A Newly Designed Water Soluble Uranyl-Salophen Complex for Anion Recognition

Gianpiero Forte,* Maria S. Maglione, Ludovico G. Tulli, Alessia Fantoni, and Antonella Dalla Cort*[a]

On the occasion of the 85th birthday of Vincenzo Balzani

A novel water-soluble uranyl-salophen (salophen = *N,N'*-disalicylidene-*o*-phenylenediaminate) complex was obtained. Solubility was achieved in aqueous methyl-β-cyclodextrin solutions, taking advantage of the host-guest interactions established with the adamantyl moieties present on the ligand skeleton. Such an approach facilitates the synthesis of the receptor and the purification processes and, in perspective, can be definitely applicable to other molecular scaffolds. UV/Vis titration experiments demonstrate that the capacity of the uranyl-salophen core to behave as a receptor for anions is retained in water and appears comparable with that previously reported for other water-soluble uranyl-salophen systems. Hence the presence of cyclodextrins does not interfere with molecular recognition processes.

Molecular recognition of anions in water is a very active field of research, constantly fueled by attractive practical applications that range from biology to medicine and to environmental analytical chemistry.[1,2] Despite being largely investigated in organic solvents, anion binding remains a challenging task in aqueous environments because of two major issues: anion solvation by water molecules and solubility of the organic receptors in water.[3]

Many receptors that operate in organic solvents bind anions through hydrogen bonding and/or electrostatic attraction.[4,5] Unfortunately, in aqueous environments such interactions generally fail to survive, overpowered by the massive presence of water molecules, unless receptors display an array of anchor points and high degree of pre-organization.[6] Until now, the strongest interaction that proved to survive in such a competitive medium is anion binding to metal cations. Such direct coordination is characterized by high binding affinities, but also by modest selectivities if no structural geometric constraints are imposed to the ligand scaffold coordinating the metal. Hence, the success of such research relies on the design of water-soluble organic ligands forming metal complexes with high thermodynamic and kinetic stability, the introduction of supplementary supramolecular interactions with the substrate to increase selectivity, and the availability of at least one coordination site of the metal for the interaction with the anion. Facing these issues can lead to selective and strong binding applicable for anion sensing in competitive media.[7,8] Indeed, metal complexes that use Lewis acid-base interactions to bind anions in water are a good answer to the problem since water is a strong hydrogen bonding agent, but a relatively poor Lewis base, lowly interfering with the recognition process as we also demonstrated in our previous papers.[9,10] Among the derivatives that use such assets to strongly bind anions in organic solvents, there are metal salophen complexes, in particular those comprising the hexavalent uranyl ion UO_2^{2+}.[11] They display a pentagonal-bipyramidal geometry, where the equatorial plane of the uranyl ion is coordinated by the four salophen donating groups, that is, the two phenolic oxygens and the two nitrogens of the azomethine groups, leaving one vacant site that can accommodate Lewis bases. So coming to the main point: how to tackle the problem of receptor solubility in water?

Over the years, researchers adopted a wealth of strategies to answer this question, beginning with the introduction of polar residues.[3,4,12] Indeed, charged groups, such as carboxylates and ammonium units, greatly increase the solubility. On the other hand, the presence of additional ionic species involves several proton equilibria, generating a complicate picture difficult to be quantitatively described. Furthermore, the non-directional electrostatic interactions lead to modest selectivity.

Although more challenging from a synthetic perspective, neutral polar group substituents do not interfere with binding measurements and represent a viable option for designing water soluble molecular structures.[13] Nevertheless, the development of hydrophilic receptors, whether charged or neutral, suffers from drawbacks that have slowed down the research in this area. Highly polar compounds, indeed, require demanding synthetic procedures and cumbersome purification protocols. Moreover, satisfactory water solubility is hard to achieve, and many receptors reported in the literature to date are soluble

[a] *Dr. G. Forte, Dr. M. S. Maglione, Dr. L. G. Tulli, A. Fantoni, Prof. A. Dalla Cort*
Department of Chemistry
Università La Sapienza
Piazzale Aldo Moro 5
00185 Roma (Italy)
E-mail: gianpiero.forte@gmail.com
antonella.dallacort@uniroma1.it

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only in aqueous solutions with variable content of organic solvents, while those operating in pure water are still quite rare.

With the aim to optimize the synthetic efforts necessary to build up water-soluble receptors, we recently devoted special attention to the use of host-guest chemistry. In this communication, we describe a novel lipophilic uranyl-salophen derivative, bearing adamantyl moieties, whose synthesis benefits from reactions carried out in classic organic solvents. Such a receptor becomes soluble in water in the presence of β-cyclodextrin (β-CD) thanks to the formation of inclusion complexes. We also demonstrate that it displays binding properties comparable with those of analogous compounds decorated with water-soluble substituents, hence definitely proving that the presence of CDs does not severely influence the association equilibria and binding affinities.

Beside the long-standing expertise of our group in the chemistry of metal-salophen derivatives, we chose these systems because they are extremely versatile, playing important roles both in chemical recognition and supramolecular catalysis. Additionally, their modular synthesis allows the easy introduction of functional groups on the building block precursors of the ligand, that is, salicylaldehyde and *o*-phenylendiamine rings. Finally, when the condensation reaction leading to the formation of the ligand is carried out in the presence of metal salts, the corresponding metal complex can be effortlessly isolated through precipitation.

In this context, we formerly reported the synthesis of the first water-soluble neutral metal-salophen receptors **1a**–**b**, Figure 1, featuring glucose moieties, and investigated their binding properties.[9,10] The zinc derivative **1a** strongly coordinates carboxylates in water and exhibits a remarkable chiral discrimination between the two enantiomers of phenylalanine, with the L-enantiomer binding stronger than the D-enantiomer by an order of magnitude.[10] To explain the observed behavior, a second interaction with one of the glucose moieties was supposed to exist, supported by theoretical calculations, confirming the supramolecular attitude of these derivatives.

The uranyl derivative **1b**, instead, shows a measurable association with fluoride and hydrogen phosphate in water and, most interestingly, exhibits a very high affinity for inorganic pyrophosphate and organic polyphosphates ADP^{3-} and ATP^{4-}.[9]

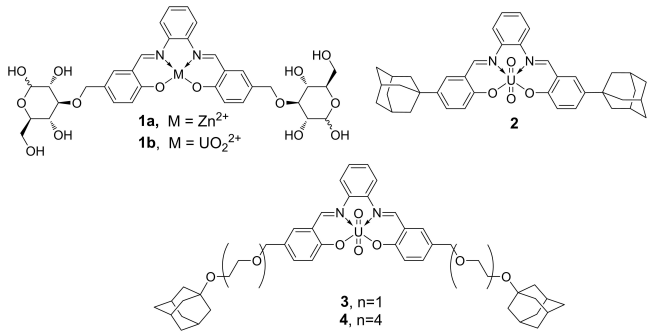


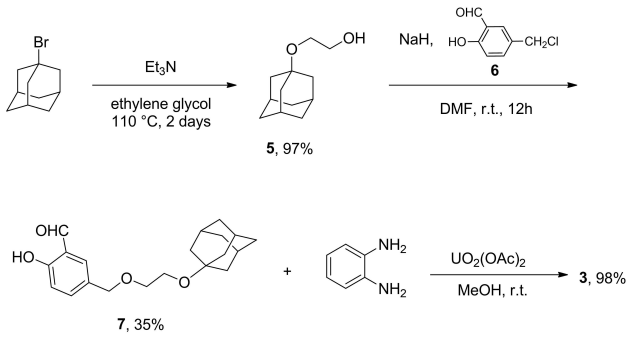
Figure 1. Chemical structures of metal-salophen derivatives.

We also reported that the solubility of metal-salophen derivatives can be further increased by introducing oligosaccharide units without affecting the binding properties.[14] The drawback of such an approach is obviously the synthesis that becomes quite demanding, especially for the tri- and tetrasaccharide-functionalized ligands.

In order to make the synthesis of water soluble metal salophen-type receptors simpler and less demanding, particularly in terms of product purification, we looked for an alternative and came up with the idea that the supramolecular inclusion of adamantyl substituents into the cavity of the β-CD could be suitably employed to bring the complexes into water. CDs are naturally occurring glucose cyclic oligomers, consisting of six, seven, or eight glucose units (named α-, β-, or γ-CD, respectively) that display a toroidal form with a hydrophobic inner cavity and a hydrophilic outer surface where hydroxyl groups are located.[15] Van der Waals and hydrophobic forces are responsible for keeping lipophilic guests inside the host cavity which is less polar than the outer surface where the hydrophilic groups are located. It is well known that CDs increase water solubility of many organic molecules[16,17] and for this reason they are widely used as delivery systems for food, drugs, and cosmetics to increase their bioavailability, taking advantage of CDs' low toxicity and immunogenicity. They form host-guest inclusion complexes with several small molecules based on their polarity and three-dimensional structure.[17]

Among the many hydrophobic guest molecules for β-CD's internal cavity, adamantane perhaps represents the most well-known example. It tightly fits into the cavity, resulting in a host-guest inclusion complex with an association constant in water greater than $10^4\ M^{-1}$.[18] To benefit from this feature, we designed salophen ligands bearing adamantyl pendant arms and produced the corresponding uranyl complexes. The first step was the synthesis of receptor **2**, Scheme S1 (Supporting Information), with the adamantane residues located in the positions *para* to the phenolic oxygens of the salicylaldehyde units. We tested the water solubility of this derivative in the presence of various concentrations of methyl-β-CD, used in the experiments because of the higher solubility compared to native β-CD. Unfortunately, **2** displays very poor solubility, even after stirring the suspension in the presence of 20 equivalents of methyl-β-CD for more than 7 days. Mild warming failed to improve solubilization, too. A possible explanation for this might be related to the structure of the uranyl-salophen core. It is known that, due to the large ionic radius of uranium, the complex is forced to bend, with a distortion of about 35° from the equatorial plane.[19] This should bring the adamantyl residues closer to each other, hampering interactions with β-CDs for steric hindrance.

To overcome this problem, we prepared aldehyde **7**, featuring a flexible spacer between the aromatic ring and the adamantyl moiety (Scheme 1). From 5-(chloromethyl)-2-hydroxybenzaldehyde **6** reacting with 1-bromoadamantane, we prepared 5-((2-((1*S*,3*S*)-adamantan-1-yloxy)ethoxy)methyl)-2-hydroxybenzaldehyde, **7**. The corresponding uranyl-salophen derivative **3**, obtained through the condensation of *o*-phenylendiamine and two molecules of **7** in the presence of uranyl



Scheme 1. Synthesis of uranyl-salophen complex **3**.

acetate, yields clear solutions when dissolved in water in the presence of methyl-β-CD in the ratio 1:16 or higher (Figure 2). To study the influence of spacer length on the solubility, we also used an extended oxyethylene chain, **4**, which actually resulted in dramatically lower solubility when compared with that of **3** under the same conditions. The reason for this can be attributed to the formation of supramolecular aggregates caused by the lipophilic nature of the complex and also by the tendency of uranyl-salophen derivatives to dimerize forming bridges between the UO_2(salophen) units, thus preventing the approach of CDs to the adamantly moieties.[20]

So we focused our attention on complex **3** which shows good water solubility in the range of 1 mM in the presence of excess of methyl-β-CD (Figure 2).

The UV/Vis absorption profile of **3**, recorded in the range 280–650 nm with 16 equivalents of methyl-β-CD, closely resembles that of complex **1b** in pure water and features a monotonic increase in the absorbance on lowering the wavelength with a shoulder around 350 nm.

To test the binding properties of **3**, we carried out UV/Vis titration experiments in CD solutions with anions whose affinity for receptor **1b** was known. Namely, we added increasing amounts of the sodium salt of the anions reported in Table 1 to an aqueous solution of methyl-β-CD (16 equivalents) containing complex **3**, in the range of 4.45×10^{-5}–9.20×10^{-5} M. The expected association constant value determines the concentration range of the guest. We collected as many points as possible in the non-linear part of the binding hyperbola (Equation (1)).

$$A = A_0 + \Delta A_\infty \frac{[R_0] + 1/K + [G] - \left[([R_0] + 1/K + [G])^2 - 4[G][R_0]\right]^{1/2}}{2[R_0]} \quad (1)$$

A experimental absorbance
A_0 initial absorbance of the receptor
$[R_0]$ analytical concentration of the receptor
[G] total guest concentration in each point, including that fraction bound to the receptor

The titration data were analyzed using a 1:1 binding model and applying a nonlinear least-squares regression method (Figure 3 and Supporting Information). The data reported in Table 1 show that the anion association constants for **3** are of comparable magnitude with those reported previously for complex **1b**. There is just a general slight increase, but an explanation, if any, is difficult to suggest. Our opinion is that the appended cyclodextrins play a minor role in influencing the anion binding affinity, ruling out competitive anion binding performed by CD units.[16]

Weak binding with an adenosine unit has been reported by Formoso ($K = 41\ M^{-1}$),[21] but of course such a contribution adds very little to the main interaction between the metal and the

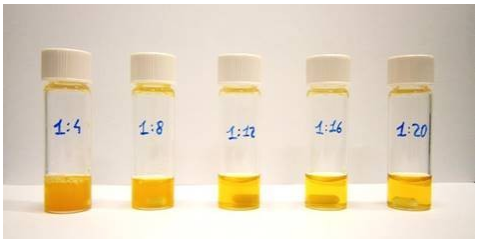


Figure 2. Compound **3** (1×10^{-3} M) in water after the addition of methyl-β-CD in the ratios 1:4, 1:8, 1:12, 1:16, and 1:20.

Table 1. Binding constants, K_a, of receptor **3** for selected anions in H_2O-containing methyl-β-CD at 25 °C.

Anion	K_a [M^{-1}][a]	
	3	**1b**[b]
CH_3COO^-	40 ± 2	17 ± 4
F^-	180 ± 8	115 ± 6
HPO_3^{2-}	720 ± 30	480 ± 34
$P_2O_7^{4-}$	$>10^4$	$>10^4$
AMP^{2-}	440 ± 34	83 ± 8
ADP^{3-}	$>10^4$	$>10^4$
ATP^{3-}	$>10^4$	$>10^4$

[a] Errors are calculated as ±2σ. [b] Values for receptor **1b** are reported for comparison.[6]

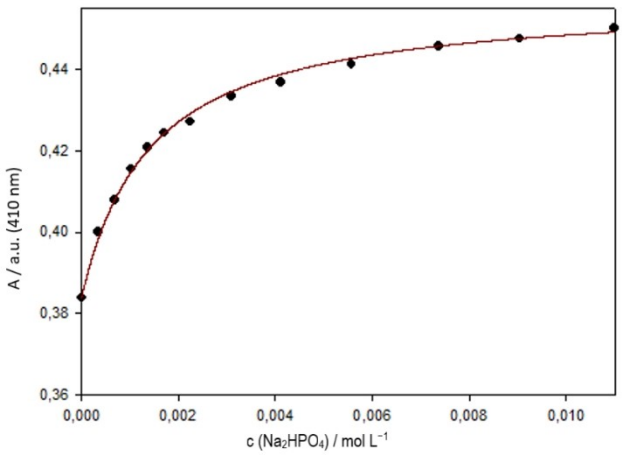


Figure 3. Titration plot of spectral changes at 410 nm of a 5.06×10^{-5} M solution of **3** upon addition of Na_2HPO_4. The line represents the parametric adjustment of a 1:1 binding isotherm to the experimental data points.

phosphate group reflected by the high binding constants reported.

In conclusion, we have prepared a first example of a lipophilic uranyl-salophen complex decorated with adamantyl substituents able to dissolve in water through the formation of inclusion complexes with methyl-β-CD, allowing the preparation of millimolar solutions. The capacity of the uranyl complex to behave as a receptor for anions is retained and plausibly is not affected by the presence of the large CD excess. We think that the reported strategy can be applied to other lipophilic scaffolds, through easy functionalization, so providing a contribution to the development of systems devoted to anion recognition in water.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: anion recognition · cyclodextrins · inclusion complexes · uranyl-salophen complexes · water-soluble receptors

[1] N. Busschaert, C. Caltagirone, W. Van Rossom, P. A. Gale, *Chem. Rev.* **2015**, *115*, 8038–8155.
[2] L. Chen, S. N. Berry, X. Wu, E. N. W. Howe, P. A. Gale, *Chem* **2020**, *6*, 61–141.
[3] S. Kubik (Ed.), *Supramolecular Chemistry in Water*, Wiley-VCH: Weinheim, **2019**.
[4] M. J. Langton, C. J. Serpell, P. D. Beer, *Angew. Chem. Int. Ed.* **2016**, *55*, 1974–1987; *Angew. Chem.* **2016**, *128*, 2012–2026.
[5] M. Morshedi, M. Thomas, A. Tarzia, C. J. Doonanband, N. G. White, *Chem. Sci.* **2017**, *8*, 3019–3025.
[6] J. Dong, A. P. Davis, *Angew. Chem. Int. Ed.* **2020**, *59*, 2–16; *Angew. Chem.* **2020**, *132*, 2–2.
[7] A. B. Aletti, D. M. Gillen, T. Gunnlaugsson, *Coord. Chem. Rev.* **2018**, *354*, 98–120.
[8] D. A. McNaughton, M. Fares, G. Picci, P. A. Gale, C. Caltagirone, *Coord. Chem. Rev.* **2021**, 427, 213573 examples there reported.
[9] A. Dalla Cort, G. Forte, L. Schiaffino, *J. Org. Chem.* **2011**, *76*, 7569–7572.
[10] A. Dalla Cort, P. De Bernardin, L. Schiaffino, *Chirality* **2009**, *21*, 104–109.
[11] A. Dalla Cort, P. De Bernardin, G. Forte, F. Yafteh Mihan, *Chem. Soc. Rev.* **2010**, *39*, 3863–3874.
[12] M. A. Beatty, F. Hof, *Chem. Soc. Rev.* **2021**, *50*, 4812–4832.
[13] S. Kubik, *Chem. Soc. Rev.* **2010**, *39*, 3648–3663.
[14] E. Bedini, G. Forte, C. De Castro, M. Parrilli, A. Dalla Cort, *J. Org. Chem.* **2013**, *78*, 7962–7969.
[15] S. V. Kurkov, T. Loftsson, *Int. J. of Pharmaceutics* **2013**, *453*, 167–180.
[16] G. Crini, *Chem. Rev.* **2014**, *114*, 10940–10975.
[17] M. Řezanka, M. J. Langton, P. D. Beer, *Chem.Commun.* **2015**, *51*, 4499–4502.
[18] M. R. Eftink, M. L. Andy, K. Bystrom, H. D. Perlmutter, D. S. Kristol, *J. Am. Chem. Soc.* **1989**, *111*, 6765–6772.
[19] A. R. Van Doorn, R. Schaafstra, M. Bos, S. Harkema, J. Van Eerden, W. Verboom, D. N. Reinhoudt, *J. Org.Chem.* **1991**, *56*, 6083–6094.
[20] K. Takao, Y. Ikeda, *Inorg. Chem.* **2007**, *46*, 1550–1562.
[21] C. Formoso, *Biochem. Biophys. Res. Commun.* **1973**, *50*, 999–1005.

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