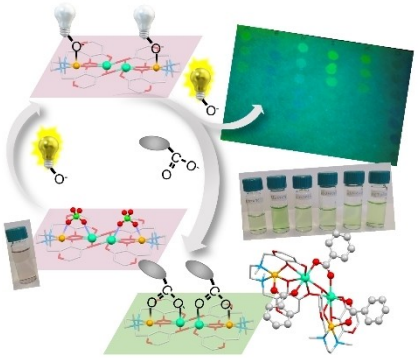
RESEARCH ARTICLE

The tetranuclear $Cu^{2+}/Ca^{2+}/Ca^{2+}/Cu^{2+}$ platform based on a maltol-containing ligand was investigated for the binding of simple carboxylates and non-steroidal anti-inflammatory drugs by means of UV-Vis spectroscopy and X-ray diffraction analysis. The complex revealed as a dual colorimetric and fluorescent chemosensor through a chemosensing ensemble approach both in solution and on a paper support.



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