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Review

The Supramolecular Attitude of Metal–Salophen and Metal–Salen Complexes

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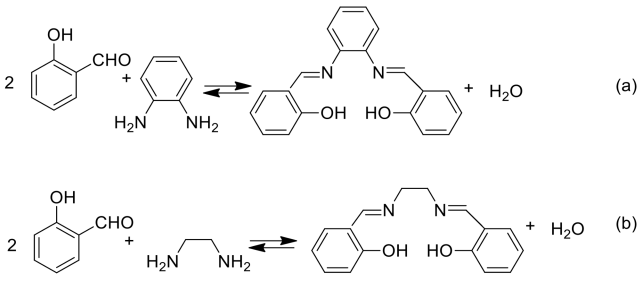
Abstract: In this review we cover some aspects of metal–salophen and metal–salen complex chemistry related to their supramolecular attitude. We examined under the lens of the non-covalent interactions their potential to behave as building blocks for auto-assembled architectures, supramolecular receptors and catalysts, although this last point has been only briefly mentioned.

Keywords: Schiff-base complexes; salen and salophen ligands; supramolecular chemistry; metal complexes; auto-assembly; molecular recognition

1. Introduction

Salophens (*N*,*N*-bis(salicylidene)phenylenediamine) and salens (*N*,*N*-bis(salicylidene) ethylenediamine) are classes of organic compounds extensively used as ligands in coordination chemistry [1]. They represent one of the oldest category of ligands, the first salen complex being described by Pfeiffer et al. in 1933 [2]. In the years such derivatives have attracted much attention and various systems have been successfully developed. A major advantage of these compounds is that they are readily accessible from cheap precursors through the condensation of a diamine (*o*-diphenylamines for salophen and aliphatic diamines for salen) with two equivalents of salicylaldehyde derivatives to obtain tetradentate Schiff bases (Scheme 1). The N_2O_2 coordination sphere reproduces the setting found for many metals in metalloproteins, since these ligands are structurally similar to porphyrins, but much easier to synthesize. Further, the possibility of incorporating two different benzylidene moieties and diamine backbones [3] provides access to a large variety of salen/salophen ligands that, after deprotonation of both phenolic oxygens, can form rather stable complexes with many transition and main group metals, with different oxidation states, coordination numbers and geometries that have shown interesting applications in many fields [4–9]. Recently also an extensive use of metal complexes with salen and salophen ligands has been reported in the design of new magnetic materials [10,11].



Scheme 1. General synthesis of salophen (**a**) and salen (**b**) ligands.

The presence of the rigid subunits, i.e., the ligand skeleton comprising three aromatic units in the case of salophen and often of cyclohexyl ring for salen ligands, and the metal that, with its coordination geometry, masters substrate's approach, provides therefore valuable assets for supramolecular design. Moreover, the possibility to introduce a large variety of substituents on the salyciladehyde rings and on the diamine unit, allows the introduction of secondary binding sites that can enhance the selectivity of the process through the establishment of weak interactions with the substrate.

Here in this short review we will try to highlight the attitude that a large number of metal–salophen and metal–salen complexes show to act as supramolecular platforms. The major focus is directed to metal–salophen complexes, although metal–salens will be also considered.

2. A Brief Survey

The first example that can be easily interpreted through the lens of weak interactions is the well-known Jacobsen–Katzuki enantioselective epoxidation of *cis*-substituted olefins by using a chiral Mn-salen catalyst and a stoichiometric oxidant such as sodium hypochloride, NaOCl, Figure 1 [12,13].

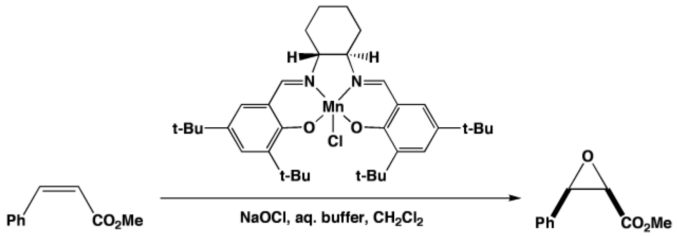


Figure 1. Jacobsen–Katsuki epoxidation. Adapted with permission from *Adv. Synth. Catal.* **2002**, *344*, 131–147. Copyright (2002) Wiley.

The metal, i.e., Manganese, coordinated to Schiff base can transmit chiral information inducing subtle conformational effects, while high-stereoselectivity can be achieved during the reaction by controlling the direction of the substrate approach (Figure 2).

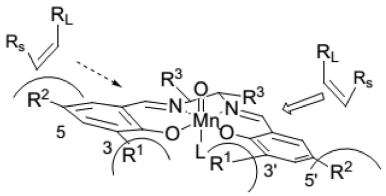


Figure 2. Alternative trajectories of the approaching olefin to the metal. Adapted with permission from *Adv. Synth. Catal.* **2002**, *344*, 131–147. Copyright (2002) Wiley.

The fact is that salen ligands coordinate tetravalently on a single plane, but this does not mean that the ligand adopts a planar asset. The five-ring created by ethylendiamine and the central metal ion can adopt a half-chair conformation, an envelope conformation or a slightly distorted form of one of these (Figure 3) [14]. This means that the possible conformation is either a stepped one (A and B), an umbrella (C) or a slightly distorted form of either [15]. The stepped conformation is chiral, but the umbrella is achiral. Though stereogenic centres are generally placed in the diamine moiety, it is established that indirect conformational effects influence the chiral information transfer too. In salen complexes the absence or presence of an axially coordinating ligand can in general either reduce or enhance the folding of the metal complex, further influencing the transmission of chiral information. This is also supported by theoretical calculations showing that axial donor ligands (Figure 3), which modify the conformation of the complex, push the metal closer to the substrate, thus enhancing the enantioselectivity of the process [16].

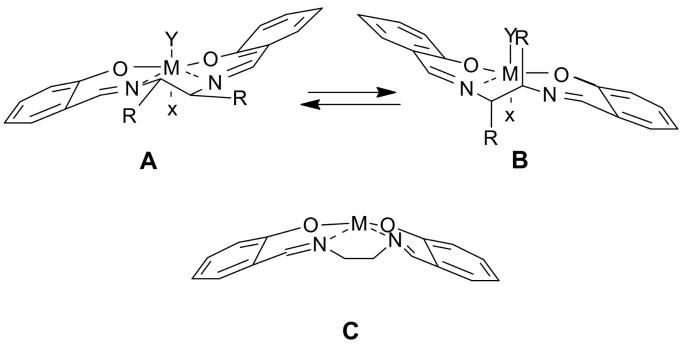


Figure 3. Stepped conformations of metal salen complexes A and B, and the umbrella conformation C. Adapted with permission from *Chem. Soc. Rev.* **2004**, *33*, 437–444. Copyright (2004) Royal Society of Chemistry.

Therefore, such feature can be looked at as a supramolecular effect since the presence, or the absence, of proper substituents can dramatically influence the enantioselectivity of the reaction.

The strategy of having stereogenic centers on the diamine skeleton and the introduction of bulky groups as substituents, can enhance the conformational effects and work in a synergistically or conversely way. The presence of binaphthyl moieties in derivatives **1** and **2** [17], (Figure 4) [12], brings an aryl group close to the metal increasing the polar π-interaction occurring between such group and an apical ligand, while the chelating diamine unit imposes ligand folding. Hence both these effects can be considered decisive in the transmission of chiral information, both being weak interactions not covalent in nature.

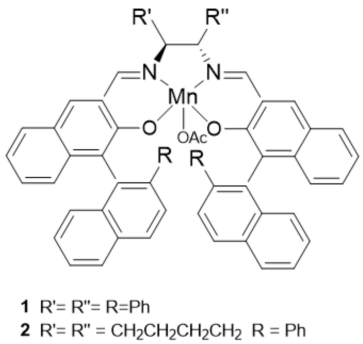


Figure 4. Catalysts for asymmetric epoxidations. Adapted with permission from *Adv. Synth. Catal.* **2002**, *344*, 131–147. Copyright (2002) Wiley.

Another kind of conformational effects, caused by the presence of the metal, master the properties of uranyl–salophen complexes. In these compounds the dication UO_2^{2+} has a well-defined preference for pentagonal bipyramidal coordination, with the two oxygens in the apical positions. After coordination of the four donor groups of the salophen ligand, the fifth equatorial site remains available to bind an additional group having a hard donor site [18]. In the absence of such guests, this site is generally occupied by solvent molecules. Some years ago, we described non-symmetrically substituted uranyl–salophen complexes as inherently chiral [19]. This because, in these derivatives, although the metal ion is not a stereogenic center, its steric bulkiness dissymmetrises the entire structure, thus introducing a curvature in an otherwise planar ligand. The large ionic radius of the uranium, in the uranyl cation, forces the ligand to be highly puckered, as shown by the computer calculated structure of the uranyl–salophen unit (Figure 5) [20], which is consistent with available X-ray crystallographic data [20,21].

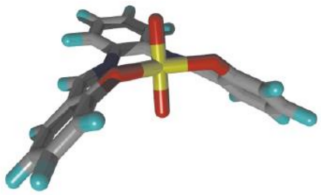
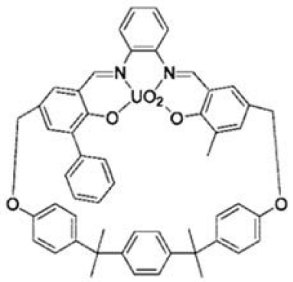


Figure 5. Computer calculated structure of the uranyl–salophen unit. Reproduced with permission from *Chem. Commun.* **2003**, 2178–2179. Copyright (2003) Royal Society of Chemistry.

We found that in non-symmetrically substituted uranyl–salophen complexes fast enantiomerization occurs due to the existence of a flipping motion that rapidly inverts the curvature and keeps the two enantiomers in equilibrium. The flipping can be significantly slowed by introducing bulky substituents in suitable positions [20]. For example, the introduction of a phenyl substituent on one of the imine carbon atoms affords a racemization half-life of such compound of about 17 h at 25 °C [20]. In the search of robust, configurationally stable complexes to be used as enantioselective receptors and catalysts, uranyl–salophen compounds with polymethylene bridges of suitable length, connecting the para positions with respect to the phenoxide oxygens, were synthesized [22]. Inclusion of the rigid unit 4,4′-(1,4-phenylenediisopropylidene)bisphenol (bisphenol P) in the chain, **3** (Figure 6), lead to an enantiomerization half-life of 61 days at room temperature, providing the possibility of using it as an enantioselective receptor [23].

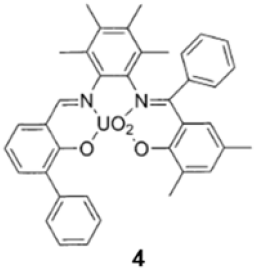


3

Figure 6. Structure of compound **3**. Adapted with permission from *J. Org. Chem.* **2008**, *73*, 6108–6118. Copyright (2008) American Chemical Society.

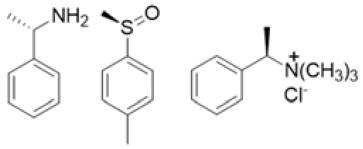
The feasibility of using quite simple uranyl–salophen complexes as enantioselective receptors, while taking advantage of their inherent chirality based on conformational issues, has been tested by an ad hoc developed NMR protocol that allows a fast, quantitative determination of host enantioselectivity directly from its racemic mixture [24].

As previously mentioned, in the non-symmetrically substituted uranyl–salophen complex **4** (Figure 7), the large radius of the uranium atom forces the salophen ligand to deviate from planarity and, as a consequence, this derivative is chiral due to the lack of any element of symmetry. Furthermore, the pendent phenyl group acts as an additional supramolecular interaction site, while the methyl group introduces more strict shape requirements by establishing unfavorable interactions with the bound substrate. Data on the enantioselective binding of **4** toward α-methylbenzylamine, **5**, methyl-*p*-tolylsulfoxide, **6**, and *N*,*N*-dimethyl-α-methylbenzylammonium chloride **7** (Figure 8), are reported in Table 1 [24]. In the case of **7**, chloride ion occupies the fifth coordination site of the uranyl, forming a large anionic complex with the uranyl–salophen receptor.



4

Figure 7. Structure of compound **4**. Adapted with permission from *Chem. Eur. J.* **2004**, *10*, 3301–3307. Copyright (2004) Wiley.



5 **6** **7**

Figure 8. Structure of compounds **5**–**7**. Adapted with permission from *Chem. Eur. J.* **2004**, *10*, 3301–3307. Copyright (2004) Wiley.

Table 1. Association constant pairs [M^{-1}] for diastereomeric complexes between host **4** and guests **5**, **6** and **7** at 25 °C. Adapted with permission from *Chem. Eur. J.* **2004**, *10*, 3301–3307. Copyright (2004) Wiley.

	5	**6**	**7**
$CDCl_3/CD_3OD$ 97:3 (*v*/*v*)	$K_{maj} = 46 \pm 3$ [a] $K_{min} = 21 \pm 1$	-	-
$CDCl_3/CD_3OD$ 99:1 (*v*/*v*)	$K_{maj} = 970 \pm 40$ $K_{min} = 450 \pm 20$	$K_{maj} = 710 \pm 20$ $K_{min} = 420 \pm 10$	$K_{maj} = 68 \pm 6$ $K_{min} = 52 \pm 5$

[a] K_{maj} and K_{min} are the binding constants of **4** with major and minor diastereomers.

The enantioselectivities obtained are encouraging and the NMR protocol used to establish them is a fast and quite general way of performing a preliminary screening of the recognition capability of chiral receptors directly from their racemic mixture.

Another kind of selectivity deriving from the stereochemistry of the coordination sites of the salen and salophen ligand is the one related to the spatial orientation of the donor atoms in the binding site [25]. If the geometry of the coordination site matches with that of the metal ion, one may expect high selectivity toward it, while no selectivity will be obtained if this does not happen, in spite of the intrinsic capability of the ligand to bind the metal. This is the case of recently reported $(A–B)_n$-type salen polymeric ligands **8**–**10** (Figure 9) [25] in which the A-part is a fluorophore based on the fluorene moiety, and the B-part is the ligand with four (ONNO) coordinating donor atoms oriented differently.

Among these, compound **10** results highly selective and sensitive to Zn^{2+} ions through a turn-on fluorescence phenomenon. In such derivative the four donating atoms do not lay in a plane and, moreover, due to the presence of a rigid cyclohexane system, N–N bond rotation is not allowed. The non-planarity of the coordination site, leading to a nearly tetrahedral arrangement, makes it more selective for Zn^{2+} ions than for Cu^{2+}, Fe^{2+} and Co^{2+}. Such suitable tetrahedral binding mode is not instead achieved by the other two polymers. Thus, selectivity is ascribable to the specific binding geometry of the ONNO site imposed by the presence of the cyclohexyl moiety in the ligand skeleton [25].

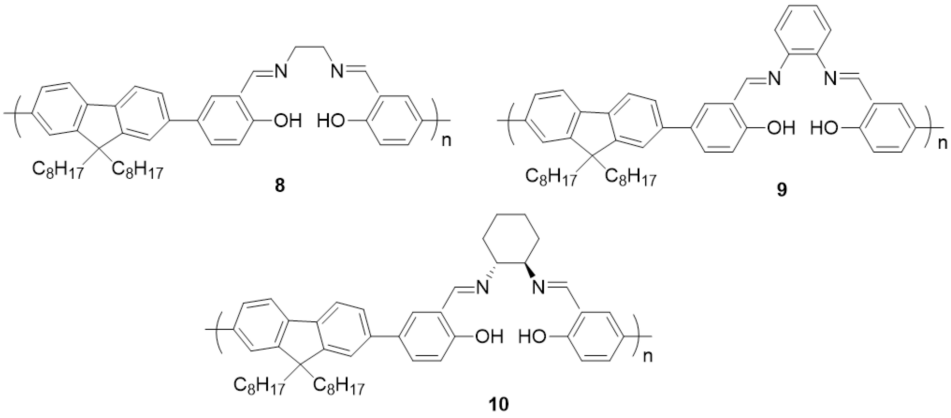


Figure 9. Structures of polymeric ligands **8**–**10**. Adapted with permission from *New J. Chem.* **2015**, *39*, 9207–9214. Copyright (2015) Royal Society of Chemistry.

The structure of the bridging 1,2-diamine is also responsible for the formation of various supramolecular architectures and nanostructures. We need to mention at this point that there is a quite strong tendency of metal salen and salophen complexes to aggregate by intermolecular interactions between the metal of one unit and the phenolic oxygen of a second unit, in solution and in the solid state [26–28]. Nevertheless, in the presence of strong coordinating species, aggregation is prevented. An observable sign of the ongoing disaggregation is the dramatic enhancement of fluorescence emission in Zn–salophen derivatives [29]. Clearly the aggregation properties of the complexes are related to the Lewis acidic character of the metal center which, in turn, is deeply connected to the nature of the bridging diamine. So, a variety of supramolecular architectures, mesomorphic, and self-assembled nanostructures have been found, which are the result of intermolecular Zn···O axial interactions involving pentacoordinated square-pyramidal Zn(II) geometries (Figure 10) [26].

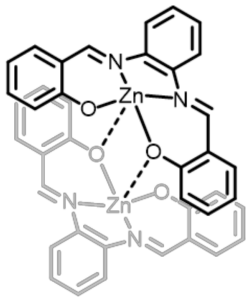


Figure 10. Formation of dimers in Zn–salophen complexes through Zn···O axial interactions. Adapted with permission from *J. Am. Chem. Soc.* **2012**, *134*, 7186–7192. Copyright (2012) American Chemical Society [26].

Recently it has been reported the complex derived from 4-methoxysalicylaldehyde and *cis*-1,2-diaminocyclohexane, **11** [30], and its behavior has been compared with that of complexes, **12**, derived from enantiopure (1*S*,2*S*)-(+)- or (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane (Figure 11) [31,32].

Figure 11. Structures of compounds **11**–**12**. Sources: (**a**) Adapted with permission from *Dalton Trans.* **2015**, *44*, 13040−13048. Copyright (2015) Royal Society of Chemistry and (**b**) from *Inorganics*, **2018**, *6*, 8.

While in the case of *cis* an asymmetric dimeric aggregate with a typical Zn(II) pentacoordination has been found (Figure 12) [30], the complexes derived from the enantiopure (1*S*,2*S*)-(+)- or (1*R*,2*R*)-(−)-trans-1,2-diaminocyclohexane involve the existence of various species in solution [32]. Such different performance evidences the influence of the defined stereochemistry of the chelate *cis*-1,2-diaminocyclohexane bridge that leads to a very rigid backbone of the dimeric aggregate [30].

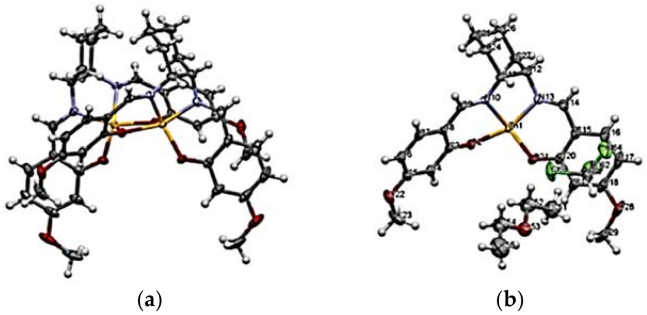


Figure 12. The dimer backbone of **11** (**a**); the asymmetric unit with the solvent molecules, and reported atom numbering for non-hydrogen atoms only (**b**). Thermal displacement ellipsoids are drawn at the 40% probability level while hydrogen atoms are represented as spheres of arbitrary radius of 0.20 Å. Adapted with permission from *Dalton Trans.* **2015**, *44*, 13040−13048. Copyright (2015) Royal Society of Chemistry.

An extra complex synthesized in the same group and derived from the enantiopure *trans*-1,2-cyclopentanediamine and 4-methoxysalicylaldehyde (1*R*,2*R*), **13**, behaves very differently from the related *trans*-1,2-diaminocyclohexane, **12** (Figure 13). This is attributed to a different coordination mode around the Zn(II) metal center as an alternative to the typical intermolecular Zn···O interactions, further demonstrating the effect of the binding site defined stereochemistry on its coordination geometry and aggregation properties [33].

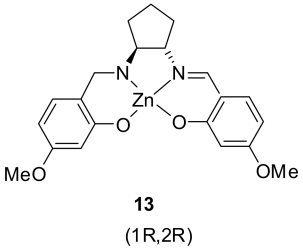


Figure 13. Structure of compound **13**. Adapted with permission from *Inorg. Chem.* **2017**, *56*, 14206–14213. Copyright (2017) American Chemical Society.

It is well recognized that supramolecular self-assembly of molecules into 1D nanostructures is an important task for developing future nanoscale technologies [34]. In this context a first example of nanofiber formation promoted by Zn···O interactions is that reported by MacLachlan and his group in 2007 [35]. A series of salophen complexes **14a–20b** (Figure 14), having peripheral linear and branched alkoxy groups, were prepared. It was found that derivatives **14a–18a** form luminescent gels in aromatic solvents such as benzene, toluene, and xylene.

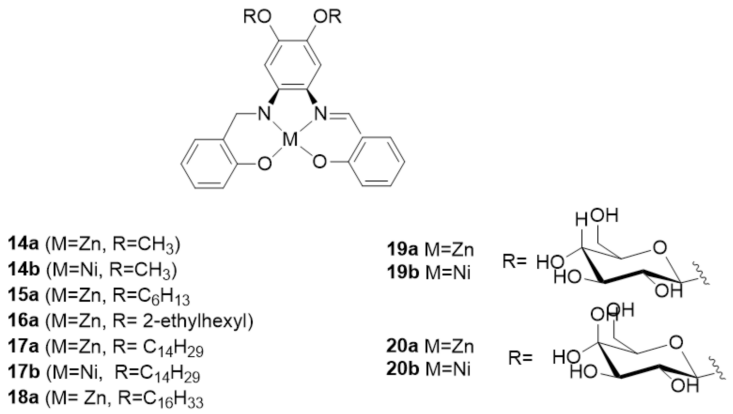


Figure 14. Structures of compounds **14a–20b**. Adapted with permission from *Angew. Chem. Int. Ed.* **2007**, *46*, 7980–7983. Copyright (2007) Wiley.

Transmission electron microscopy (TEM) showed that complexes **14a–18a**, when cast from methanol, all form 1D fibers that can further assemble into bundles. Authors claim that the 1D assembly involves Zn···O interactions rather than hydrogen-bonding or π–π interactions between the salophen complexes. Instead the work performed by our group on a Zn(II)–salophen derivative functionalized with L-valine residues, **21** (Figure 15) [28], able to gelate in acetonitrile by self-assembly into helical long fibers through hydrogen bond formation between the residues, points out that a major contribution to the thermodynamic stabilization of the gel comes from the existence of π–π stacking interactions, while Zn···O contacts seem to be less important. This because the addition of certain amines able to axially coordinate to the zinc metal center (e.g., quinuclidine) [36] does not prevent gel formation. Indeed, only pyridine inhibits gel formation and this because pyridine is the only one able to compete, through its insertion between layers, with the π–π stacking interactions.

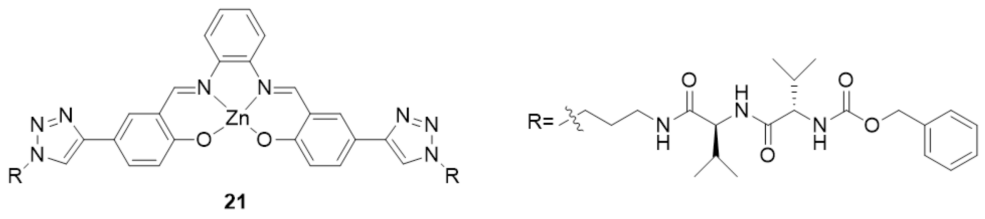


Figure 15. Structure of compound **21**. Adapted with permission from *RSC Adv.* **2016**, *6*, 57306–57309. Copyright (2016) Royal Society of Chemistry.

Kleij and coworkers reported the unique self-assembly behavior of bis-Zn(salophen) **22–25** (Figure 16). They show strong self-assembly behavior through linking coordination motifs that are fundamentally different from those usually found for the self-assembly of mononuclear Zn–salophens [26]. This happens both in solution as well as at the solid–liquid interface. Oligomeric $(Zn–O)_n$ coordination motifs are established within the assembly and this is extremely different from that of mononuclear Zn(salphen) analogues that form dimeric structures having a typical Zn_2O_2 central unit, as previously illustrated in Figure 10.

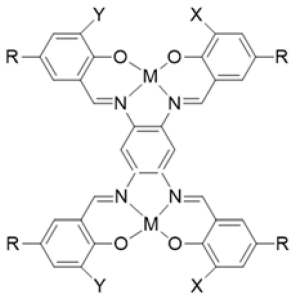
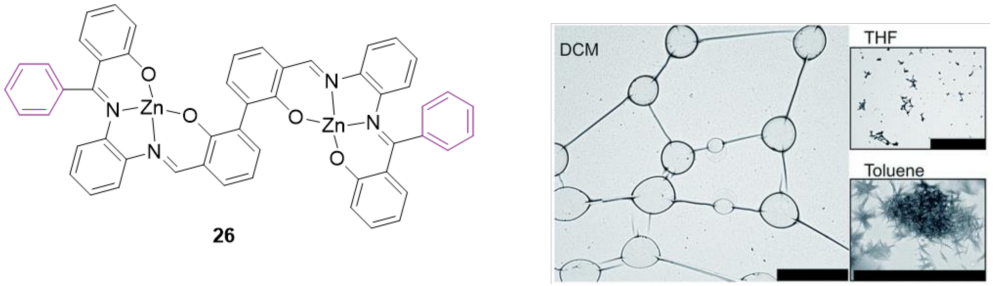


Figure 16. Structure of compounds **22**–**25**. Reproduced with permission from *J. Am. Chem. Soc.* **2012**, *134*, 7186–7192. Copyright (2012) American Chemical Society.

The same group showed also that compound **26** (Figure 17) can assemble into neuron-like networks of microrings interconnected with nano thin strings. Compound **26** forms a 1D coordination polymer, whose fibers are elastic enough to fold into toroidal globules upon solvent evaporation, while being able to connect separate chains into extended networks [37].



(**a**) (**b**)

Figure 17. Schematic representation of bis-Zn(salophen) complex **26** ((**a**) purple hexagons highlight the key phenyl substituents) and self-assembled structures, obtained by drop-casting of complex **26** from various solvents ((**b**) the scale bars indicate 5 mm). Adapted with permission from *Soft Matter* **2018**, *14*, 1181–1194. Copyright (2018) Royal Society of Chemistry.

The intermolecular interactions displayed by this type of Schiff base building blocks are the result of various contacts including intermolecular M–O coordination patterns, van der Waals and/or Coulombic anisotropic interactions with different possible orientations controlled by the dielectric properties of the solvents used (dichloromethane, DCM; tetrahydrofuran, THF; or toluene) (Figure 17). Thus, such kind of studies evidence that it is possible to modulate molecular self-assembly properties of Schiff base scaffolds to obtain more complex, controlled nanoarchitectures.

Metallo salen and salophen complexes are popular bioinorganic model compounds and functional enzyme mimics. Their biological activity and rich photophysical properties have been investigated focusing on their potential applications as therapeutics and biosensors [9]. It has been reported that several salen- and salophen-based transition metal complexes may interact with or modify DNA. Binding to DNA and DNA modifications performed by such complexes can be controlled by the charge on the salen unit and by the selection of the central metal ion [38] providing in this way new insight into the field of DNA nanotechnology.

Human telomeric DNA consists of hundreds of 5′-TTAGGG repeat sequence TTAGGG, that end in an overhanging single-stranded of around 200 nucleobases [39]. This can fold into guanine-rich

quadruplex (G-quadruplex) structures under physiological conditions. The activity of telomerase enzyme is much higher in human cancer cells and this is the reason why its inhibition has been identified as an important target for cancer chemotherapy. The inhibition can be obtained through the stabilization of the quadruplex structures performed by small molecules whose features are: (1) a π-delocalized system that is capable to stack on the face of a guanine quartet; (2) a partial positive charge that is able to stay in the center of the quartet, increasing stabilization through the substitution of the cationic charge of the potassium or sodium that normally occupies that site; (3) the presence of positively charged substituents capable to interact with the grooves and loops of the quadruplex and with the negatively charged backbone phosphates. Over ten years ago, the first example of a G quadruplex binder based on metal salophens was reported, **27** (Figure 18) [40].

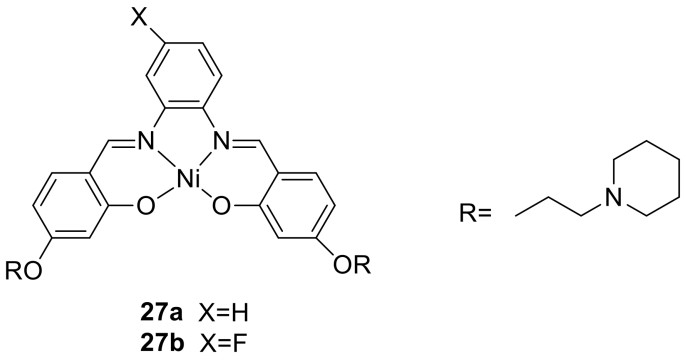


Figure 18. Structure of compounds **27a** and **27b**. Adapted with permission from *J. Am. Chem. Soc.* **2006**, *128*, 5992–5993. Copyright (2006) American Chemical Society.

The planar nickel(II) complexes **27a** and **27b** are excellent G-quadruplex DNA stabilizers. The reason is a combination of structural and electrostatic factors. The planar arrangement of the salophen rings, mastered by coordination to nickel, and their appropriate spacing make the complexes perfect to stack on top of guanine tetrads. Moreover, the protonated piperidine substituents interact with the grooves and loops of the quadruplex [41].

3. The Ability to Behave as Supramolecular Receptors

After illustrating some intriguing aspects of the chemistry of metal–salen and metal–salophen derivatives related to supramolecular assembly phenomena, we wish to highlight their potential to act as supramolecular receptors.

As already mentioned, the majority of metal–salophen complexes can be described as immobilized Lewis acids able to coordinate Lewis bases by accommodating them in the apical position or in the equatorial one, whenever present. Hence the selectivity of binding can benefit from the predictable directionality of coordinative interactions and from a well-defined structural preorganization of the receptor. For example, uranyl–salophen complexes can bind molecules with donor groups by means of the fifth equatorial site that remains still available after the coordination of the salophen ligand to the UO_2^{+2} ion. Therefore, high is their capability to act as receptors for anionic guests [42]. The introduction of additional groups, able to interact in a favorable manner with the guest, provides a second binding site that can help not only the affinity, but, in many cases, also the selectivity of the process enhancing the supramolecular attitude of such derivatives. Some examples are here reported in which simple modifications of the ligand skeleton introduce elements leading to selective recognition (Figure 19).

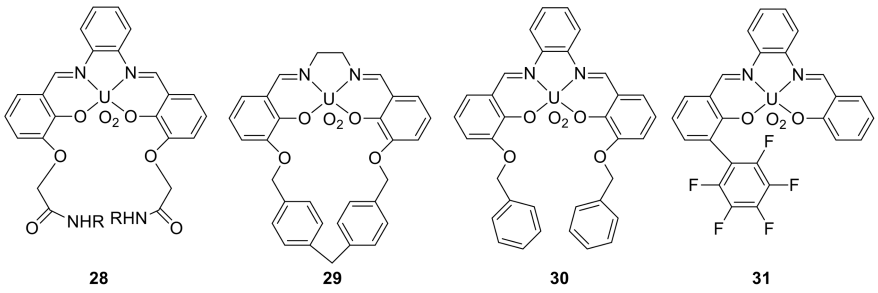


Figure 19. Structures of compounds **28**–**31**. Adapted with permission (compound **28**) from *J. Am. Chem. Soc.* **1994**, *116*, 4341–4351. Copyright (1994) American Chemical Society. (**b**) Adapted with permission (compound **29**) from *New J. Chem.* **2008**, *32*, 1113–1116. Copyright (2008) Royal Society of Chemistry. (**c**) Adapted with permission (compound **30**) from *J. Am. Chem. Soc.* **2005**, *127*, 3831–3837. Copyright (2005) American Chemical Society. (**d**) Adapted with permission (compound **31**) from *Chem. Eur. J.* **2016**, *22*, 18714–18717. Copyright (2016) Wiley.

In compound **28** the contribution to phosphate ($H_2PO_4^-$ as tetrabutylammonium salt in DMSO) complexation given by the appended arm through H-bond interaction, is clearly reflected in the marked downfield shifts $\Delta\delta$ = 0.7–0.9 ppm of the NH signals. Under the same conditions, complexation with chloride, sulphate, thiocyanate and perchlorate is not observed [43].

A remarkable specificity for fluoride anion in DMSO solution is achieved by receptor **29** in which the space surrounding the metal center is delimited by a short bridge featuring a diphenylmethane unit. From the X-ray crystal structure of its methanol solvate results that the cavity where the UO_2^{2+}-bound methanol is hosted has a 5.3 × 4.5 Å rectangular shape, which can obviously accommodate a fluoride anion, but it is not spatially suitable for linear coordination in the equatorial plane of even an anion as small as cyanide. Indeed, such selectivity, when compared with those relative to a large variety of anion competitors, is no less than 10^5 higher [44].

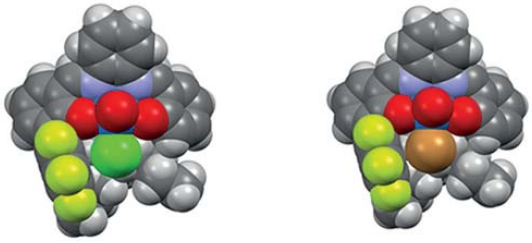
Compound **30**, endowed with aromatic pendant arms, have been used as a ditopic receptor for alkali metal [45] and quaternary ammonium halide [46] contact ion pairs in chloroform. As usually, recognition of hard anions, chloride, bromide etc., is ensured by strong binding to the hard Lewis acidic uranyl center, whereas cation–π interactions can be established between the aromatic side-arms and the cation partner of the ion pair. The contribution to the binding of cation–π interactions is clearly pointed out by the increase of binding constants when the appended phenyl is replaced by a more extended aromatic structure such as a naphthyl unit. This has been confirmed also in the solid state by X-ray analysis [45,46].

Compound **31**, characterized by the presence of a perfluorinated appended aromatic arm located much closer to the metal center highlights the stabilizing contribution, both in solution and in the solid state, of the weak and often elusive anion–π interaction to halide recognition. Indeed, the presence of the perfluorophenyl unit, acting as π-acceptors, further stabilizes the formation of the host-guest complex between the receptor and halides in chloroform solution. This has been confirmed unequivocally also by X-ray analysis, (Figure 20) [47].

Small structural modifications of the ligand skeleton in zinc–salophen complexes also help unravelling their supramolecular vocation. As already mentioned the molecular structure of zinc–salophens reported in the literature features the zinc atom in a five-coordinate square pyramidal geometry, in which the ligand occupies the basal plane and a solvent molecule occupies the apical position. The solvent can be easily replaced by a donor group since Zn has an established Lewis acidic character, which allows strong binding of suitable donor ligands at the axial coordination site [48].

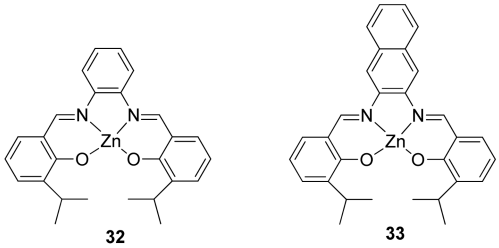
We synthesized two different Zn–salophen derivatives **32**–**33** (Figure 21) and used them for the molecular recognition of inorganic phosphates PO_4^{3-}, $P_2O_7^{4-}$, and $P_3O_{10}^{5-}$, and nucleotides adenosine 5′-monophosphate, AMP^{2-}, adenosine 5′-diphosphate, ADP^{3-}, and adenosine 5′-triphosphate, ATP^{4-}, in ethanol [49]. Both inorganic phosphate and nucleotide anions are bound

by these complexes, but only the association to nucleotides produces relevant changes in the spectral properties showing a ADP^{3-} > ATP^{4-} >AMP^{2-} selectivity. The observed trend can be related to the distance occurring between the phosphate group hosted in the zinc apical coordination site and the adenosine moiety providing the best simultaneous interaction of the metal with the phosphate, and the π–π stacking of adenine with the aromatic region of the receptor [49].



(**a**) (**b**)

Figure 20. CPK presentation of X-ray crystal structures of [**31**@Cl] (**a**) and [**31**@Br] (**b**). Adapted with permission (compound **31**) from *Chem. Eur. J.* **2016**, *22*, 18714–18717. Copyright (2016) Wiley.



32 **33**

Figure 21. Structure of compounds **32** and **33**. Adapted with permission from *Inorg. Chem.* **2009**, *48*, 6229–6235. Copyright (2009) American Chemical Society.

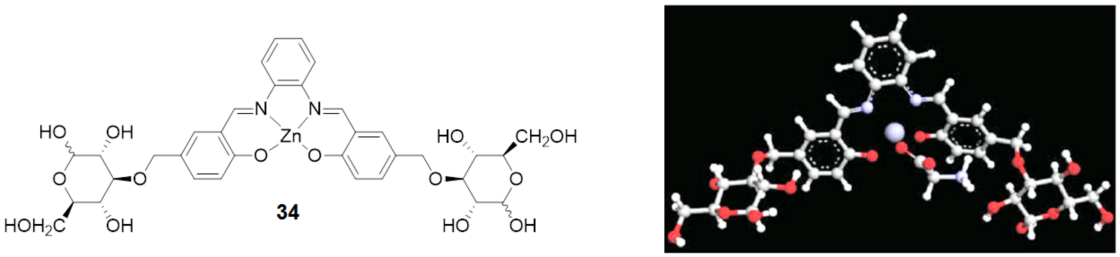
Zinc–salophen derivative **34** with appended D-glucose moieties in the 5,5′ positions (Figure 22), shows strong affinity toward carboxylate anions in water, association constants higher than 10^6 M^{-1} [50]. Therefore, its ability to bind aminoacids was tested too. The association constants measured were in all cases much lower than those measured for simple carboxylate anions, suggesting that the presence of the positively charged ammonium group decreases the strength of binding.

The complexation of aminoacids appears to be also strongly dependent on the aminoacid structure: the bulkier the substrate, the lower affinity is measured, see Table 2.

Table 2. Association constants (K, M^{-1}) for complexes between compound **34** and selected aminoacids and carboxylate anions at 25 °C. Adapted with permission from *Chirality* **2009**, *21*, 104–109. Copyright (2008) Wiley-Liss, Inc.

	L	**D**
Formiate	$>10^6$	
Acetate	$>10^6$	
Glycine	3800 ± 500	
Alanine	2010 ± 60	2900 ± 500
Valine	1500 ± 200	1070 ± 40
Phenylalanine	2500 ± 600	260 ± 10
Leucine	58 ± 7	26 ± 7
Proline	<10	62 ± 6
Tryptophan	<5	<5

The ability to establish two hydrogen bonds between the ammonium group of the aminoacid and two oxygen atoms of one of the two D-glucose moieties, strongly reduces the conformational flexibility of the host–guest complex and forces the bound substrate in a position in which the size and the shape of the side chain have a remarkable effect on the strength of the complex (Figure 22) and Table 2. This is fully supported by the finding that in all cases the L and D enantiomers of a given aminoacid are bound with different association constants. The high selectivity, K_L/K_D ratio of 9.6, found in the case of phenylalanine, has been explained by postulating a third point of contact between the phenyl ring and the aromatic surface of the ligand [50].



(**a**) (**b**)

Figure 22. Structure of compound **34** (**a**); ball and stick representation of the global minimum geometry of the **34**@glycine complex (**b**). Adapted with permission from *Chirality* **2009**, *21*, 104–109. Copyright (2008) Wiley-Liss, Inc.

4. Towards Conclusions

In this work we covered some aspects of metal–sal(oph)en complex chemistry, i.e., those related to their supramolecular attitude. We examined under the lens of the non-covalent interactions their potential to behave as building blocks for auto-assembled architectures, supramolecular receptors and catalysts, although this last point has been only briefly mentioned.

In general catalysis can be considered a supramolecular phenomenon since all the key steps of a catalytic cycle are usually triggered by supramolecular interactions. Such interactions play their main role in the recognition of substrates, in the orientation and assembly of the reactive species to generate new species. Thus, transition states of catalytic cycles can definitely be considered supramolecular adducts. In this perspective also organocatalysis can be treated as a supramolecular process.

Hence, we wish to conclude here with the example of a uranyl–salophen catalyst that displays the appreciable features of a supramolecular catalyst, resembling those found in Nature.

Compound **35** (Figure 23) effectively catalyses with high turnover the reaction of benzoquinone with 1,3-cyclohexadiene, (Scheme 2), while its homologous **36**, without the appended aromatic arm, is completely inactive [51]. Moreover, no binding affinity is displayed by **35** toward both reactants and reaction products. A simple and general analysis of catalytic power and transition state stabilization tells that the binding of the transition state produces catalysis, whereas inhibition comes out from the binding of reactants and/or products [52]. In the presence of **35** we do observe catalysis and this indicates that the catalyst should have a high affinity for the transition state accompanied by negligible affinities for the reactant(s) and product(s). Such behavior is indeed that of an ideal supramolecular catalyst that interacts only with the transition state of the reaction, and does not display any product inhibition.

To conclude we showed that even extremely well-explored molecules such as metal–salen and –salophen complexes can provide very interesting opportunities for supramolecular studies through the exploitation of several weak, non-covalent interactions. The supramolecular attitude of these scaffolds makes them perfect candidates for a series of important applications especially in the field of materials [53,54] and biological studies [55–57].

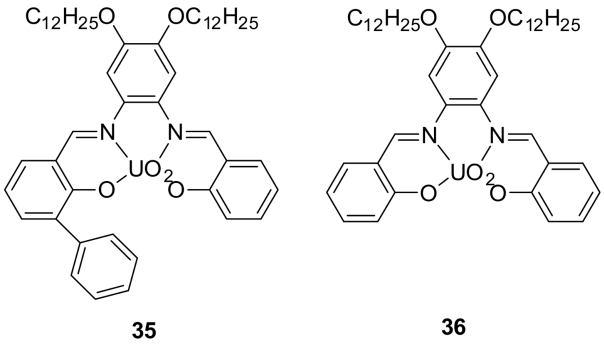
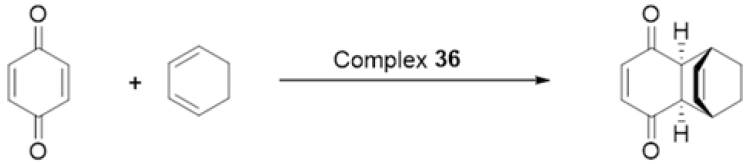


Figure 23. Structure of compounds **35** and **36**. Adapted with permission from *Chem. Commun.* **2005**, 3867–3869. Copyright (2005) Royal Society of Chemistry.



Scheme 2. Reaction of benzoquinone with 1,3-cyclohexadiene catalyzed by uranyl–salophen derivative **36**. Adapted with permission from *Chem. Commun.* **2005**, 3867–3869. Copyright (2005) Royal Society of Chemistry.

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