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REGULAR ARTICLE

Effects of complexation with a metal ion on the intramolecular hydrogen bonds in acylphloroglucinols

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Abstract

Complexation with a metal ion of an organic molecule containing one or more intramolecular hydrogen bonds (IHBs) influences the characteristics of the IHBs. These influences are here investigated computationally for the complexes of selected antioxidant acylphloroglucinols with a Cu^{2+} ion, and also the complexes of a number of structurally-related molecules meant to highlight the influence of specific molecular features. All the low energy conformers of acylphloroglucinols (compounds structurally derived from 1,3,5-trihydroxybenzene and characterised by the presence of a CRO group) contain an IHB between the sp^2 O of CRO and a neighbouring phenol OH. Additional O–H···O or O–H···π IHB are present when the molecule contains substituents with groups that can form IHBs. The results show various effects that can be ascribed to complexation, such as changes in the IHB parameters and in the red shift of the vibrational frequency of the donor OH caused by the IHB. For O–H···O IHBs, complexation may cause the transfer of the proton from the donor to the acceptor O atom, more frequently when the acceptor is an sp^2 O (i.e. for stronger IHBs). In some cases, IHBs that are not present in the uncomplexed conformers appear in the complex. The type and extent of the changes depend mainly on the site/s to which the Cu^{2+} ion binds and, to a less extent, also on the geometry features of the conformer. Some changes offer clear indications of weakening or strengthening of specific IHBs for specific binding sites of the ion.

Keywords Acylphloroglucinols · Antioxidants · Complexes of organic molecules with metal ions · Effects of complexation on molecular properties · Intramolecular hydrogen bonding

1 Introduction

Acylphloroglucinols (ACPLs, Fig. 1, [1]) are a broad class of compounds structurally derived from 1,3,5-trihydroxybenzene (phloroglucinol) and characterised by the presence of a CRO group. Many of them are of natural origin and exhibit a variety of biological activities, including antibacterial, antimalarial, anticancer, antioxidant, and others.

Antioxidants offer protection against reactive oxygen species in the body, thus contributing to the prevention of neurodegenerative diseases such as ischaemia, Alzheimer's disease and Parkinson's disease [2–4]. More recently, other beneficial effects on human heath have been reported, including anticancer, anti-inflammatory, antibacterial, antiviral and cardioprotective [[5] and references therein]. Phenol OHs are known to confer antioxidant properties to compounds containing them. Possible mechanisms for this activity have been objects of intensive studies [5–16]. The antioxidant activity is generally enhanced by the presence of two *ortho* phenol OHs, whose intramolecular hydrogen bond (IHB) contributes to stabilise the radical form appearing during the antioxidant action mechanism, and by the presence of additional OH groups or C=C double bonds in substituents [5, 7]. All ACPLs reported to have interesting antioxidant activity [1] have either additional OH groups, or additional C=C double bonds, or both, in the substituents attached to the acylphloroglucinol moiety.

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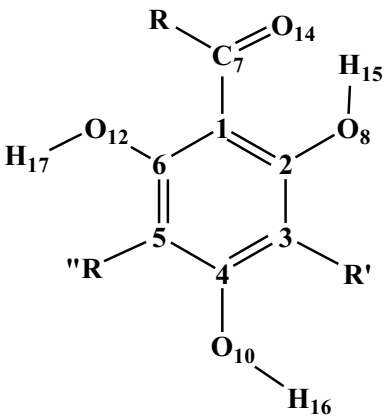

Fig. 1 General structure of acylphloroglucinols and atom numbering utilised in this work. The first C atom of R (after C7) is given the number 13, the first C atom of *R′* is given the number 9 and the first C atom of *R″* is given the number 11

Nearly all ACPLs are characterised by the presence of an IHB between O14 and either H15 or H17 [17]; it is here termed 'first IHB', following a practice introduced in [18] and maintained in all the other works on ACPLs belonging to this series of studies [e.g. 17, 19–22]. Since the acceptor is an sp^2 O, the first IHB is a moderate-bordering-to-strong IHB [17]. When a substituent contains one or more additional OH groups or O atoms, additional O–H···O IHBs can form [22]. If a substituent contains one or more π bonds, O–H···π IHBs can form when a phenol OH and the substituent are suitably oriented [20]. The lowest energy conformers of ACPLs are those containing the maximum number of simultaneous IHBs possible for the given molecule [20, 22].

The study of a molecule's complexes with a Cu^{2+} ion provides information about its ability to reduce other species (which is also related to its antioxidant ability [23, 24]) and about the ion's preferences to bind to the electron-rich sites available in that molecule. It also provides general information about the effects of complexation on the properties of the molecule. Complexes with a Cu^{2+} ion have already been calculated for selected antioxidant ACPLs: hyperjovinol A [HPJ-A, [25]), arzanol (ARZ, [26]) and hyperguinones A and B (HPG-A and HPG-B [27]). Complexes of a number of structurally-related molecules have also been calculated to expand the basis for comparisons. These include 1-[3-geranyl-2,4,6-trihydroxyphenyl]-2-methylpropan-1-one (GTM, [28])—an ACPL differring from HPJ-A because *R′* is a geranyl chain, whereas in HPJ-A the C17=C18 double bond of the geranyl chain (Fig. 2) is absent and an OH is attached to C18. They also include a number of auxiliary structures which accompanied the study of HPJ-A, GTM, and HPG-A and HPG-B. These studies focused mainly on the descriptive and energetics aspects of complexation, such as relative energies, molecule-ion affinity, distances of the ion from each binding site, and spin density maps highlighting the distribution of the unpaired electron in the positive molecular ion resulting from the electron transfer that reduces the Cu^{2+} ion. Information on the IHBs had been included as part of the description of the complexes, but without specific focus on the effects of complexation on the IHBs.

IHBs play important roles for biologically active molecules, because they largely determine conformational preferences (which are relevant for biological activities) and influence a number of physicochemical properties [29, 30] as well as biological and pharmaceutical properties [31, 32]. They may take part in the mechanism through which some activities are exerted, including aspects such as molecular recognition and selective binding [33, 34]. They are also involved in the antioxidant and antiradical activity of some ACPLs [35, 36]. Since the complexation with a Cu^{2+} ion may also be part of the activity mechanism of some antioxidants [10], it becomes important to obtain information about the effects of complexation on the IHBs present in antioxidant molecules.

The current work focuses on the effects of complexation on the IHBs present in antioxidant ACPLs, and attempts to identify patterns. To this purpose, it considers the calculated complexes of naturally-occurring antioxidant ACPLs (HPJ-A, ARZ, HPG-A and HPG-B), of GTM and of a number of auxiliary structures meant to selectively highlight the influence of specific features of the molecular structure on the effects of complexation. Table 1 lists all the molecules considered, listing the acronyms with which they are denoted in the present work and providing concise information about their characterising features and about the expected roles of each auxiliary structure (in terms of the features whose influences it is expected to highlight). Figure 2 shows the structures of all these molecules and the atom numbering utilised here. Among the auxiliary structures, Y1, Y2, Y3, Y4, Y5, Y6 and B had been considered in the study of the complexes of HPJ-A [25] and are selected for the current work because they have a complete acylphloroglucinol moiety (while other auxiliary structures considered in [25] did not); GTM-PR and GTM-P2 had been used as auxiliary structures in the study of GTM [28] and X in the study of HPG-A and HPG-B [27]. Because of the representativeness needs of the current study, many additional complexes than those considered in [25] have been calculated for HPJ-A, Y1, Y2, Y3, Y4, Y5, Y6 and B; similarly, several additional complexes have been calculated for GTM, GTM-PR and GTM-P2 with respect to [28].

The results indicate that complexation may cause several effects: proton transfer from the donor to the acceptor O atom in O–H···O IHBs; changes in the parameters of the IHBs; changes in the red shift of the vibrational frequencies of the donor OH caused by an IHB; and also the appearance of IHBs that are not present in the

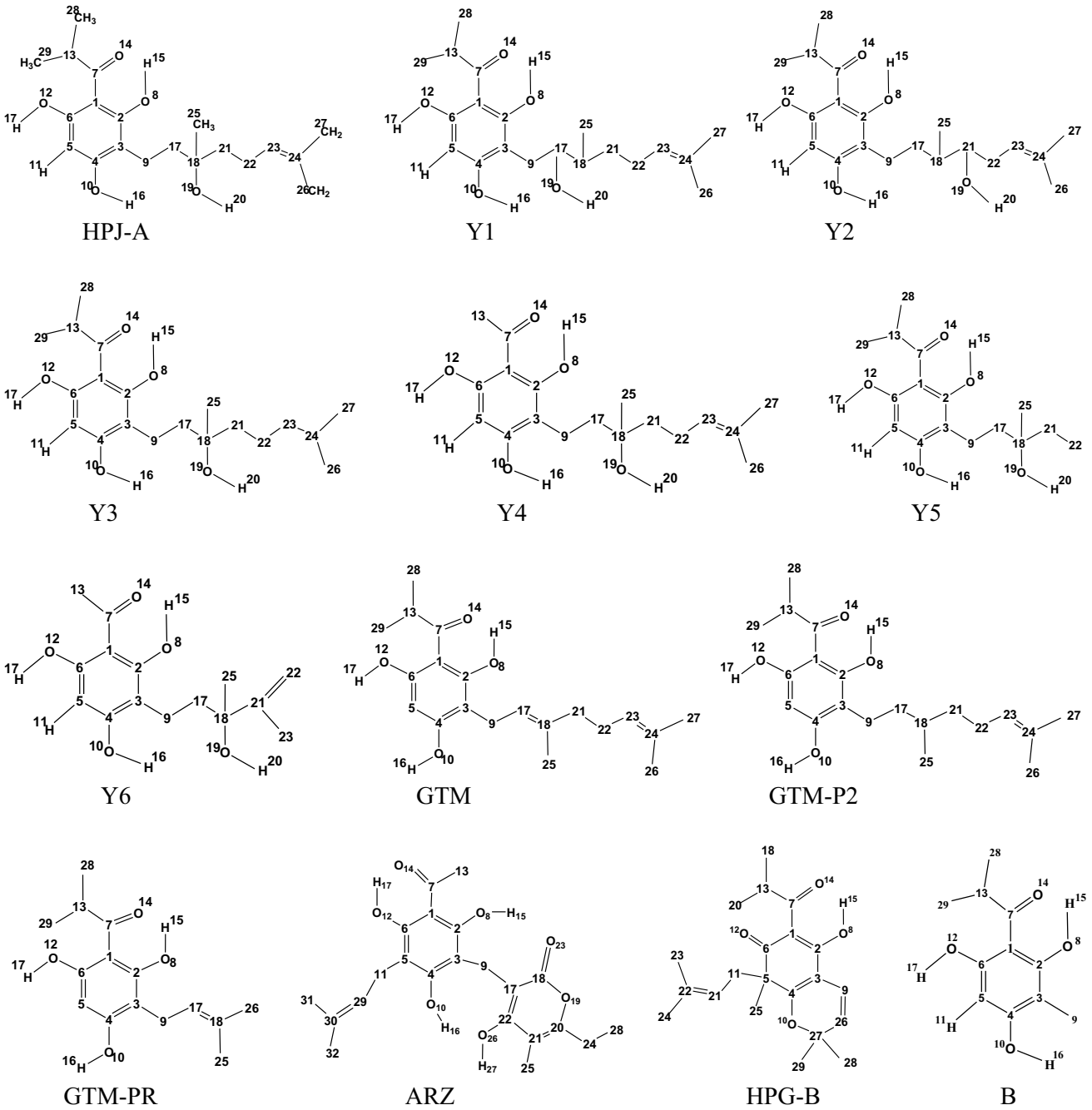

Fig. 2 Molecular structures considered in this work. The C atoms are denoted only by their numbers. The structures are identified only by their acronyms because of space reasons; the meanings of the acronyms are explained in Table 1

uncomplexed conformers. Some IHBs appeared to be weakened by the complexation, whereas some others are strengthened. The effects depend primarily on the binding site/s of the ion and considerably less strongly on the type of conformer. The most typical example of IHB that is weakened is the first IHB when the ion binds to O14 (its acceptor atom). O–H···π IHBs are considerably strengthened in several complexes.

Detailed tables showing the changes in quantities relevant to the evaluation of the effects of complexation on the IHBs are included in the Electronic Supplementary Information (ESI). These tables group the information according to the "associations" of the molecules and their complexes; thus, the values of a specific change (e.g. in the IHB parameters or in the red shift) for HPJ-A and its auxiliary structures are presented in one table, those for HPG-B and its related or

Table 1 List of the molecules considered in the present work, their characteristics and their roles

Acronym denoting the molecule	Molecule's characteristics and its roles in this study
HPJ-A	Hyperjovinol A, an antioxidant ACPL [1]
ARZ	Arzanol, an antioxidant ACPL [1]
HPG-B	Hyperguinone B, an antioxidant ACPL [1]. R is an isopropyl group
HPG-A	Hyperguinone A, an antioxidant ACPL [1]. It differs from HPG-B (shown in Fig. 2) only because R is an ethyl group
X	Structure considered in [27]. It differs from HPG-B only because R is an isobutyl group
GTM	ACPL differing from HPJ-A by having a standard geranyl chain at C3, without the additional OH present in HPJ-A [1]. Useful to check the significance of the additional OH
GTM-P2	Structure differing from GTM because the C17=C18 double bond is replaced by a single bond. Useful to check the importance of the C17=C18 double bond
GTM-PR	Structure differing from GTM because the substituent at C3 is a prenyl chain. Useful to check possible difference between the effects of a prenyl chain and of a geranyl chain
Y1	Structure differing from HPJ-A because the OH in the substituent is one position closer to the phloroglucinol moiety (attached to C17 instead of C18). Meant to check the effect of the position of the OH group
Y2	Structure differing from HPJ-A because the OH in the substituent is one position farther away from the phloroglucinol moiety (attached to C21 instead of C18). Meant to check the effect of the position of the OH group (together with Y1)
Y3	Structure differing from HPJ-A because the C23=C24 double bond is replaced by a single bond. Meant to verify the possible relevance of the C23=C24 double bond
Y4	Structure differing from HPJ-A because R is a methyl instead of an isopropyl. Meant to check the possible relevance of the size of R
Y5	Structure differing from HPJ-A because the atoms after C22 have been removed. Meant to check the possible relevance of the C23=C24 double bond (together with Y3) and the possible relevance of the length of *R′*
Y6	Structure differing from Y5 because the atoms after C22 have been removed, but a C23 atom has been bonded to C21 with a double bond. Meant to check possible influence of the distance of the double bond from the additional O19–H20 group and of the presence of a double bond after this group, in a context different from that of the geranyl chain
B	The simplest ACPL with the same *R* as HPJ-A and $R' \neq H$ [18]. Meant to check the relevance of the geranyl-type *R′* and the functions it contains (the additional OH and the C23=C24 double bond)

All the molecules are shown in Fig. 2, except HPG-A and X, because their relevant atom numbering is evident from that of HPG-B

auxiliary structures in another, and so on. When expedient, ESI tables and figures may be cited in the text; then, their numbers are preceded by an S, to make them easily recognisable as belonging to ESI. Their numbering is independent of the numbering of figures and tables in the text, and also of the order in which they are cited in the text.

All the distances reported are in Å and all the frequency-related values are in cm^{-1}.

2 Computational details

Since this work focuses on the effects of complexation on IHBs, only complexes of conformers containing at least one O–H···O or O–H···π IHB have been considered and calculated. For each conformer, all the possible binding sites for the ion, including binding to two or three simultaneously accessible sites, have been considered.

All the complexes have been calculated in vacuo at the DFT level with the B3LYP functional [37–39] and with the 6-31+G(d,p) basis set for the C, O and H atoms and the LANL2DZ pseudopotential [40] for the Cu^{2+} ion—a basis set option which is particularly suitable for complexes with metal ions [41, 42]. The reasons for selecting these methods were explained in [25, 26] and are not repeated here. The fact that all the complexes are calculated with the same method ensures comparison viability.

As already mentioned, numerous additional complexes have been calculated within the current work for HPJ-A and related structures, to have an adequate number of complexes for each molecule, including the auxiliary ones, in view of the search for possible patterns. Some new uncomplexed conformers and 39 new complexes were calculated for HPJ-A (adding to the 47 presented in [25]). All the complexes of Y1, Y2, Y3, Y4, Y5, Y6, and B considered here were calculated specifically for this work, because the few that had been included in [25] had been calculated with the 6-31+G(d,p) basis set for all the atoms, including the ion (which had appeared acceptable because of the purely auxiliary role of these structures in that work). Within the current work, all the complexes have been calculated using the LANL2DZ pseudopotential for the Cu^{2+} ion, to enhance the quality of the results as well as ensure comparison meaningfulness. Since all these complexes are

thus new, their geometries and relative energies are shown in Figs. S1–S9.

Vibrational frequencies (harmonic approximation) were calculated for the main molecules and for some auxiliary structures, in order to evaluate the changes in the red shifts of the vibrational frequency of the IHB donor on complexation. All the computed frequency values were scaled by 0.9848, as recommended for DFT/B3LYP/6-31 and with the(d,p) calculations [43].

All the calculations were performed on desktop computers with Gaussian 03, version D01 [44]. Visualisation utilised GaussView 4.1 [45] and Chem3D 8.03 [46].

3 Results

3.1 Selection and naming of molecules, conformers and complexes

Among the molecules listed in Table 1 and shown in Fig. 2, HPJ-A, ARZ, HPG-A and HPG-B are ACPLs reported to have good antioxidant activity, and GTM is a geranylated ACPL reported in [1] and useful for comparisons with HPJ-A. All the other structures are used here as auxiliary structures, with the role/s outlined in Table 1. The auxiliary structures related to HPJ-A are denoted with simple symbols starting with the same uppercase letter (Y1, Y2, Y3, Y4, Y5, Y6) to facilitate their identification as pertaining to the same group (structure B has been considered in other works and, therefore, maintains the symbol introduced for it in [18] and utilised in subsequent works, for the sake of consistency).

The atom numbering utilised for the main molecules (HPJ-A, ARZ, HPG-A, HPG-B, and GTM) is the same as in the works in which they were first considered. The atom numbering for the phloroglucinol moiety is the same as in all previous works on ACPLs (Fig. 1). The atom numbering of the substituents (Fig. 2) attempts to ensure that it is the same for corresponding functions in related structures (e.g. for the atoms forming π bonds or for the additional OH group in a chain attached to C3). This also means that some intermediate numbers may be missing for structures with fewer atoms (e.g. auxiliary structures). It is not easy to unify the atom numbering for rings in *R′* or constituting *R′* (e.g. ARZ and HPG-A) and, therefore, no attempt in this regard has been finalised.

Following a practice utilised in all previous works on ACPLs (since [18]), conformers are denoted with acronyms providing complete information about their characterising features, such as presence of specific IHBs, orientation of the OH groups, etc., by denoting each feature with a lowercase letter. Table 2 lists the letters utilised for all, or most, of the molecules considered here. Some symbols may have different meanings for different molecules; for instance, η and ξ have the meaning indicated in Table 2 when *R′* or *R″* are geranyl or prenyl chains (and this is the same meaning used in previous studies on ACPLs), but they denote specific O–H···O IHBs in the case of ARZ, as recalled in the caption of Table S4. Other letters have been introduced in specific works to denote specific characteristics of a specific molecule and are not recalled in Table 2, although they are present in the acronyms of the corresponding complexes; examples are the letters denoting the variety of possible geometries of *R′* in GTM and related structures [28]; their meaning is not recalled in the ESI tables concerning these molecules, because they are not directly referring to IHBs (this option responds to the need of limiting the number of symbols to those relevant to more than one molecule, and to those relevant to the scope of the current study, focusing on IHBs, to avoid undesirable cumbersomeness).

The site/s to which the Cu^{2+} ion binds are indicated in the acronyms denoting the complexes by writing "Cu" followed by the site/s concerned. Thus, e.g. HPJ-A-d*-r-v1-Cu–O19–π2 is a complex of the HPJ-A molecule where the H15···O14 first IHB is present (d) and has undergone a proton transfer on complexation (*), O10–H16 is oriented towards *R′* (r), O12–H17 is oriented away from R (absence of the letter u), the H20···O8 IHB is present (v1) and the Cu^{2+} ion binds to O19 (mentioned explicitly) and to the C23=C24 double bond (π2); GTM-s*-w-u-j-Cu–O10–π1–π2 is a complex of the GTM molecule where the H17···O14 first IHB is present (s) and has undergone a proton transfer on complexation (*), O10–H16 is oriented away from *R′* (w), O8–H15 is oriented towards *R* (u), the *R′* chain has a geometry specified by the letter j [28] and the Cu^{2+} ion binds to O10 (mentioned explicitly) and to the C17=C18 (π1) and C23=C24 (π2) double bonds; and so on. In the text, the molecule is specified within each acronym; however, this is not necessary in tables reporting data for the same molecule, because the molecule is specified in the caption.

3.2 IHBs present in the molecules considered

The first IHB characterises all the ACPLs having at least one OH group *ortho* to CRO and is present in all the molecules considered here. Except for the HPG molecules, where only H15···O14 is possible, all the other molecules have conformers with H15···O14 and conformers with H17···O14. HPJ-A and related molecules can form additional O–H···O IHBs because of the presence of O19–H20; the H15···O19 and H16···O19 IHBs are present also in the conformers of the uncomplexed molecules, whereas H20···O8 appears only in some complexes (including low energy ones). The ARZ molecule can form a variety of additional O–H···O IHBs with different patterns ([26], recalled in the caption of Table S4). GTM and related molecules, and HPG-B and related molecules, cannot form additional O–H···O IHBs.

Table 2 Symbols utilised to specify geometrical characteristics in the acronyms denoting conformers and complexes

Symbol	Meaning
d	The H15···O14 first IHB is present
s	The H17···O14 first IHB is present
q1	The H15···O19 s IHB is present
q2	The H16···O19 s IHB is present
v1	The H20···O8 s IHB is present
v2	The H20···O10 s IHB is present
ξ	When the molecule contains a prenyl geranyl chain attached at C3: presence of the O8–H15···π1 interaction When the molecule contains a prenyl geranyl chain attached at C5: presence of the O12–H17···π1 interaction
η	Presence of the O10–H16···π1 interaction
ξ2	Presence of the O8–H15···π2 interaction
η2	Presence of the O10–H16···π2 interaction
ξ♣	Presence of the O19–H20···π2 interaction, with O19–H20 having an f1 arrangement
η♣	Presence of the O19–H20···π2 interaction, with O19–H20 having an f2 arrangement
*	Proton transfer occurring on complexation. The asterisk follows the letter denoting the IHB concerned
π1	The C=C double bond closer to the phloroglucinol moiety in an open-chain substituent: C17=C18 in a geranyl or a prenyl chain attached at C3; C29=C30 in ARZ (prenyl chain attached to C5); C21=C22 in HPG-B and related structures (prenyl chain attached at C5)
π2	The C=C double bond farther away from the phloroglucinol moiety in a geranyl or a geranyl-type chain attached at C3. Any other double bond appearing after the position to which O19–H20 is attached (like C21=C22 in Y6) or in rings pertaining to *R*′ (like in ARZ or in HPG-B)
π3	A third C=C double bond appearing in substituents (e.g. C20=C21 in ARZ)
r	H16 is oriented to the side of C3
w	H16 is oriented to the side of C5
u	H15 or H17, not engaged in the first IHB, is oriented towards the *R* chain
f1	For molecules containing O19–H20 in *R*′: the geometry of *R*′ corresponds to removal of q1
f1	For molecules containing O19–H20 in *R*′: the geometry of *R*′ corresponds to removal of q2
′	Distinguishing the higher energy one or two conformers with similar (but not identical) characteristics
″	Distinguishing the highest energy one or three conformers with similar (but not identical) characteristics

O–H···π IHBs have significant influence on the geometry of the portion of a molecule containing a π bond in the vicinity of an OH and geometrically accessible to it [47–51]. They have also proved to have relevant roles in the stabilisation of ACPLs in which they are present [22]. GTM and related molecules, as well as ARZ, can form comparatively strong O–H···π IHBs.

Weaker O–H···π interactions may involve O19–H20 and π2 in HPJ-A, Y1, Y2, Y4, and Y6. They show some stabilizing effect in a number of uncomplexed conformers (Fig. S1). However, they are not always maintained on optimisation of inputs in which they are present, and keeping systematic track of them would become unnecessary cumbersome. Only few examples have been singled out, to highlight both their possible presence and their comparatively small effects. The ξ♣ and η♣ symbols denoting them do not refer to different donors (as the ξ and η symbols for the other O–H···π IHBs), but only to different geometries/orientations of *R*′.

3.3 Identified effects of complexation on the IHBs of ACPLs

3.3.1 General remarks

Complexation with a metal ion brings major changes in the molecule concerned, because it implies some geometrical changes to accommodate the ion, the acquisition of a positive charge following the transfer of an electron to the ion (which gets reduced) and the consequent presence of an unpaired electron. The molecule's IHBs also undergo some changes, which may be minor or substantial, depending mainly on the binding site of the ion. The following changes appear frequently and will be analysed in separate sections:

- Proton transfer from the donor O atom to the acceptor O atom, in O–H···O IHBs;
- Changes in the geometric characteristics (parameters) of IHBs;

- Changes in the red shifts (lowering of vibrational frequencies) of the donor OHs;
- Appearance of IHBs which are not present in the conformers of the isolated molecule.

It appears particularly important to elucidate whether a given IHB is strengthened or weakened by the complexation, also in view of the fact that complexation with a metal ion might be involved in the biological activity mechanism and that IHBs may also have some role in it. Such role may be exerted differently (or not exerted) if a given IHB becomes weaker or stronger (for instance, a stronger IHB might not break in favour of intermolecular interactions). The energy of an IHB is generally not easy to evaluate because its removal brings changes in the molecular geometry and, therefore, the energy difference between a conformer in which it is present and a conformer from which it is absent does not correspond only to the energy of the IHB [52–57]. Indications about an IHB strength can be given by quantities related to it, such as its parameters and the red shift it causes on the vibrational frequency of the donor group. Therefore, changes in the parameters and changes in the red shift can be considered reliable indications about whether a given IHB is strengthened or weakened by the complexation of the molecule with a metal ion.

The following subsections analyse the changes brought about by complexation on the characteristics of IHBs individually. It may be useful to recall that molecular computations pertain to modelling activities and, therefore, computational results provide indications about what happens at the molecular level. Thus, for instance, a statement like saying that "an increase in the length of a certain IHB *is caused* by the ion binding to a certain site" is meant to be understood as "the results indicate that an increase in the length of a certain IHB is related to the ion binding to a certain site". However, the former mode of expression is used more frequently for the sake of conciseness and to avoid frequent repetitions of more elaborated wordings.

3.3.2 Proton transfer in an IHB

Proton transfer is a frequent effect for O–H···O IHBs, above all when the acceptor is an sp^2 O and above all for the first IHBs (consistently with the fact that stronger hydrogen bonds are characterised by lower barrier to the proton transfer process [58]). The H atom of the donor OH moves closer to the other O atom, with consequent reversal of the donor and acceptor roles. Figure 3 shows illustrative examples considering different IHBs, different molecules, different binding sites of the ion and also different conformers of the same molecule.

The proton transfer never appears when the ion binds to the acceptor O; it may appear or not appear for other binding sites. The dependence on the geometry of the rest of the molecule does not show clear-cut patterns. For instance, in the complexes of HPG-A (Fig. 3), it appears in (m) (n) and (o), which have the same binding site of the ion and different geometries of the prenyl chain at C5; it appears in (l) but not in (q), although they differ only by the geometry of *R*. In the cases in which the proton transfer concerns the H15···O19 or H16···O19 IHBs, O19 may become an oxonium ion (e.g. complexes (r) and (u) in Fig. 3). For structures Y3 and Y5 (the structures where there is no double bond in *R*′), this may lead to the separation of O19 as a water molecule (Fig. S10).

Corresponding complexes with and without proton transfer for the same binding site/s of the ion and analogous geometries of the molecule may result from the optimisation of slightly or—in other cases—substantially different inputs. The effect of complexation on them may be different. For instance, for the Y1-d*-w-Cu–O8–O19 and Y1-d-w-Cu–O10–O19 complexes, the length (Å) of the first IHB changes by −0.058 and −0.132, respectively, with respect to the isolated conformer, the O···O distance by −0.040 and −0.071 and the IHB bond angle by 0.6° and 2.3°. For HPG-A, the length of the first IHB decreases slightly only in few cases, none of which entails a proton transfer. This is also clearly highlighted by the cases when corresponding optimised complexes with and without proton transfer are both available. For instance, the ion binding to O12 and π1 causes a slight increase in the length of the H15···O14 IHB in HPG-A-d*-a-Cu–O12–π1 and HPG-A-d*-a-^-Cu–O12–π (by 0.047 and 0.077 Å, respectively) and a slight decrease (−0.037 and −0.033 Å) in HPG-A-d-a-Cu–O12–π1 and HPG-A-d-a-^-Cu–O12–π1, where there is no proton transfer; correspondingly, the bond angle decreases by 3.1° and 4.1° when there is the proton transfer, and by 1.8° and 1.9° when there is no proton transfer.

3.3.3 Changes in the IHB parameters

The length of an IHB (H···O distance) is one of the features that provide indications about its strength, and length comparisons enable realistic comparisons of the strength of different IHBs. Tables S1–S5 report the changes in the parameters of the IHBs in the considered complexes with respect to the corresponding uncomplexed conformers. The changes are taken as ≪value in the complex minus value in the corresponding uncomplexed conformer≫, so that a positive value indicates an increase in the given parameter on complexation and a negative value a decrease. A length increase indicates weakening of the IHB, whereas a decrease indicates strengthening. For the IHB angles, an increase indicates strengthening. It has also to be noted that the extent to which the parameters of the first IHB may change is limited by its geometry constraints, as it closes a 6-member ring containing two double bonds (one of which

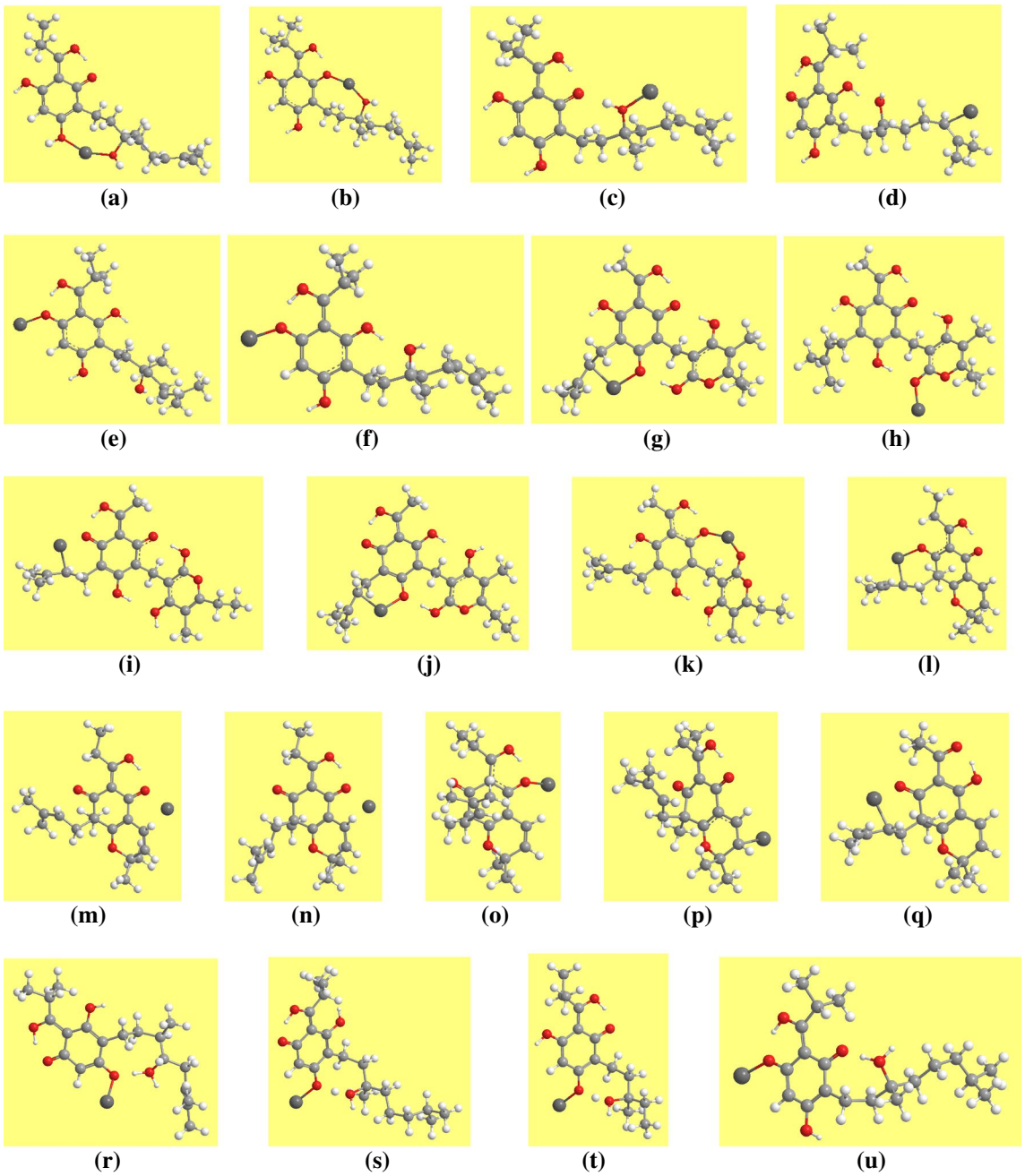

Fig. 3 Examples of proton transfer in IHBs in different molecules, on complexation. Transfer of H15 from O8 to O14 (**a**, **b**, **c**) and of H17 from O12 to O14 (**d**, **e**, **f**) in HPJ-A. Transfer of H15 from O8 to O14 (**g**, **h**), of H17 from O12 to O14 (**i**, **j**) and of H16 from O10 to O19 (**k**) in ARZ [26]. Transfer of H15 from O8 to O14 (***l***–**q**) in HPG-A [27]. Transfer of H16 from O10 to O19 in Y2, Y3 and Y5 (**r**, **s**, **t**). Transfer of H15 from O8 to O19 in Y3 (**u**)

pertaining to the benzene ring), and this creates considerable geometry rigidity.

In all the ESI tables, IHBs between the same donor and acceptor O atoms are grouped together, whether a proton transfer has occurred or not. The acronyms denoting the complexes provide information about this; for instance, "d" denotes the H15···O14 first IHB and "d*" denotes the case where a proton transfer has occurred, so that the IHB length considered is the H15···O8 distance. In the tables where the IHBs are indicated individually, the two situations are clearly distinguished in the IHB columns (e.g. H15···O14 or H15···O8).

The analysis of the changes in terms of the ion binding site/s is important, because the binding site/s has proven

the main responsible for the extent and direction of the changes; therefore, it is carried out for all the complexes considered in this work. In the tables presenting this type of analysis, the binding sites are listed in the following general sequence: three simultaneous binding sites, when they are possible (e.g. O8, π1 and π2, in table S3); two simultaneous sites, at least one of which is an O atom (e.g. O10–π1, O12–π1, O8–O23, O10–O23, O8–O26, O10–O26 in Table S2); simultaneous binding to two π sites (e.g. π1 and π2 in Table S3); sp^2 O atoms (e.g. O14 in all the tables, and O23 after O14 in Table S4); the other O atoms (e.g. O8, O10, O12 and O19 in Table S2); only one π site at a time (e.g. π1, π2, π3 in Table S4; the benzene ring is listed as the last of the π–systems binding sites, because it appears less frequently); simultaneous binding to O8 and O14 or to O12 and O14 in conformers without the first IHB (e.g. Table S2).

The most general observation is the increase in the length of the first IHB when the ion binds to O14 (the acceptor O), accompanied also by a decrease in the IHB angle, both suggesting weakening of the IHB. In the case of HPJ-A and related structures, binding of the ion to other sites may cause only minor changes, or a decrease in the first IHB bond length. For HPJ-A, simultaneous binding to O10 and O19 causes both a decrease in the bond length and an increase in the bond angle, suggesting strengthening of the IHB (Table S2). For GTM (Table S3), both binding to O14 and binding to O12 cause an increase in the H15···O14 length; binding to the other sites mostly causes a slight decrease. For ARZ (Table S4) binding to most sites (other than O14) either causes a slight length decrease, or may cause a slight increase or a slight decrease without clearly identifiable patterns. In the case of HPG-A and related molecules (Table S5), the length of the only IHB present (H15···O14) increases also when the ion binds to O8, in a way comparable to when it binds to O14; the decrease in the bond angle is greater than for the other molecules when the ion binds to O14, and binding to most of the other sites also causes a decrease in the bond angle.

The length of H15···O23 or H16···O23 in ARZ increases when the ion binds to O23 (which, like O14, is an sp^2 O), whereas it decreases significantly when the ion binds to O14, or to O12 or to O26. As for the other IHBs in ARZ (H15···O26, H16···O26, H27···O8, H27···O10), the ion does not bind to the acceptor O. H15···O26 shows significant length decrease when the ion binds to O8 (which is the donor O); H16···O26 when the ion binds simultaneously to O8 and O23; H27···O8 when the ion binds to O26, or to π1, or to π3.

The complexes of HPJ-A and related structures show noticeably smaller changes in the IHB lengths than the complexes of ARZ. Considerably greater strengthening of the H15···O19 and H16···O19 IHBs (decrease in the bond length, increase in the bond angle) than in the other related structures appear in Y3 and Y5, i.e. the structures where there is no double bond in *R′* (Table S2).

It is not possible to identify a bond length (as distance between two nuclei) in the case of the O–H···π IHBs, because the acceptor is a whole electron cloud. However, the distances of the H atom from the two C atoms forming the double bond provide indication of how close the H atom comes to the π bond. The changes in these distances are reported in Table S6 for GTM and in Table S7 for ARZ. For GTM, the distances decrease considerably when the ion binds simultaneously to O10 and π2, and when it binds to O12. For ARZ, the distances decrease considerably for most of the binding sites.

3.3.4 Changes in the red shift for the stretching vibration of the donor OH

The formation of an H-bond causes a lowering of the frequency of the infrared vibrational modes of the donor OH. The red shift related to the highest-frequency vibrational mode of an OH (stretching mode) is usually taken into account, because of its considerable magnitude; therefore, the 'red shift' term will hereafter be referred to the lowering of the frequency of this mode.

The red shift provides indications on the strength of the H-bond: the greater the red shift, the stronger the H-bond. The red shift changes on complexation are expressed by much greater numbers than the changes in IHB parameters, thus facilitating comparisons about the IHB strengthening or weakening. Changes in the red shifts on complexation are reported in Tables S8–S12 for selected complexes. The changes are calculated as ≪red shift in the complex minus red shift in the corresponding conformer of the isolated molecule≫; therefore, a positive value (increase in the red shift) indicates strengthening of the IHB and a negative value indicates weakening. The values are reported without decimal digits, because the evaluation accuracy may not be adequate for including decimal digits. Since the binding site of the ion is the major responsible for the red shift changes, analysis in terms of the binding sites is considered for all the cases; the binding sites are listed according to the criteria explained in the previous section.

The changes in the red shifts confirm weakening of the first IHB when the ion binds to O14. Given the importance of this indication, the ranges of the decrease are reported in Table 3. A similar (although less marked) phenomenon is observed with other IHBs in which the acceptor is in sp^2 O, namely H15···O23 and H16···O23 in ARZ, whose red shift decreases by 99–274 and 127–263 cm^{-1}, respectively.

In some cases, the red shift may increase or decrease for the same binding site and the same molecule. In other cases, it only increases. Table 4 summarises the cases when it increases considerably, providing the ranges of the increase.

Table 3 Ranges of the decrease in the red shift of the vibrational frequency of the OH forming the first IHB when the Cu^{2+} ion binds to O14

Molecule	Red shift decrease (cm^{-1})		Molecule	Red shift decrease (cm^{-1})	
	O8–H15	O12–H17		O8–H15	O12–H17
HPJ-A	261–394	247–451	ARZ	276–563	273–401
GTM	266–385	281–395	HPG-A	750–908	
GTM-P2	231–385	266–377	HPG-B	789, 852	
GTM-PR	323, 373	233–412	X	778, 843	

The ranges consider the magnitude (the absolute value) of the decrease

It has also to be recalled that the increase often depends extensively on the geometry of the conformer. The orientation of the OHs not engaged in IHBs may have considerable influence. For instance, for the complexes of GTM, there is considerable difference between non-u and u conformers; thus, the increase for non-u d-w and d-r conformers is 126–219 cm^{-1} when the ion binds to π1 and 189–343 cm^{-1} when it binds to π2; the increase for the corresponding d-w-u and d-r-u conformers is 408–435 and 320–529 cm^{-1}, respectively. The orientation of O10–H16 may also influence the change. For instance, the red shift increase for O12–H17 is 182 cm^{-1} for GTM-PR-s*-w-ξ-Cu–O12 and 616 cm^{-1} for GTM-PR-s*-r-ξ-Cu–O12, which differ only by the orientation of O10–H16.

The red shift change may also depend—sometimes extensively—on the other IHBs present in a conformer. For instance, the red shift of O8–H15 increases only by 10 cm^{-1} for ARZ-2-d*-r-αδ-Cu–π1(ext) and by 662 cm^{-1} for ARZ-1-d-r-ξ-δ-Cu–π1. For the ARZ-2-d*-w-ξ-α-Cu–O10–O23, ARZ-1-d*-w-ξ-α-Cu–O10–O23, ARZ-2-d*-w-η-α-Cu–O10–O23 and ARZ-1-d*-w-η-α-Cu–O10–O23 complexes, the red shift of O8–15 decreases slightly (by 34–48 cm^{-1}), while it increases by 348 cm^{-1} for the ARZ-1-d*-w-η-Cu–O10–O23 complex.

For HPG-B and related structures, the red shift of O8–15 decreases—often considerably—for most of the binding sites.

The O–H···π IHBs also cause red shifts in the vibrational frequencies of the donor OHs. For GTM, the red shift in the vibration of O8–H15 caused by the H15···π1 IHB (Table S9) increases sharply when the ion binds to O8, to π2 and simultaneously to O8 and π2. The red shift in the vibration of O10–H16 caused by the H16···π1 IHB (Table S9) increases sharply when the ion binds to O10 or simultaneously to O10 and π2. For ARZ (Table S10), the increase in the red shift is quite large in most cases; it may be 2-4-fold with respect to that of the O–H···O IHBs. The red shift of O12–H17 decreases only when the ion binds to π1, which is the acceptor of the IHB (no inputs have optimised to complexes with the ion binding to π1 and maintaining the H16···π1 IHB).

3.3.5 Appearance of IHBs not present in the uncomplexed conformers

The H20···O8 and H20···O10 IHBs do not appear in the conformers of uncomplexed HPJ-A and related molecules, except for a couple of conformers of structure Y6; inputs having these IHBs optimise to geometries without them. However, H20···O8 is present in a number of complexes, either being maintained through optimisation from inputs containing it or appearing as a result of the optimisation of inputs not containing it. This IHB is important, because it is present in a number of low energy complexes, including the lowest energy complex of HPJ-A. Since it is not present in any conformer of the uncomplexed molecules, those complexes could not be included in the S1–S12 comparison tables for lack of a reference with respect to which to evaluate the changes. Thus, the parameters of the IHBs of these complexes are reported in a separate table (Table S13) to give an idea of the characteristics of the H20···O8 IHB. The parameters indicate that this bond is stronger when the ion binds to O19.

It is also interesting to note that H20···O8 does not appear in the complexes of Y3 and Y5, whose *R′* does not contain any double bond, while it appears also in the complexes of Y6, although its *R′* is shorter than the others (but contains the C21=C22 double bond after O19–H20). Although the comparison of complexes of more other molecules would be necessary to make a final inference, the behaviour observed with HPJ-A and related molecules suggests the possibility that the presence of a double bond in *R′* might be needed for the formation of H20···O8 in complexes where the conformer has suitable geometry.

4 Discussion and conclusions

The current work focuses on the effects of complexation with a metal ion on the IHBs present in ACPL molecules. This seems to be a rather novel focus, as most of the works considering IHBs in relation to the formation of complexes focus on the role that IHBs may take in this formation, or on the competition between IHB and intermolecular interactions [e.g. [59–61]]. The present work focuses on what happens to the IHBs in the molecule as a result of complexation with a metal ion. The number and variety of investigated molecules and the variety of IHB patterns present in them, as well as the number of complexes for each molecule, can be considered adequate to validate the major inferences of the study.

Table 4 Ranges of the increase in the red shift of the vibrational frequency of the OHs forming IHBs when the increase on complexation of the molecule is considerable

Molecule	Ion binding site	Red shift increase (cm^{-1})			
		O8–H15	O12–H17	Other OH	
HPJ-A	O10–O19	586–985	399–576		
	O19	234–504	430–762		
	O10	116–654	341–618	O10–H16	(q2) 814–961
	π2	203–592	366–808	O10–H16	(q2) 170–224
GTM	O10–π1–π2	159, 468	348, 694		
	O8–π1	8–204	229, 420		
	O10–π1	669–950	444–738		
	O10–π2	168, 465	723	O10–H16	(η) 618–645
	π1–π2	113–469	383–757		
	O10	442–553	231–572	O10–H16	(η) 22–414
	π1	126–435	393		
	π2	189–629	456–908		
GTM-P2	O8–π2		358–604		
	O10–π2	165–634	476–1453		
	O10	366–715	305–375		
	benz	409	407–558		
GTM-PR	O10	(ξ) 300, 409	270–1013		
	O12	(ξ) 182, 615			
	π1	276–291			
ARZ	O10–π1	(γ) 497–729	147–465	O10–H16	(δ) 211–961
	O10–π1			O10–H16	(ε) 281–289
	O8–O23		(ξ) 516–632	O10–H16	(ε) 192–216
	O8–O23			O10–H16	(η) 502, 519
	O10–O23	(β) 132–270	81–637	O10–H16	(η) 707–795
	O10–O23		(ξ) 521–607		
	O14	(γ) 178–1037	(ξ) 180–588	O10–H16	(η) 226–453
	O23		26–783	O10–H16	(η) 257–359
	O23		(ξ) 474–585		
	O8		182–238		
	O10		(ξ) 417–503	O10–H16	(δ) 124–393
	O12	(γ) 475, 508	(ξ) 812, 839	O10–H16	(η) 158–245
	O26		384	O26–H27	(α) 394–1109
	O26		(ξ) 616, 680		
	π3		(ξ) 573		
	Benz		(ξ) 443, 445	O26–H27	(α) 407–1445

When no indication is given for O8–H15 and O12–H17, the first IHB is considered. In all the other cases, the IHBs are indicated through their symbols (in parentheses) immediately before the range of values

The following main effects of complexation have been identified: proton transfer from the donor to the acceptor O; IHB weakening or strengthening, highlighted by changes in their parameters and in the red shift they cause; and appearance of IHBs that are not present in the uncomplexed conformers. All the changes depend primarily on the binding site/s of the ion and, to a lesser extent, on the characteristics of the conformer.

The most generalised phenomenon appears to be the considerable weakening of the O–H···O IHB in which the acceptor is an sp^2 O, when the ion binds to the acceptor O. This includes the first IHB, which is the most stabilising IHB in ACPLs and is maintained in solution, including water solution [8]. The weakening caused by the complexation is likely sufficient to make it more prone to breaking.

The proton transfer from the donor to the acceptor O appears frequently, above all for the stronger IHBs in which the acceptor is an sp^2 O. The proton transfer phenomenon has been investigated extensively, both as singly-occurring phenomenon [e.g. [62–70]] and as coupled to electron transfer (e.g. in biological and other processes [71]). The proton transfer highlighted by the results of the current study

concerns an individual hydrogen bond, and is related to the transfer of an electron from the molecule to the ion. It might thus be viewed as a proton transfer coupled with the transfer of an electron from the molecule within which the proton transfer occurs to a charged species. The fact that the molecule acquires an overall charge in the process may be a feature worthy of separate investigation for a better understanding of the extent to which the proton transfer may be considered coupled to the electron transfer, and of the characteristics of the coupling.

A variety of factors influence the extent of the effects of complexation on the IHBs. The presence of a C=C double bond in *R′* may have different types of influence. For instance, the strengthening of H15···O19 and H16···O19 is considerably greater in Y3 and Y5 (structures with no C=C double bond in *R′*) than in the other related structures; furthermore, Y3 and Y5 are the only structures, in the HPJ-A and Y series, where the H20···O8 IHB (an IHB not present in uncomplexed conformers) does not appear on complexation. The effects on the first IHB may be different for complexes in which there is no proton transfer and complexes in which the transfer occurs. Differences related to the orientation of the phenol OHs (e.g. between non-u and u conformers, or between r and w conformers) can also be easily identified on comparing pairs of corresponding conformers, but no clear-cut patterns appear evident.

The O–H···π IHB is often strengthened by the complexation. The increase in the red shift it causes may reach up to being fourfold the increase for an O–H···π IHB.

Overall, the results provide a comprehensive and detailed picture of the possible effects of the complexation of ACPL molecules with a metal ion on the IHBs present in the molecules.

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