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# Halogen bonding: a general route in anion recognition and coordination†

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This critical review describes how halocarbons can function as effective binding sites of anions via halogen bonding, the noncovalent interaction whereby halogen atoms accept electron density. The focus is on the binding and coordination of oxyanions, by far the most numerous class of anions in organic chemistry. It is shown how a large variety of inorganic and organic oxyanions can form discrete adducts and 1D, 2D, or 3D supramolecular networks with chloro-, bromo-, and iodo-carbons. Specific examples are discussed in order to identify new supramolecular synthons based on halogen bonding and to outline some general principles for the design of effective and selective receptors based on this interaction. The interaction allows for several other anions to self-assemble with halocarbons and mention is also given to the halogen bonding-based coordination of halides, polycyano- and polyoxometallates (72 references).

## 1. Introduction

The basic notion of the mutual matching of elements possessing complementary features has been developed in many cultures and exploited after quite different prospects.<sup>1,2</sup> Examples

can also be found in the body of knowledge of many scientific disciplines, the acid–base couple being an instance in chemistry.

Anions are electron rich species, and when the notion of mutual matching of elements possessing complementary features is used to design their binding, any electron poor species is understood as a candidate interacting site.<sup>3</sup>

Indeed, polycationic macrocycles had been used in some very elegant early works for the binding of anions in water by electrostatic interactions.<sup>4</sup> After the seminal papers of Pascal<sup>5</sup> and Sessler,<sup>6</sup> arrays of protons bound to electronegative elements (e.g. polyamides, polyureas, and polypyrroles) have been extensively used for the effective and selective binding of a variety of anions by hydrogen bonding.

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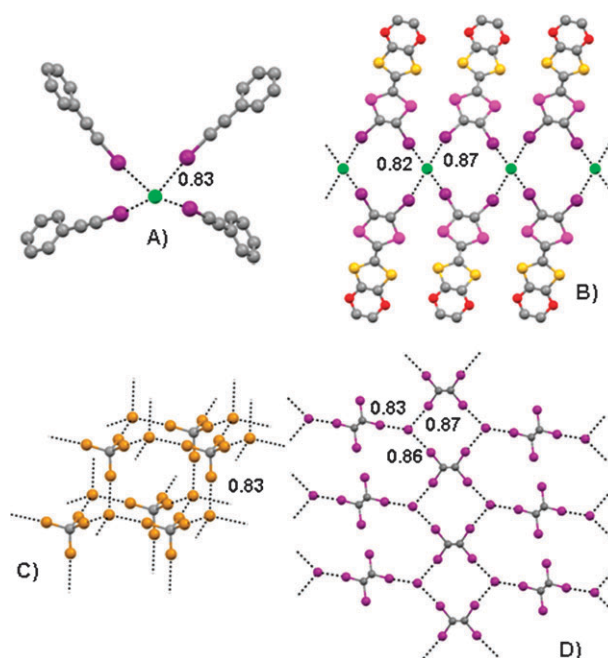
Electron deficient metal centres (as in macrocycles containing mercury<sup>7</sup> or tin<sup>8</sup> atoms) as well as boron<sup>9</sup> and silicon<sup>10</sup> sites have been employed for binding anions by metal or Lewis acid coordination. After Atwood's results pinpointing the opportunity, "anion- $\pi$ " interactions, involving electron deficient aromatic rings, are now receiving growing interest as an alternative route towards the synthesis of anion hosts.<sup>11</sup>

While chlorine, bromine, and iodine atoms in halocarbons are commonly viewed as electron rich sites, the electron density distribution around these atoms is highly anisotropic and an electropositive region frequently exists on the extension of the carbon-halogen bond ( $\sigma$ -hole).<sup>12</sup> In this review we describe how chloro-, bromo-, and iodo-carbons can effectively work as electron poor sites for the binding of anions *via* halogen bonding (XB).

XB is any  $D \cdots X-Y$  interaction in which X is an electrophilic halogen (Lewis acid, XB-donor), D is a species donating electron density (Lewis base, XB-acceptor), and Y is carbon, nitrogen, halogen, *etc.*<sup>13</sup> For the general aspects of XB driven self-assembly processes and for cases where the electron donating species is a neutral site (*e.g.* a lone pair possessing heteroatom) the reader is referred to recent reviews on the topic.<sup>14</sup>

Halogens and interhalogens are particularly good XB-donors.  $I_3^-$  and  $Br_3^-$  can be considered the simplest and best known examples of halogen bonded (X-bonded) adducts formed by anions and also polyiodides, and to a minor extent polybromides, that have received considerable attention.<sup>15</sup> However, in this review we will regard as XB-donors only halocarbons where halogens form one covalent bond.<sup>16</sup> Attention is focused on these XB-donors due to their virtually unlimited structural diversity and their greater interest for the synthesis of receptors. Halides are frequently occurring anions in organic chemistry and the one-, two-, and three dimensional architectures afforded on self-assembly of chloride, bromide, and iodide anions with halocarbons have already been discussed (Fig. 1).<sup>17</sup>

Attention has also been recently paid to the XB driven binding of some rather uncommon anions (*e.g.* polycyano- and polyhalometallates,<sup>18</sup> Fig. 2), but surprisingly the focus has never been made on the XB driven binding of oxygen centred anions, despite their being by far the most frequently occurring anions in organic chemistry.<sup>19</sup>



**Fig. 1** Tetracoordinated chloride anions given by tetraphenylphosphonium tetrakis(1-iodo-2-phenylacetylene) chloride (A) and bis(2-(4,5-diiodo-1,3-diselenol-2-ylidene)-5,6-dihydro-(1,3)dithiolo(4,5-b)-(1,4)dioxin) chloride (B); tetracoordinated bromide anions formed by tetraethylammonium bromide carbon tetrabromide solvate (C); tri-coordinated iodide anions given by tetra-n-butylammonium iodide tetraiodoethene (D). Cations and hydrogens are omitted for clarity, but in (B), Pauling ionic radii of  $Cl^-$ ,  $Br^-$ , and  $I^-$  are 181, 195, 216 pm, respectively. Colour code: grey, carbon; blue, nitrogen; red, oxygen; violet, iodine; green, chlorine; light brown, bromine; bright pink, selenium; yellow, sulfur.

In this review we will fill this gap, showing how both organic and inorganic oxyanions (*e.g.* carboxylates, sulfonates, perchlorates, and nitrates) can afford adducts under XB control.

The general characteristic of XB driven binding of oxyanions will be presented first then a selected inventory of specific cases will be analyzed in detail.

Anion binding by halocarbons has been studied in solution using various techniques (UV, ESR,  $^{19}F$  and  $^{13}C$  NMR) thus allowing for the determination of association constants, and related thermodynamic parameters.<sup>20</sup> Nonetheless, this review

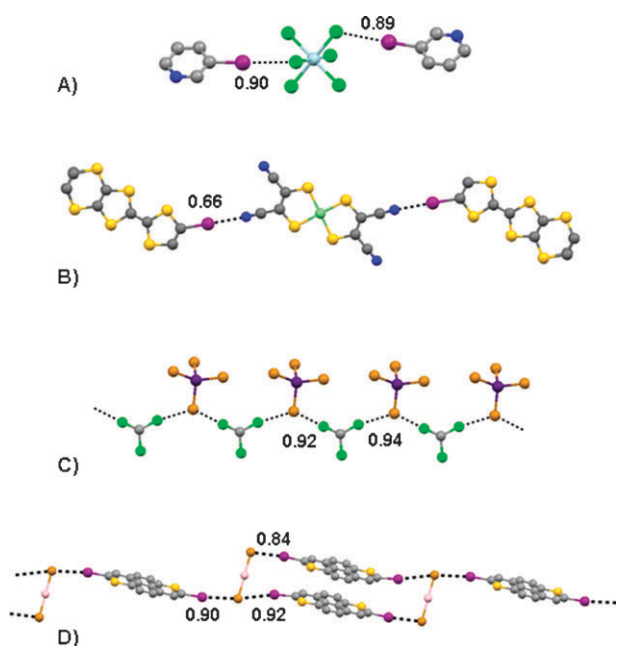


**Maurizio Sansotera and Gabriella Cavallo**

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**Fig. 2** Dicoordinated polyhalometallates and polycyanometallates form: trimeric adducts in bis(3-iodopyridinium) hexachloro-platinum(IV) (A) and in bis(3-iodo-3',4'-ethylenedithiotetrathiafulvalene) bis-(*cis*-1,2-dicyanoethylene-1,2-dithiolato-*S,S'*)-nickel (B); infinite chains in ((*N,N'*-bis(2,6-diisopropylphenyl)tritypycenylimidoformamidium) tetrabromo-indium(II) chloroform solvate (C, cation omitted for clarity); a necklace of rings in tris(2,7-diiodo-1,6-dithiapyrene) bis(dibromo-gold) (D). The Pauling ionic radius of  $N^-$  is 247 pm; hydrogens have been omitted for clarity. Colour code: platinum, light blue; nickel, light green; indium, purple; gold, pink; other colours as in Fig. 1.

presents the ability of halocarbons to bind oxyanions by focusing on adducts formed in the solid state. The Cambridge Structure Database (CSD) is analysed and the presence of an XB is assumed in an X-ray structure when the halogen–oxygen distance is shorter than the sum of the van der Waals radius of the XB-donor (175, 185, and 198 pm for Cl, Br, and I, respectively) and the Pauling ionic radius of the XB-acceptor oxygen (176 pm). All figures are ball and stick representations of crystal structures. As a measure of strength of XB, we define ‘normalized contact’, the ratio  $Nc = D_{ij}/(rvdwi + rP_j)$ , where  $D_{ij}$  is the distance between the atoms  $i$  and  $j$  and  $rvdwi$  and  $rP_j$  are the corresponding van der Waals radius and Pauling ionic radius for the halogen atom and oxygen anion, respectively.  $Nc$  is a useful indicator of the interaction strength, better than the distance  $D_{ij}$  itself, because it allows distances between different halogen/anion couples to be compared.  $Nc$  values have been reported close to the dotted lines denoting XBs in the figures.

In crystals anion–cation association spans from very loose (as is the case, for instance, with onium or cryptated cations) to quite tight (e.g. in the presence of some transition or lanthanoid metal cations). In other words, the anion can be naked or firmly pinned in the coordination sphere of the cation and form a well defined chemical entity which is no more an anion. Nevertheless these associated anions retain their inherent ability to donate electron density and their binding by halocarbons is widely documented in the CSD.<sup>21</sup>

Their coordination profile is a modified version of the naked anions and, for the sake of simplicity, we discuss in this review only structures of poorly associated anions, namely structures wherein cations and anions show no appreciable contacts, other than ion-pairing.

## 2. Oxyanions

### 2.1 General features

**Critical assessment of the CSD.** Only a very small portion of the structures deposited in the CSD and showing the presence of X-bonded oxyanions have been purposefully obtained in the frame of studies pursuing XB-based anion coordination. This forcefully proves the inherent tendency of halocarbons to drive XB-based self-assembly processes of oxyanions. On the other hand, this requires a judicious evaluation of the data and selection of the more meaningful examples, rather than a barely statistical analysis, if the identification of general principles is pursued. The lack of design and engineering has always to be remembered in order to frame all proposed considerations properly.

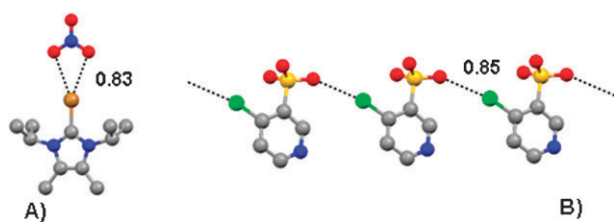
For instance, the number of  $O^- \cdots X-C$  short contacts in the CSD increases moving from I–C, to Br–C, to Cl–C (as is the case when other XB-acceptors, for instance nitrogen derivatives, are used). This relative abundance cannot be assumed as an indication that the tendency of halocarbons to coordinate oxyanions increases from iodocarbons, to bromocarbons, to chlorocarbons. Indeed, the opposite is true. The remarkably larger amount of  $O^- \cdots Cl-C$  short contacts is mainly due to the serendipitous formation of most of the adducts and chlorocarbons are much more common in the CSD than bromo- and iodocarbons. Oxygen anions are usually hard bases and the general preference for hard-acid/hard-base pairing (over the hard/soft pairing) may also affect XB driven oxyanion recognition by halocarbons. However, specific studies are required to assess the relevance of this preference over the relative abundance discussed above.

**Candidate components of XB-based oxyanion receptors.** It is well known that the XB strength is affected by the electron density on the interacting sites. The stronger the electron withdrawing ability of atoms and groups close to the halogen is, the more pronounced the electropositive region on the halogen is, and its interaction with anions, electron rich sites, will be particularly strong. This is the reason why haloperfluorocarbons<sup>22</sup> and halogen substituted heterocyclic cations (e.g. halo-pyridinium,<sup>23</sup> -imidazolium and -tetrathiafulvalenium<sup>24</sup> derivatives) form remarkably short contacts with oxyanions, both organic and inorganic (Fig. 3).

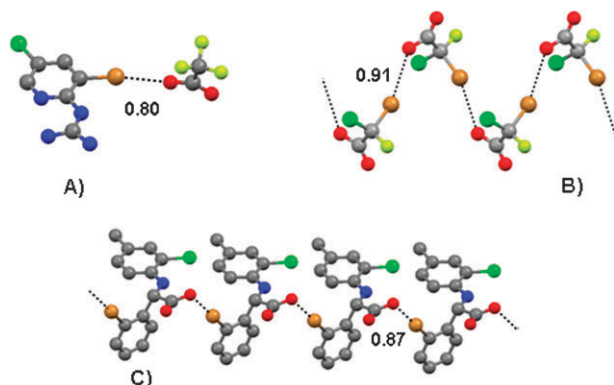
These moieties may thus be considered as particularly good candidate components for the design and synthesis of XB-based oxyanion receptors.

When different halogens are accessible to the oxyanions, the heaviest, namely the most polarisable, is preferentially involved in its coordination (Fig. 4),<sup>25</sup> consistent with a  $\sigma$ -hole more pronounced moving from chlorine, to bromine, to iodine (which is typically the best XB-donor).

It can thus be generalized that iodine and bromine should be preferred to chlorine in the design of receptors with high



**Fig. 3** Bidentate coordination of nitrates by 2-bromo-1,3-diisopropyl-4,5-dimethylimidazolium nitrate (A) and infinite chain formation on sulfonate coordination in 4-chloropyridine-3-sulfonic acid (B). Hydrogens have been omitted for clarity. Colour code as in Fig. 1.



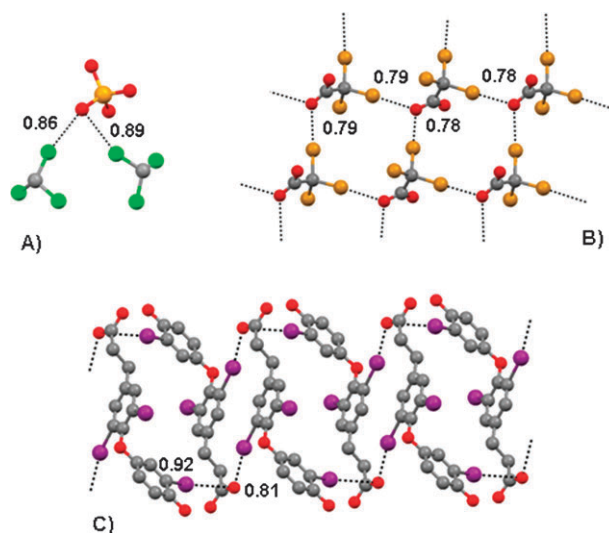
**Fig. 4**  $\text{O}^- \cdots \text{Br}$  interactions are favoured over  $\text{O}^- \cdots \text{Cl}$  interactions in *N*-(3-bromo-5-chloro-2-pyridinyl)guanidinium trifluoroacetate (A), in strychnine (S)-(+)-bromochlorofluoroacetate (B, cations omitted for clarity), and in (*R*)-ethyl(dimethyl)ammonium (2-bromophenyl)-*N*-(2-chloro-4-methylphenyl)glycinate (C). Hydrogens omitted for simplicity. Colour code: Yellowish green, fluorine; other colours as in Fig. 1.

binding constants. Conversely, the more electron rich a XB-acceptor site is, the stronger the XB it gives rise to, and oxyanions are thus expected to give rise to strong, namely short, XBs with respect to neutral electron donating species. The  $N_c$  values reported in figures are frequently very low, corresponding to strong interactions; this is even more remarkable if we remember that most of these X-bonded assemblies have been obtained serendipitously.

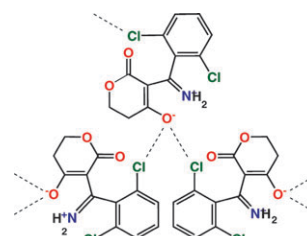
**XB and anion coordination sphere.** As is the case for other anions, the number of ligands which form the coordination sphere around oxyanions largely exceeds the requirements of the neutrality principle both in the solid state and in solution.<sup>26</sup> In most cases these ligands are hydrogen bonding (HB) donors, as in organic materials strong (*e.g.*  $-\text{OH}$ ,  $-\text{NH}_2$ , *etc.*) and weak (*e.g.*  $-\text{CH}$ ) HB-donor sites are ubiquitous. Oxyanion binding by halocarbons asks for the halogen for hydrogen substitution in the coordination sphere of the anion.<sup>27</sup> Only few halogen atoms, if any, are present in the large majority of organic compounds and so it is no surprise that in the absence of design such substitution typically occurs only at one site of the coordination sphere of the oxyanion while, in principle, it could occur at two, three or even at all the sites. In many systems the chemical composition and the need to balance the cation and anion charges determines the ratio between XB-donor and -acceptor sites and a mismatching

between their numbers may occur. This frequently limits the number of XBs formed by the oxyanion and the manifestation of the potential of oxyanions as XB-acceptors becomes partial.

**Bifurcated XBs.** Any negatively charged oxygen has three lone pairs which can be exploited for tight and selective binding. Up to three XBs could be formed with three halogens at the right distance and with the right orientation. No XB based oxyanion receptor has been described to now and this may be the reason why negatively charged oxygens typically form only one XB. Bifurcation at oxygen is exceptional and involves perhalogenated modules or highly halogenated modules<sup>28</sup> or solvent molecules,<sup>29</sup> namely systems where the  $\sigma$ -hole of the halogen atom can be likely located in the due position (Fig. 5). It is interesting to observe that if the overall crystal packing requirements are satisfied, even two chloro-carbon moieties, which are weak XB-donors, can be bound to oxyanions (Fig. 5A, Scheme 1). When an oxyanion lone pair is binding a halocarbon, the electron density on the oxygen



**Fig. 5** Dicoordination at oxygen: of a perrhenate anion by two chloroform molecules in trichloro-(tripyrazolylmethane-*N,N',N''*)-rhenium(iv) perrhenate chloroform solvate (A), of a carboxylate anion by two tribromomethyl residues in 3-bromopyridinium tribromoacetate (B), and of a carboxylate anion by a triiodoarene moiety in *N,N*-diethanolammonium 3,5,3'-tri-iodothyropropionate (C). Hydrogens and cations have been omitted for clarity. Colour code: orange, rhenium, other colours as in Fig. 1.



**Scheme 1** Dicoordination of an enolate oxygen by two chloroarene residues in 3-((2,6-dichlorophenyl)iminomethyl)-5,6-dihydro-4-hydroxy-2H-pyran-2-one.

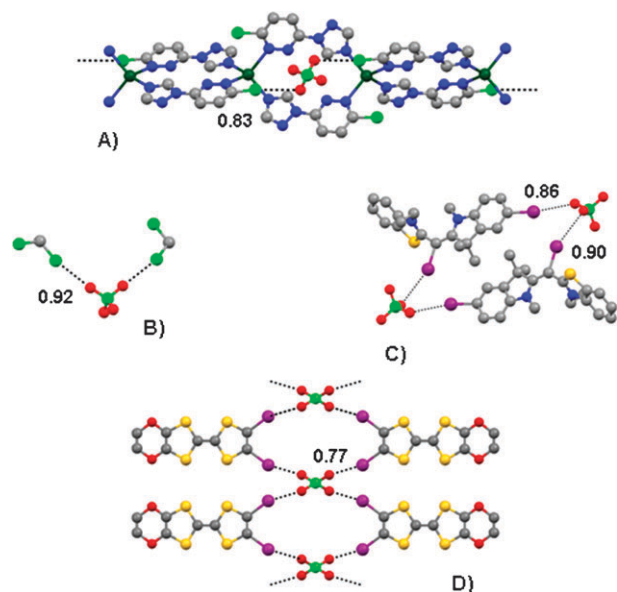
decreases as well as the propensity of other lone pairs on oxygen to form XBs. This may also partially account for the limited number of bifurcated oxygens.

In polyoxygenated anions, such as sulfonates, nitrates, or perchlorates, any oxygen possesses two or three lone pairs which can function as XB-acceptors and the geometric requirements for anion coordination *via* multiple XBs are less demanding than for mono- and dioxygenated anions.

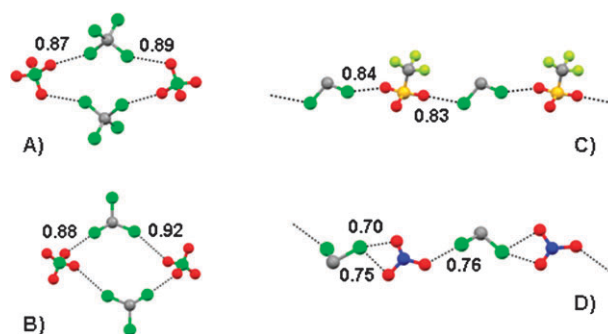
This offers greater chances for the anion to sort out the  $\sigma$ -hole of a halocarbon in the solid state even in the absence of a tailored design of the overall crystal packing. Indeed, halocarbons binding to two or more different oxygen atoms of such anions, while uncommon, are not exceptional. For instance, adducts are described where perchlorate anions form one,<sup>30</sup> two,<sup>31</sup> or four<sup>32</sup> XBs (Fig. 6).

**XB and solvent clathrates.** Systems wherein the XB-donor is a clathrated solvent form a numerous class of X-bonded supramolecular oxyanions. When hydroxyl compounds (*e.g.* water and alcohols) are used as solvents, anion coordination by receptors based on HB competes with anion coordination by the solvent and solvent inclusion in the crystal of the anion–receptor adduct may be favoured by its specific binding *via* HB. Similarly, XB formation favours the inclusion and tight binding of halogenated solvents (usually  $\text{CH}_2\text{Cl}_2$  and  $\text{CHCl}_3$ ,<sup>33</sup> but also  $\text{CCl}_4$ <sup>34</sup>) in crystals wherein oxyanions function as XB-acceptors (Fig. 7).

In other words, the inherent ability of anions to function as strong XB-acceptors and to involve halogenated solvents in



**Fig. 6** Bidentate perchlorate anion wherein the anion: is chelated by *catena*-tetrakis( $\mu_2$ -1-(6-chloropyridazin-3-yl)-1,2,4-triazole-*N,N'*)-di-silver(I) cation (A), forms a solvate trimer in ( $\mu_2$ -acetato-*O,O'*)-bis( $\mu_2$ -oxo)-(*N,N*-bis(2-pyridylmethyl)ethylamine-*N,N',N''*)-di-manganese diperchlorate dichloromethane solvate (B, cations omitted for clarity); forms a cyclic tetramer in 6-iodo-2-(iodo(3-ethyl-1,3-benzothiazol-2(3*H*)-ylidene)methyl)-1,3,3-trimethyl-3*H*-indolium perchlorate (C). Tetradentate perchlorate anion in bis(4,5-diiodo-4',5'-ethylenedioxy-tetrathiafulvalene) perchlorate (D). Colour code: dark green, silver; other colours as in Fig. 1.



**Fig. 7** Bidentate perchlorate anions form cyclic tetramers with  $\text{CCl}_4$  in (*cis*-2,6,9,13-tetrathiaabicyclo(12.4.0)octadecane)-nickel(II) diperchlorate carbon tetrachloride nitromethane solvate (A) and with  $\text{CHCl}_3$  in bis( $\mu_2$ -8-(2-pyridylsulfanylmethyl)quinoline)-di-silver(I) diperchlorate chloroform solvate (B). Bidentate trifluoromethane sulfonate anions form infinite chains with  $\text{CH}_2\text{Cl}_2$  in pentafluorophenyl-(tris(2-diphenylphosphinoethyl)amine)-mercury(II) trifluoromethanesulfonate dichloromethane solvate (C). Tridentate nitrate anions form infinite chains with  $\text{CH}_2\text{Cl}_2$  in bis( $\mu_4$ -1,2,4,5-tetrakis(benzimidazol-1-ylmethyl)-benzene)-bis( $\mu_2$ -nitrate-*O,O'*)-tetra-silver(I) dinitrate dichloromethane methanol solvate (D). Cations and hydrogens have been omitted for clarity. Colour codes as in Fig. 1 and 4.

the formation of X-bonded and supramolecular anions matches the need to fill potential voids in the crystal packing and halogenated solvents are frequently found in the coordination sphere of oxyanions.

## 2.2 Inorganic oxyanions

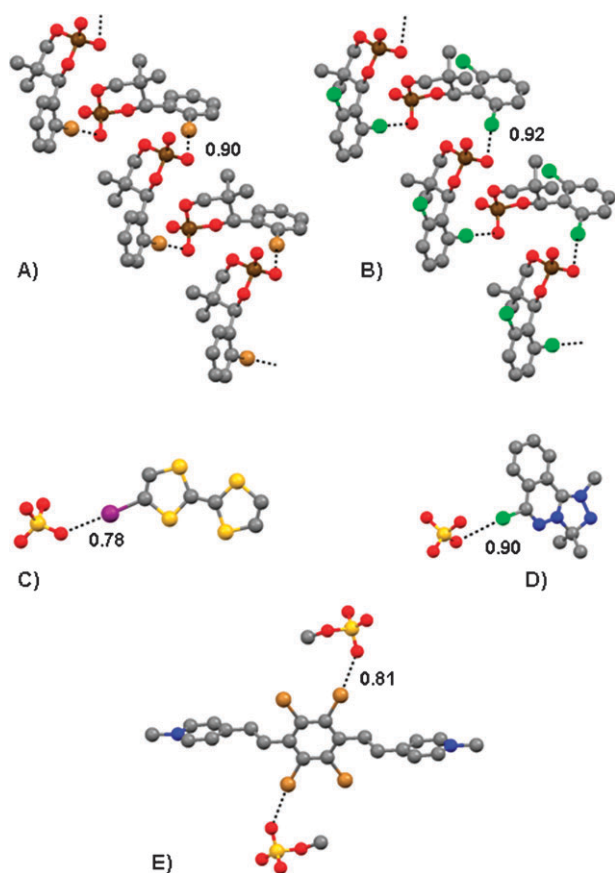
X-Bonded oxyanions span both organic and inorganic moieties over a wide diversity of electronic and geometric features. As far as inorganic oxyanions are concerned, a limited number of structures are reported where halocarbon groups coordinate phosphate,<sup>35</sup> perrhenate (Fig. 5A),<sup>29</sup> sulfate,<sup>36</sup> and complex polyoxometallate<sup>37</sup> anions (Fig. 8). A particularly interesting example is a 5-iodocytidylyl dinucleoside where the phosphodiester anion is coordinated by the iodine atom in position five of the nucleobase (Scheme 2).<sup>38</sup>

**Nitrates.** Numerous structures show nitrate anions bound to halocarbons.<sup>23a,24a,33f,39</sup> Dimers, trimers, or infinite chains are formed where the anion is mono-, bi-, or tridentate and the XB develops in the anion plane, orthogonal to it (involvement of  $n$  and  $\pi$  orbitals, respectively) or after intermediate geometries (Fig. 3A, 7D and 9).

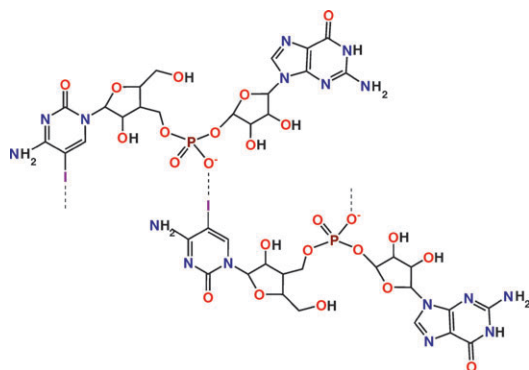
**Perchlorates.** The inorganic oxyanion by far most frequently coordinated by halocarbons<sup>23b,31e,f,33d,h,40</sup> is the perchlorate anion and it gives one, two or four X-bonds as a function of the number of XB-donor sites available (Fig. 6, 7 and 10).

According to the Hofmeister series,<sup>41</sup> perchlorate anions are highly hydrophobic and, moving from the relative abundance of X-bonded perchlorate anions, it might be surmised that the more hydrophobic an anion moiety is, the more likely its involvement in XB formation. This is consistent with the relative ease of coordination of different halide anions.<sup>13</sup>





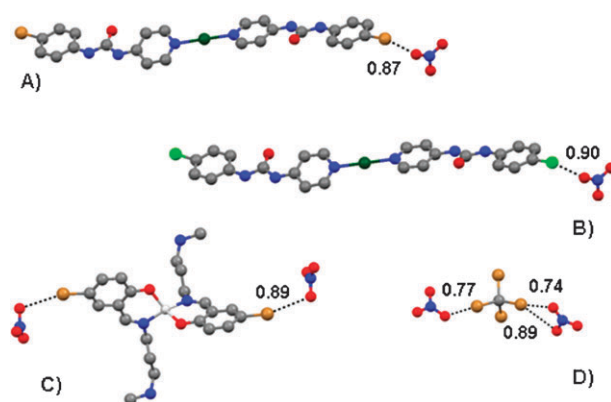
**Fig. 8** Monocoordination of phosphoric esters forms infinite chains from (*R*)-(+)-4-*o*-bromophenyl-2-hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide (A) and from (*R*)-(+)-4-(2,6-dichlorophenyl)-2-hydroxy-5,5-dimethyl-1,3,2-dioxaphosphorinane (B). Monocoordination of sulfate anion forms dimers from 4-iodotetrathiafulvalenium hydrogen sulfate (C) and from 1,3,3-trimethyl-2,3-dihydro-1,2,4-triazolo(5,4-*a*)-4'-chlorophthalazine bisulfate (D); trimers are formed from (*E,E*)-2,3,4,5-tetrabromo-1,4-bis(2-(*N*-methylpyridinium-4-yl)vinyl)-benzene methylsulfate (E). Cations, hydrogens, and neutral cocrystallizing molecules have been omitted for clarity. Colour code: phosphorus, dark brown, other colours as in Fig. 1.



**Scheme 2** Dimers formed by ethidium 5-iodocytidylyl-(3'-5')-guanosine.

### 2.3 Organic oxyanions

**Phenolates and enolates.** Halocarbons coordinate the whole set of organic oxyanions, from those having the simplest



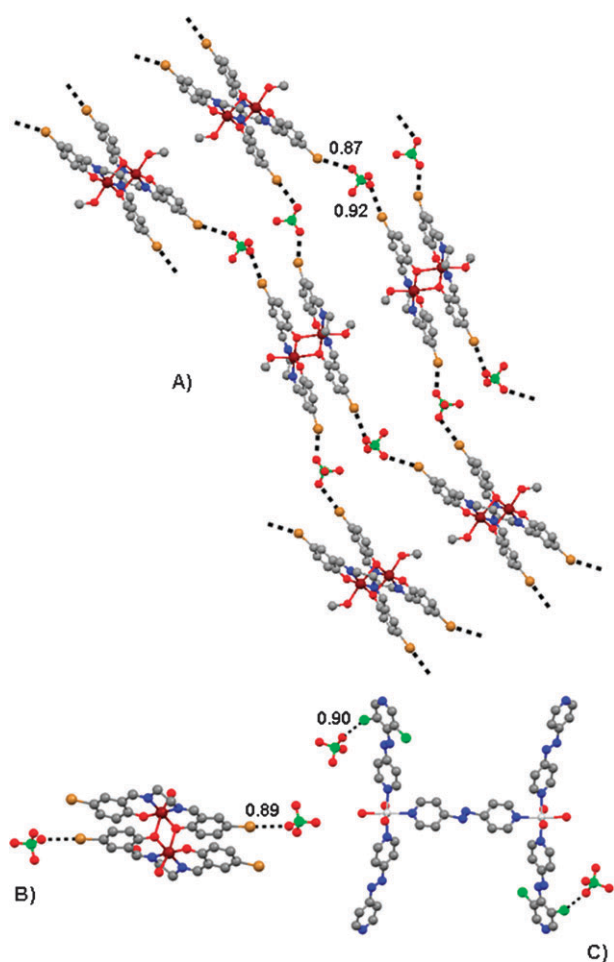
**Fig. 9** Monodentate nitrate anions in: bis(*N*-(4-bromophenyl)-*N*-(4-pyridyl)-*N*-urea)-silver(I) nitrate (A), its chloro analogue (B), and bis(4-bromo-2-(3-(methylammonio)propyliminomethyl)phenolato-*N,O*)-zinc(II) dinitrate (C). Mono- and bidentate nitrate anions in tetrakis(μ<sub>4</sub>-1-(2-methyl-5-pyrimidinyl)-3,5-bis(3-pyridyl)benzene)-octakis((1,2-diaminoethane)-palladium) tetrabromomethane clathrate hexadecanitate (D). Cations, cocrystallized molecules, and hydrogens have been omitted for clarity. Colour code: light grey, zinc; other colours as in Fig. 1.

structures to the most complex ones; discrete adducts and one-, two-, or three dimensional aggregates are formed. For instance, simple halogen substituted phenolates<sup>42</sup> form X-bonded dimers or infinite chains. Similar behaviour is shown by a variety of enolates (formed from β-diamides,<sup>43</sup> β-diester, <sup>44</sup> β-ketoesters,<sup>28e,45</sup> or easily enolizable ketones<sup>46</sup>) and they give rise to an even greater variety of adducts than phenolates (*e.g.* trimers and tetramers) (Fig. 11).

**Carboxylates.** A particularly numerous class of X-bonded adducts are formed by carboxylate anions which usually work as monodentate XB-acceptors. Similar to nitrate anions, the interaction develops both in the carboxyl plane and orthogonal to it or after intermediate geometries. Halogen substituted benzoates,<sup>21g,28b,47</sup> mono-,<sup>48</sup> di-,<sup>28d,49</sup> and trihaloacetates<sup>28a,50</sup> (Fig. 5B), as well as other aliphatic carboxylates<sup>25c,48a,51</sup> wherein the halogen is far from the anionic site work as self-complementary moieties and afford dimers, infinite chains with or without pendants, ribbons, or 2D nets (Fig. 12).

Interestingly, in triiodothyronine (T3, the active thyroid hormone), the iodine in position 3 coordinates the carboxylate anion and an X-bonded infinite chain is formed (Fig. 13).<sup>52</sup> A similar iodine-carboxylate coordination is observed in the sodium salt of the prohormone tetraiodothyronine (T4) and in other diiodo and triiodo analogues of T3.<sup>28c,53</sup> Another case of biological interest comes from permethrin, an insecticide and acaricide belonging to the pyrethroid family. The organization in the solid of a salt of permethrinic acid is characterized by the self-assembly of the anion under control of COO<sup>−</sup>...Cl XBs.<sup>54</sup>

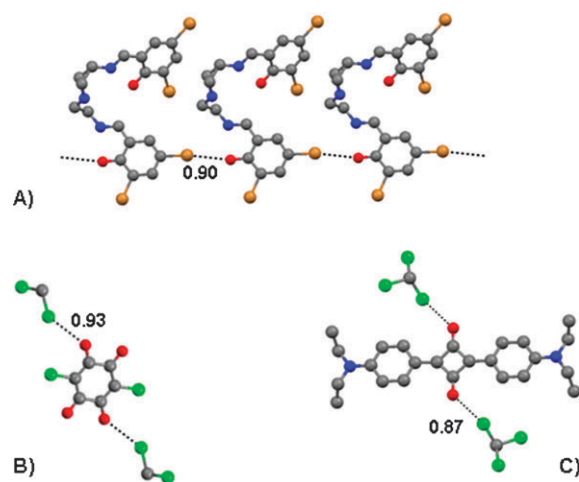
**Sulfonates.** Also halogen substituted sulfonates, both aliphatic<sup>55</sup> and aromatic,<sup>56</sup> can work as self-complementary modules. The sulfonate anion usually functions as monodentate XB-acceptor and dimers, trimers, or infinite chains are formed (Fig. 3B). Occasionally the sulfonate anion is bidentate<sup>57</sup> and 2D supramolecular anions can be produced (Fig. 14).



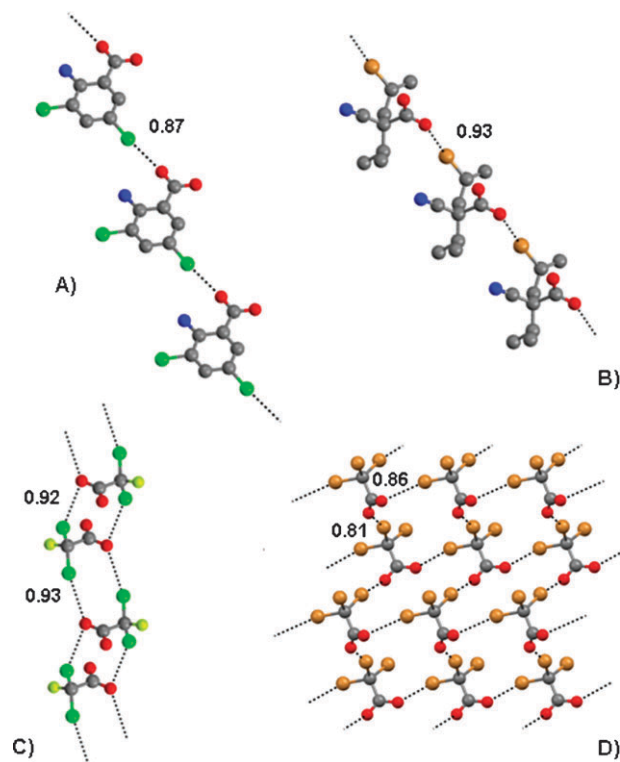
**Fig. 10** Dicoordinated perchlorate anions form a 2D net in bis(( $\mu_2$ - $N,N'$ -bis(5-bromosalicylaldehyde)ethylenediamino)-methanol-manganese(III)) (A) and a trimer in ( $\mu_2$ -4,4'-azopyridine)-bis(triaqua-(4,4'-azopyridine)-(2,6-dichloro-4,4'-azopyridine)-zinc(II)) tetrakis(4,4'-azopyridine) tetraperchlorate decahydrate (C, cations omitted). Monodentate perchlorate anions form trimers in bis(diaqua-( $N,N'$ -bis(5-bromosalicylidene)ethane-1,2-diamine)-manganese) bis(( $\mu_2$ - $N,N'$ -bis(5-bromosalicylidene)ethane-1,2-diamine)-aqua-manganese) tetraperchlorate tetrahydrate (B) and hydrogens have been omitted for clarity. Colour code: Bordeaux, manganese; other colours as in Fig. 1.

X-Bonded adducts may also be given by sulfonic acids, the anion being formed on protonation of crystallization water.<sup>58</sup> Even the trifluoromethanesulfonate anion,<sup>59</sup> despite its low nucleophilicity, can share one of the oxygen lone pairs with an halocarbon moiety, typically dichloromethane and chloroform (Fig. 7C).

**Miscellanea.** The importance of XB in the binding and recognition of organic oxanions extends far beyond the moieties described above. In fact, there are a number of zwitterionic functionalities wherein a positively charged heteroatom is bound to a negatively charged oxygen (e.g. phosphine oxides and other phosphorus(V) derivatives,<sup>60</sup> sulfoxides,<sup>61</sup> nitroxide radicals<sup>62</sup>). It is thus not surprising that these “oxyanionic” moieties can be coordinated by halogen atoms possibly present in the compound (or in a clathrated solvent). For instance, the crystal packing of the *N*-oxides of

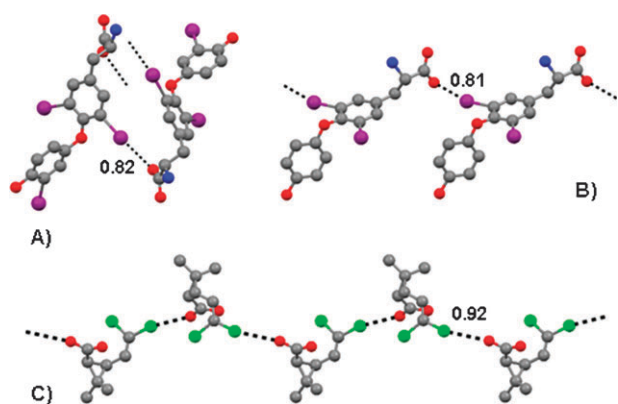


**Fig. 11** Infinite chains formed on phenolate coordination in 4,4',6,6'-tetrabromo-2,2'-(2,8-diazonia-5-azanona-1,8-diene-1,9-diyl)diphenolate (A); trimers formed on dichloromethane coordination in 4,4'-(azodimethylene)dipyridinium chloranilate dichloromethane solvate (B) and on chloroform coordination by a 3-oxocyclobut-1-en-1-olate derivative (C). Cations and hydrogens have been omitted for clarity. Colour codes as in Fig. 1.

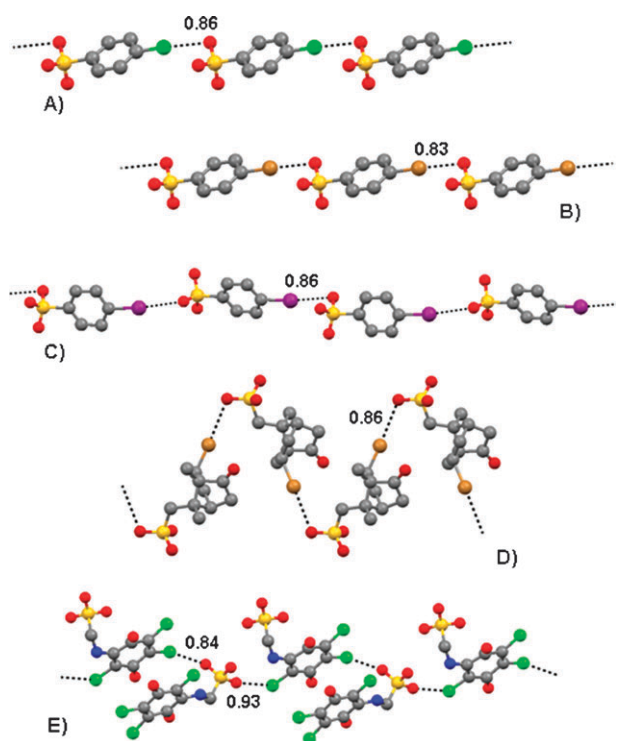


**Fig. 12** Monodentate carboxylates form infinite chains in: ammonium 2-amino-3,5-dichlorobenzoate (A) and D-(−)-threo-1-phenyl-2-ammonio-1,3-propanediol-(−)-β-bromoallyl-isopropyl-cyanoacetate (B). Ribbon formed by bidentate carboxylate in oxonium dichlorofluoroacetic acid pentahydrate (C). 2D net formed by bidentate tribromoacetate in *N,N,N',N'*-tetramethyl-1,4-diammoniumbutane tribromoacetate (D). Cations and hydrogens have been omitted for clarity. Colour codes as in Fig. 1 and 4.





**Fig. 13** Infinite chains formed by: 3,5,3'-tri-iodo-L-thyronine (A), 3,5-di-iodo-L-thyronine-*N*-methylacetamide (B), *O*-9-(2,6-diisopropylphenylcarbamoyl)quininium (1*S*,3*S*)-(-)-*cis*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (C). Cations and hydrogens have been omitted for clarity. Colour codes as in Fig. 1.



**Fig. 14** Monodentate sulfonate anions form infinite chains in 4-(4'-hydroxy-3'-methoxystyryl)-1-methylpyridinium 4-chlorobenzene-sulfonate (A), in its bromo (B) and iodo analogues (C), and in ammonium (-)-(1*S*)-6-*endo*-bromo-2-oxobornane-8-sulfonate (D); bidentate sulfonate anions form infinite chains in  $\beta$ - $\beta$ -bis(bis(ethylene-dithio)tetrathiafulvalene) 2-(sulfomethylamino)-3,5,6-trichloro-1,4-benzoquinone hemihydrate (E). Cations and hydrogens have been omitted for clarity. Colour codes as in Fig. 1.

various halogenated azines (*e.g.* pyridines<sup>63</sup> and pyrazines<sup>64</sup>) and of some mesoionic compounds (*e.g.* sydnone<sup>65</sup> and furazan *N*-oxides<sup>66</sup>) is controlled by oxygen–halogen interactions.

A zwitterionic Lewis structure can be written also for the nitro group which in fact is a fairly strong XB-acceptor<sup>67</sup> where both oxygen atoms of nitro groups can be bound to the same halogen atom (thus forming bifurcated XBs).

### 3. Conclusions

The use of electron poor halocarbons in order to bind oxyanions has received only occasional interest<sup>24b</sup> and the potential of oxyanions in XB-based self-assembly remains largely unexplored.

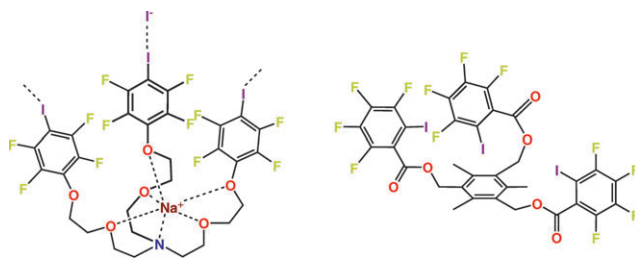
Hopefully this review has succeeded in showing that XB can be expected to emerge as a general route for oxyanion-coordination and templated assembly.<sup>17</sup>

One of the main difficulties in anion coordination comes from the tendency of anions to be strongly solvated in protic solvents such as water. A possible strategy to tackle this challenge is the use of attractive interactions different from those traditionally used, up to now HB being the first choice. In this respect, the competitive advantages of XB still remain to be investigated, the selected supramolecular oxyanions discussed in this review being not obtained as a result of purposefully designed oxyanion-coordination studies.

Oxyanions such as phosphate and sulfate are inorganic analytes commonly targeted by coordination and sensing studies due to their biological interest, but to the best of our knowledge there are no examples in the literature of receptors using XB-donor groups that have shown selectivity towards the coordination of these types of oxyanions. On the other hand, halide ions participate readily as XB-acceptors in the solid state,<sup>17,68</sup> and recently the generality and utility of this noncovalent interaction have gained appreciation in halide anion recognition.<sup>69</sup> The observation that in crystalline networks a single halide can accept multiple XBs, prompted the design of a few halide receptors based on multidentate XB-donors (Scheme 3).

In particular, the recently published mesitylene receptor (Scheme 3, right) has shown a strong affinity for halides but a weak one for oxyanions. This may be related to the limited size of the receptor cavity and to the fundamental differences between XB and HB, *e.g.* the non-negligible contribution of dispersion and/or charge-transfer to XB. If the coordination of bulky and not spherical anions is pursued, as is the case of oxyanions, a particularly careful receptor design is needed as the higher directionality of XB, compared to HB, imposes particularly demanding geometrical constraints. It should also be taken into account that while hydrogens can frequently work as bidentate HB-donors, halogens exceptionally form more than one XB.<sup>67,70</sup>

The use of XB to increase affinity and selectivity of an oxyanion for a biological receptor is a particularly remarkable issue, but few experiments have assessed the energetics of XBs in these systems. Recently, it has been attempted to use a XB



**Scheme 3** Halide receptors based on multidentate XB-donors.

as a functional replacement of a HB in the oxyanion hole of ketosteroid isomerase.<sup>71</sup> Specifically, semisynthetic enzymes containing *para*-halogenated phenylalanine derivatives were used to replace the tyrosine HB-donor. Formation of an XB to the oxyanion in the transition state would be expected to rescue the effects of mutation to phenylalanine. Unfortunately, this strategy proved to be unsuccessful and all of the halogenated enzymes were comparable in activity to the phenylalanine mutant. A successful story has involved an inhibitor of Factor Xa, an arginine specific serine protease which is of particular interest in thrombosis therapy.<sup>72</sup> When bound to the enzyme, an amidine substituent of a biphenylsulfonamide inhibitor was hydrogen bonded to aspartate 189 of Factor Xa. When a halogen atom was used to replace the amidine group in the biphenylsulfonamide inhibitor, XB replaced HB in the substrate binding pocket. The iodine substituted inhibitor had an inhibition constant lower than the bromine and chlorine analogues, namely it gave the stronger interaction, the O<sup>−</sup>...I XB being 3.2 Å.

Anion coordination and anion-templated assembly processes under the control of XB are still in their infancy but they are expected to have a bright future. New supramolecular synthons in anion coordination chemistry allow entirely new families of molecular components to be involved in self-assembly and self-organization processes. As a result, new sensing systems with unprecedented characteristics and properties are expected. The examples reported in this review herald how XB can be expected to emerge as a general and effective tool for the coordination and tight binding of oxyanions.

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## Notes and references

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