Halogen bonding in water results in enhanced anion recognition in acyclic and rotaxane hosts

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Halogen bonds (XB) are the attractive interactions between electron-deficient halogen atoms and Lewis bases, an intermolecular interaction akin to hydrogen bonds (HB). However, the design of XB based receptors able to strongly and selectively recognize anions in water is not trivial due to solubility effects and the competition of solvent molecules for the binding sites. In this work these issues were solved using permethylated ß-cyclodextrins as stoppers of the rotaxane's axle component. We have demonstrated the superiority of XB over HB for strong anion binding in water (a two orders of magnitude difference), to the extent that recognition by a simple acyclic axle is achievable. Quantification of iodide binding by rotaxane hosts revealed that the strong binding by the XB-rotaxane is driven exclusively by favourable enthalpic contributions arising from the XB interactions, whereas weaker association with the HB analogous receptor is entropically driven. Further insights into the structure of the halide complexes in water were obtained through molecular dynamics (MD) simulations. The structure of the iodide complex presented in Fig. 1 shows the anion is almost within the host cavity, exposed to few water molecules. The anion binding is mediated by HB with the macrocycle and by XB with the axle components, depicted as yellow and purple dashed lines, respectively. The cooperative action of both interactions led to a confined 3D histogram built with the positions occupied by the iodide throughout the MD simulation (Fig. 2). The combination of the experimental and theoretical findings show that XB in water are a strong and selective alternative to HB, leading to a superior binding affinity for iodide over bromide and chloride. In summary, this study highlights the superiority of XB over HB as an intermolecular interaction to be exploited in several fields such as green chemistry, structural biology and drug discovery.

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FIGURE 1
Representative snapshot from the MD simulation, showing the iodide binding to the rotaxane through two XB and HB interactions, surrounded by four water molecules. The N–H···I– and C–I···I– bonding interactions are drawn as purple and yellow dashed lines, respectively. The cyclodextrin stoppers are depicted by a space-filling model. Carbon atoms are shown in cyan in the axle and in orange in the macrocycle, and oxygen, nitrogen and iodine atoms are shown in red, blue and purple, respectively. Selected hydrogen atoms are shown in white.

FIGURE 2
3D histogram built with the positions occupied by the iodide (purple) along the MD simulation. The remaining color details as given in Fig.1.