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Chiroptical sensing of perrhenate in aqueous media by a chiral organic cage†

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A chiral cage is proposed as an effective chiroptical sensor for perrhenate (surrogate for $^{99}TcO_4^-$) in water, fruit juice and artificial urine media. The key mechanism for the chiroptical sensing resides in the change of dihedral angle of the binaphthyl unit and H-bonds with the guest, resulting in ample changes of the CD signal as a consequence of the binding event.

Chiroptical sensors are an emerging class of molecular or nanoscale composites for the selective detection of a wide range of chemical and biological analytes. The appearance or the modulation of the circular dichroism (CD) spectroscopy signal often represents the key channel of chiroptical readout.[1] CD spectroscopy can offer better levels of detection compared with optical absorption and emission spectroscopies and electrochemistry-based methods; it is in fact frequently used in biosensing, where high sensitivities are required.[2] Moreover, it can be selective and free of interference from non-chiral species absorbing in the same region of the UV-vis spectrum.

Organic cages, such as bistren systems, are amongst the prototypical and most studied hosts, and their outstanding properties for recognition[3,4] and sensing[5] of anions in solution have been extensively demonstrated. Amongst anions, ReO_4^- and TcO_4^- have received considerable attention since both are applied as radiopharmaceuticals,[6] and the hazardous $^{99}TcO_4^-$ species is a pollutant generated by nuclear power plants.[7] Due to the similar features of these two anions, the non-radioactive ReO_4^- is often employed as a surrogate of TcO_4^- in anion binding studies, exploiting the synergistic contribution of multiple noncovalent interactions (*e.g.* H-/X-bonding, electrostatic, anion–π, *etc.*) within the cavities of tailor-made receptors[8] or materials (such as MOFs).[9] Only a few examples of optical molecular sensors for ReO_4^- detection in water are known, mainly based on a fluorescent response for the detection.[10] However, self-absorption and the heavy-atom effect, which can be very significant in complex matrices, may hamper the application of fluorescence-based devices in real samples.

Chiral cages are rare and their applications in sensing of anions are limited to organic solvents.[11] Axially-chiral π-extended compounds are particularly suitable for application in chiroptical sensing, since the expression of chirality is embedded into a chromophore, inducing ample CD activity. We have previously demonstrated that 1,1′-binaphthyl-2,2′-diol (BINOL) based probes are excellent examples, exhibiting a "spring-like" behaviour, with an intense CD signal modulation upon subtle changes in their conformation upon binding.[12]

In this work, we show that a suitably modified cryptand, containing a BINOL-based chiral moiety as one of the spacers, can be successfully employed for the selective sensing of ReO_4^- in acidic aqueous solution and complex matrices. The new molecular system acts effectively as a supramolecular chiroptical probe and highlights the potential of CD spectroscopy as a selective, sensitive and orthogonal tool for the detection of anions in aqueous media.

Cages **1** and **2** (Fig. 1) have been synthesized in high yields using a reductive amination protocol from an "open-shell" bistren

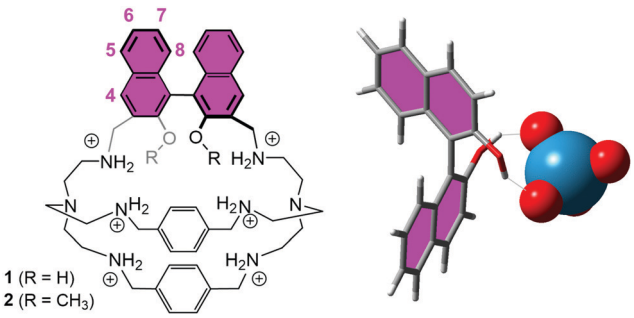

Fig. 1 Structures of **1** and **2** (left) in their hexaprotonated form (relevant protons are labeled in pink), and the mechanism of the chiroptical readout for the sensing of perrhenate based on theoretical calculations (right).

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precursor and enantiopure (*R*)-3,3′-diformyl-1,1′-binaphthyl-2,2′-diol or (*R*)-3,3′-diformyl-1,1′-binaphthyl-2,2′-dimethylether, adapting our previous procedure (details in the ESI†). In previously reported bistren cages, dialdehydes used as precursors were based on 1,4-substituted aromatic or heterocyclic cores, in which the distance between the reactive groups is approximately 6 Å. The greater distance between the two reactive aldehyde groups in the 3,3′ positions of the binaphthyl spacers (*ca.* 8 Å) does not suppress the possibility of efficient macrocyclization, and results in only a slight distortion of the molecular system, with accessible cavities for **1** and **2** and an overall C2 symmetry imparted by the chiral element. The computed models of the preferred conformers of **1** and **2** are shown in Fig. S1 (ESI†).

The (*R*)-BINOL moiety has a double role. On the one hand, it can serve as the signalling unit, due to both the strong variation of CD spectra and the modulation of its fluorescent emission[13] in response to a binding event.

On the other hand, the BINOL unit has H-bonding groups, and can cooperate with the positively charged NH donors in the binding process. The active role of the BINOL OH groups as H-bonding donors is unravelled in this work by comparing the binding properties of **1** with those of a methylated analogue system **2**. Because of the scarce solubility in pure water, the determination of the acid/base properties of **1** and **2** through potentiometric titrations had to be performed in aqueous mixtures, containing 35% and 70% (v/v) MeOH for **1** and **2**, respectively (see details in the ESI†). In accordance with our previous studies,[7b,8b] the most suitable form for ReO_4^- binding is the one presenting all the secondary amino groups protonated: $[\mathbf{1}H_6]^{6+}$ and $[\mathbf{2}H_6]^{6+}$. These forms prevail at pH 2 for both cryptands. In these pH conditions, the solubility of the cages was high enough (>1 mM) to allow anion binding studies to be performed in 100% H_2O.

Anion binding was found to have very little effect on the UV-vis spectrum of $[\mathbf{1}H_6]^{6+}$. The receptor showed the typical absorption band of the binaphthyl chromophore (λ_{max} = 229 nm), attributable to the π–π* transition, and a less intense band around 320 nm. Changes were negligible or attributable to the residual absorbance of the added analyte so that reliable binding constants for the anions studied (ReO_4^-, SO_4^{2-}, ClO_4^-, NO_3^-, Cl^- as their sodium salts; *e.g.* see Fig. S5, ESI†) could not be calculated. For example, in the case of ReO_4^- (Fig. S6, ESI†) a linear increase of the absorbance around 215 nm is observed in the titration, due to the absorption of the anion itself.

CD titrations were instead much more revealing (Fig. 2). The CD spectrum of the free receptor $[\mathbf{1}H_6]^{6+}$ displays the typical exciton couplet of the binaphthyl systems centred at 230 nm ($\Delta\varepsilon_{225}/\Delta\varepsilon_{235}$ = +49/−55 M^{-1} cm^{-1}), and a lower energy band around 320 nm (+7 M^{-1} cm^{-1}), also typical of the chiral chromophore. The exciton couplet is strongly affected by the added anion: ReO_4^-, in particular, promotes a slight blue-shift of the component at higher energy, and a remarkable increase of the intensity at both 222 and 235 nm (Fig. 2). The CD band around 320 nm is also affected (Fig. S8, ESI†). Similar trends were found with the other investigated anions (Fig. S9–S14, ESI†). In the case of ReO_4^-, a remarkable enhancement (+240%) of the component at 223 nm was observed (Fig. 3).

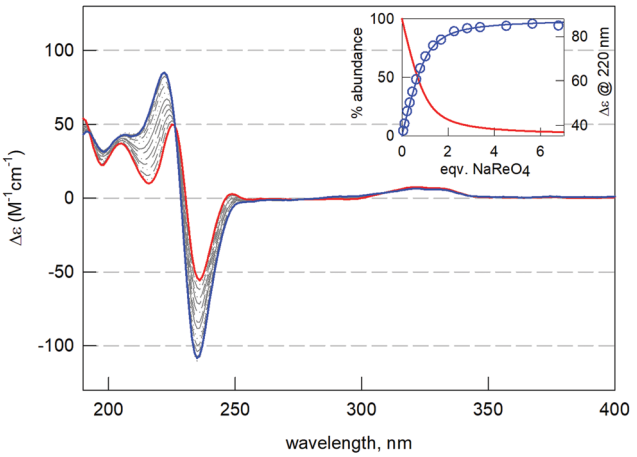

Fig. 2 CD titration of $[\mathbf{1}H_6]^{6+}$ (0.1 mM in 0.05 M CF_3SO_3Na, pH 2) with $NaReO_4$ (red and blue lines: initial and final spectra, respectively). Inset: Distribution diagram of the species (red line: % free $[\mathbf{1}H_6]^{6+}$; blue line: % $[\mathbf{1}H_6(ReO_4)]^{5+}$), superimposed to the experimental profile (circles).

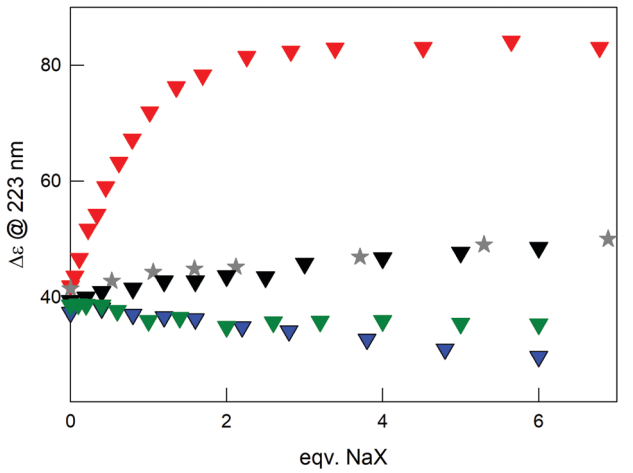

Fig. 3 Experimental titration profiles obtained from the CD titrations on $[\mathbf{1}H_6]^{6+}$ (0.1 mM) with solutions of different sodium salts (symbols: red, $NaReO_4$; blue, $NaNO_3$; green, Na_2SO_4; black triangles, $NaClO_4$; grey stars, NaCl).

The enhancement of the CD band associated to the couplet can be explained with a change of the dihedral angle between the naphthyl planes of the binaphthyl chromophore following anion binding, and the H-bonding between BINOL OH groups and ReO_4^-.

The large variation of the couplet upon subtle variations of the dihedral angle between the naphthyl units of the chromophore has been initially observed and rationalized by Superchi, Meijer and coworkers,[14] and subsequently developed by us[12] in a variety of BINOL-based macrocyclic supramolecular systems to be used as chiroptical sensors.

^{1}H-NMR spectra of $[\mathbf{1}H_6]^{6+}$ in the presence of excess equivalents of anions (Fig. S16, ESI†) in D_2O revealed small (Δppm < 0.1) but detectable shifts, with the most pronounced belonging to several proton resonances of the binaphthyl moiety, affected by the electronic perturbations due to the

Table 1 Anion binding constants ($\log K_{11}$) determined for $[\mathbf{1}H_6]^{6+}$ in aqueous solution at pH 2 (by addition of CF_3SO_3H), using various spectroscopic techniques: CD, spectrofluorimetry, ^{1}H-NMR[a]

NaX	Log K_{11}CD	Log K_{11}fluo	Log K_{11}NMR
$NaReO_4$	4.74(2)	4.70(1)	4.77(6)
Na_2SO_4	4.10(1)	4.21(4)	3.91(3)
$NaClO_4$	3.20(3)	n.a.	n.a.
$NaNO_3$	3.55(2)	n.a.	n.a.
NaCl	2.61(2)	n.a.	n.a.

[a] The uncertainty on the last figure is represented in parenthesis. *n.a.*: not available.

change of dihedral angle and the H-bonds. With two representative anions, ReO_4^- and SO_4^{2-}, full titrations were performed to allow the calculation of the binding constants (Fig. S17 and S18, ESI†). Emission spectroscopy could also be used for anion binding studies. Upon excitation at 284 nm the aqueous solution of $[\mathbf{1}H_6]^{6+}$ at pH 2 showed a fluorescence emission (λ_{max} = 370 nm). Anions were found to promote partial quenching, with 30% quenching in the case of ReO_4^- and SO_4^{2-}, whereas the effect of the other anions was significantly less remarkable (Fig. S19–S21, ESI†).

Association constants were determined and compared using various spectroscopic techniques (^{1}H-NMR, spectrofluorimetry and CD): the obtained values are remarkably consistent, and point to the formation of a 1 : 1 receptor : anion complex (Table 1). The binding constant trend shows a marked selectivity of $[\mathbf{1}H_6]^{6+}$ for ReO_4^-; absolute values are lower when compared to more symmetrical cryptands in otherwise identical conditions,[8b,9] probably due to the distorted cavity of the receptor. However, the affinity for this anion is still very high, also considering that the binding studies were carried out in concentrated triflate medium.

The decisive role of the hydroxyl groups in the BINOL cage is revealed by comparison with the methylated analogue cage, $[\mathbf{2}H_6]^{6+}$; in this case, CD titrations with anions revealed that association has a very small impact on the CD spectrum: in fact, spectra recorded in the presence of 10 eqv. NaX are almost superimposable to the spectrum of free $[\mathbf{2}H_6]^{6+}$ (Fig. S15, ESI†), testifying the negligible specific interactions of the anions with the binaphthyl moiety. Upon excitation of $[\mathbf{2}H_6]^{6+}$ at 284 nm, an intense emission band (λ_{max} = 360 nm), sensitive to ReO_4^- and SO_4^{2-} anions, was observed. The obtained binding constants (4.19(3) and 3.72(2) log units for ReO_4^- and SO_4^{2-}, respectively, Fig. S22–S25, ESI†) indicate a lower anion affinity compared to the non-methylated system $[\mathbf{1}H_6]^{6+}$. Such reduced affinities, combined with the reduced CD responses to anions, suggest an active cooperation of the BINOL OH groups in $[\mathbf{1}H_6]^{6+}$ in the anion binding.

Further insights into the structural features of the two cages upon complexation were gained through theoretical calculations (see ESI† for details). These showed significant differences in the preferred geometry of $[\mathbf{1}H_6(ReO_4)]^{5+}$ and $[\mathbf{2}H_6(ReO_4)]^{5+}$ (A and B in Fig. 4). In the most stable conformer of $[\mathbf{1}H_6(ReO_4)]^{5+}$, the cage geometry is quite similar to that of $[\mathbf{1}H_6]^{6+}$ with some variation of the dihedral angle of the binaphthyl unit. The perrhenate anion is hosted within the

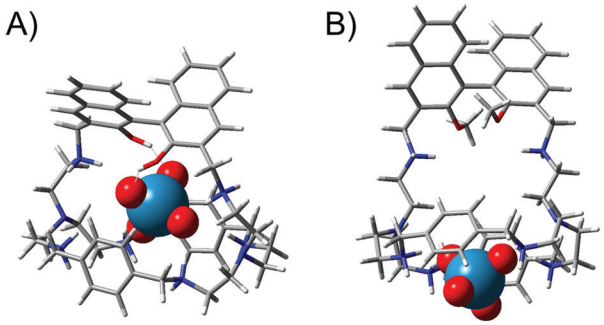

Fig. 4 Three-dimensional plots of the preferred conformers of (A) $[\mathbf{1}H_6(ReO_4)]^{5+}$ and (B) $[\mathbf{2}H_6(ReO_4)]^{5+}$.

receptor cavity, where it forms H-bonding interactions with the BINOL O–H groups as well as with the cationic N–H donors. Conversely, in the case of $[\mathbf{2}H_6(ReO_4)]^{5+}$, the binaphthyl moiety does not contribute to the complexation of ReO_4^-, which, in the preferred conformer, lies in the bottom part of the cage and interacts only with the cationic N–H donors. These results are in line with the CD titration results with $NaReO_4$.

The obtained results, and the selectivity window clearly emerging from the CD titrations with ReO_4^- (Fig. 3), encouraged us to verify the possible application of $[\mathbf{1}H_6]^{6+}$ as a chiroptical probe in complex aqueous media, such as beverages or biological fluids. For these studies, either artificial urine medium (AUM; see ESI† for details) or fruit juice were properly diluted and brought to pH 2 with aqueous CF_3SO_3H, and then were employed as solvent media in the preparation of both receptor and guest solutions (see ESI† for details).

Commercial pineapple-lime juice contains biological ingredients (mixed fruit juice) and sweeteners (steviol glycosides) with absorption in the UV-vis spectra at the wavelength of interest and thus it was chosen as an example of a real matrix. On the other hand, AUM is an example of a synthetic matrix that, besides mimicking human urine as ingredients, contains a large excess of mixed potential competitors for the receptor binding (see Table S2, ESI†). Despite potential obstacles, CD titrations on $[\mathbf{1}H_6]^{6+}$ with ReO_4^- were successful in both matrices and we could determine the binding constants, which were found to be 4.53(1) and 3.93(2) log units, in juice and AUM, respectively (see Fig. 5 and Fig. S28, ESI†), in close agreement with the values obtained in noncompetitive aqueous media (Table 1). No reliable values could be obtained by UV-vis titrations (see Fig. S30 and S31, ESI†), further strengthening the orthogonality and the practical utility of the chiroptical sensing approach.

In conclusion, we have reported a chiral molecular cage, $[\mathbf{1}H_6]^{6+}$, characterized by significant chiroptical and fluorescent responses to ReO_4^- in an aqueous solution. The chiroptical response is the consequence of the interaction with the atropoisomerically-chiral π-extended BINOL group, promoting a strong CD response upon substrate binding. The enhanced sensing response and anion binding capability of $[\mathbf{1}H_6]^{6+}$, compared to the methylated analogue system $[\mathbf{2}H_6]^{6+}$, are attributable to the contribution of the O–H donors on the

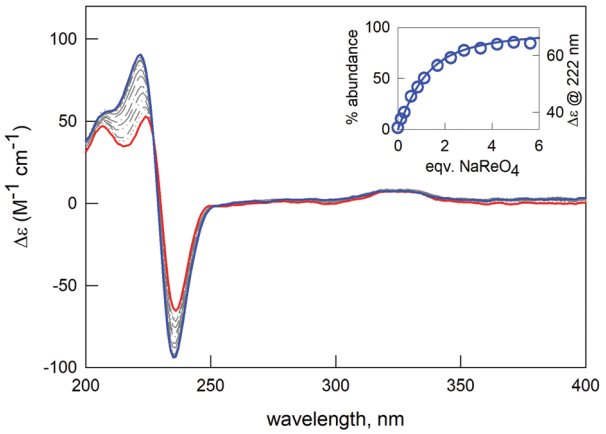

Fig. 5 CD titration of $[\mathbf{1}H_6]^{6+}$ (0.05 mM) with $NaReO_4$ in 10× diluted fruit juice at pH 2. Red and blue lines correspond to the initial and final spectra, respectively. Inset: % of $[\mathbf{1}H_6(ReO_4)]^{5+}$ *vs.* equivalents of $NaReO_4$ (blue line) superimposed to the experimental profile (blue circles).

BINOL moiety, as suggested by CD and computational studies. As far as we know, this is the first example of a chiroptical receptor in which the participation of BINOL O–H groups in anion binding is effective in pure water.[13,15] In addition, the CD response was also proven to be effective when operating on complex matrices, where interferences are present due to competition for the receptor or matrix masking effects. Due to the strong similarity of ReO_4^- with $^{99}TcO_4^-$, the chiral molecular cage $[\mathbf{1}H_6]^{6+}$ can be proposed as a chemical probe for the sensing of ^{99}Tc in water.

Considering the scarce number of chiral organic cages in the literature,[11] we believe that the results reported in this work will substantially contribute to raising the attention and the applicative technological interest on the use of simple yet efficiently designed supramolecular systems for the chiroptical sensing and the selective removal of hazardous anions.[7–10]

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Conflicts of interest

There are no conflicts to declare.

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