Oxo-Anions Recognition by Mono- and Bis-Urea Pendant Arm Macrocyclic Complexes

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ABSTRACT: The novel macrocyclic copper(II) complexes, $[2]^{2+}$ and $[3]^{2+}$, carrying one or two nitrophenylurea fragments appended onto an azacyclam or diazacyclam framework, exploit the hydrogen-bond forming abilities of the urea subunits, alongside with the metal-ligand interaction, in the recognition of anionic species. Equilibrium studies in acetonitrile performed on $[2]^{2+}$ and $[3]^{2+}$ show that nitrophenylurea pendant arms strongly interact with anionic species such as carboxylates and phosphates, which display both coordinating tendencies towards copper(II) and good affinity towards urea subunits. Stability constants of the adducts are considerably higher than those determined for the interaction of the same anions with a "plain urea" reference compound, confirming the synergistic action of metallo-macrocyclic and urea subunits. Complex $[2]^{2+}$ forms 1:1 adducts with acetate, benzoate, hydrogendiphosphate, and dihydrogenphosphate, while complex $[3]^{2+}$ interacts with the same anions according to both 1:1 and 1:2 stoichiometries, with the exception of hydrogendiphosphate, which forms only the 1:1

adduct with a distinctly high association constant (logK > 7). Spectrophotometric investigations suggest that oxo-anionic species interact with the complexes according to a "bridged" mode, inducing the macrocyclic systems to adopt a scorpionate-like conformation, confirmed by crystallographic studies on the [**3**]$^{2+}$/succinate adduct.

INTRODUCTION

Molecular recognition of anionic species has attracted increasing interest during the last decades,[1-3] due to the important role played by anions in biological and environmental processes.[4, 5] A very large number of artificial systems for recognition and sensing of anions have been designed and synthesized by properly exploiting supramolecular concepts.[6-12]

Recognition of anionic species can be based on electrostatic interactions, as shown by the pioneering work of Lehn and Schimdtchen,[13, 14] who developed positively charged concave receptors able to incorporate inorganic anions. In this kind of receptors, selectivity is mainly based on the matching of the geometrical features (shape and size) of both anion and cavity.

Hydrogen bonding, despite its fundamentally electrostatic nature, has a directional character and, in principle, allows a better discrimination between anions with different structural and electronic features than genuine electrostatic interactions.[15]

Therefore, a variety of molecular receptors have been developed, which perform the recognition of their anionic targets by establishing a complementary set of hydrogen bonds.[8, 16-19]

Some classes of compounds, for instance cyclic and acyclic polyammonium receptors interact with anions by combining pure electrostatic and hydrogen bonding interactions.[20-23]

Among hydrogen bonding donor groups, urea and thiourea have been frequently employed as anion binding fragments. In fact, they are able to form two H-bonds in a parallel fashion,

displaying an enhanced complementarity towards Y-shaped oxo-anions (e.g. carboxylates). Seminal papers by Wilcox and Hamilton[24, 25] showed the excellent anion complexation properties displayed by urea-containing molecular receptors. Since then a large number of receptors and sensors containing one or more urea/thiourea units in their structure have been reported.[26-33]

Metal-ligand interactions can also be conveniently employed to perform anion binding and recognition as anions may exhibit definite coordinating tendencies towards metal ions.[34-38] Coordinative interaction are usually stronger than electrostatic interactions (including the hydrogen bond); moreover they display a more definite directional character and may impose further geometrical constraints, which contribute to increase selectivity in the recognition process. A metal-ligand subunit included in the structure of an anion receptor should be coordinatively unsaturated, thus leaving one (or more) binding site(s) available for the anionic substrate and should establish with it kinetically labile interactions to provide a fast and reversible interaction (as requested for the recognition process).[34] On the other hand metal centers should be firmly retained into the receptor structure in order to prevent release of the metal ion and loss of the anion-binding ability.

Macrocyclic complexes fulfil these requirements as: (i) they are usually characterised by high thermodynamic stability and are kinetically inert[39-41] (ii) they may interact at the axial position(s) with additional ligand(s) and this interaction is kinetically labile.

A relatively small number of synthetic receptors have been reported, which exploit coordinative and hydrogen bonding interactions at the same time.[42, 43]

In particular, a few years ago we reported the synthesis and solution behaviour of a couple of receptors for anion characterised by a macrocyclic complex framework.[44] Copper complexes

[**1a-b**]$^{2+}$ incorporating a urea subunit are able to recognise oxo-anions exploiting the cooperative effect due to the proximity of a coordinatively unsaturated metal center and a hydrogen-bond donor group. It should be noted that compounds [**1a-b**]$^{2+}$ were obtained by a template reaction in which ureas were used as "locking fragments",[41, 45] therefore a nitrogen of the urea group is incorporated into the macrocyclic azacyclam framework. This prevents to fully exploit the tendencies of urea moieties to form several hydrogen bonds at the same time (in particular towards Y-shaped anions).
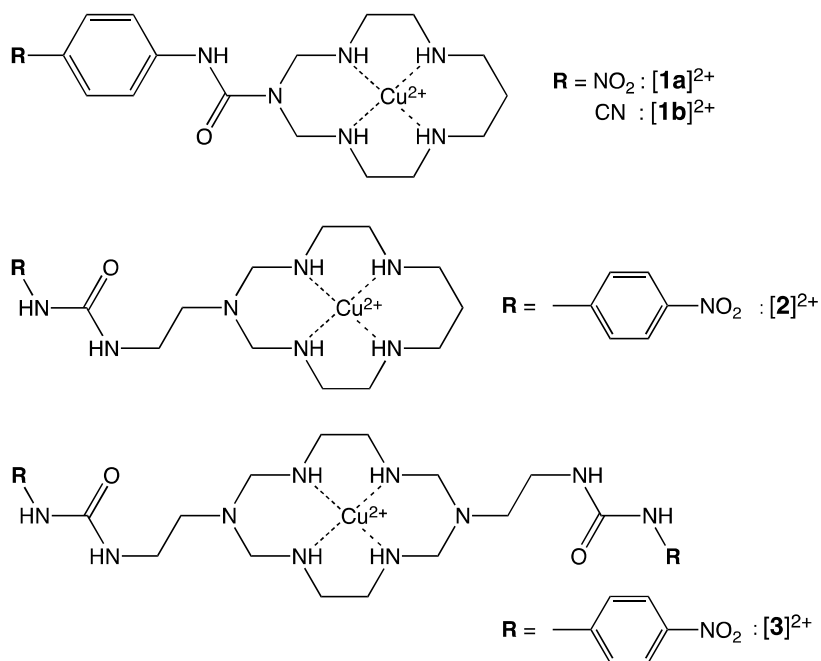
We report here the synthesis of two novel macrocyclic compounds, [**2**]$^{2+}$ and [**3**]$^{2+}$, in which one or two genuine urea fragments are appended onto an azacyclam or diazacyclam structure, respectively. In principle, these compounds could fully exploit the hydrogen-bond forming abilities of urea subunits, alongside with the metal-ligand interaction, in the recognition process. Equilibrium studies in acetonitrile performed on [**2**]$^{2+}$, [**3**]$^{2+}$ and "plain urea" reference compound **6** have shown that nitrophenylurea pendant arm(s) strongly interact with carboxylate

and phosphate anions and that the proximate copper(II)-macrocycle subunit considerably increases their binding ability toward the oxo-anions.

EXPERIMENTAL SECTION

General procedures and materials. All reagents for syntheses were purchased from Sigma/Aldrich and used without further purification.

N-*tert*-butoxycarbonyl-diaminoethane, en-BOC, was prepared according to literature.[46] Copper complex of 1,8-bis(2-aminoethyl)-1,3,6,8,10,13-esaazaciclotetradecane was prepared according to literature method and isolated as bis-ammonium tetra-perchlorate salt, [**5**](ClO$_4$)$_4$.[47]

Mass spectra were acquired using a Thermo-Finnigan ion trap LCQ Advantage Max instrument equipped with an ESI source. Infrared spectra were acquired by a Spectrum X100 Perkin FTIR instrument equipped with an attenuated total reflectance (U-ATR) apparatus. UV/Vis spectra were recorded using a Varian Cary 50 or Cary 100 spectrophotometer with a quartz cuvette (path length: 1 or 0.1 cm).

All titrations were performed at 25°C on solutions of [**2**](ClO$_4$)$_2$ and [**3**](ClO$_4$)$_2$ in acetonitrile. Aliquots of freshly prepared standard solutions of [Bu$_4$N]X (X = CH$_3$COO$^-$, C$_6$H$_5$COO$^-$, NO$_3^-$, H$_2$PO$_4^-$ and HSO$_4^-$) and [Bu$_4$N]$_3$HP$_2$O$_7$ in MeCN were added and a UV-vis spectrum of the resulting solution was taken after every addition. Spectra intensities were corrected for the dilution factor. Solutions of succinate and glutarate in MeCN were prepared by addition of stoichiometric amounts of [Et$_4$N]OH to solutions of the corresponding dicarboxylic acids. Titration data were processed with the Hyperquad software package[48] to determine the equilibrium constants. Care was taken that in each titration, the *p* parameter (*p* = [concentration

of complex]/[maximum possible concentration of complex]) was lower than 0.8, a condition required for the safe determination of a reliable equilibrium constant.[49]

Safety note. Perchlorate salts of metal complexes are potentially explosive and should be handled with care. In particular, they should never be heated as solids.[50]

Synthesis of [4](ClO$_4$)$_3$. N,N'-bis(2-aminoethyl)propane-1,3-diamine (2,3,2-tet, 0.4 g, 2.5 mmol), en-BOC (0.4 g, 2.5 mmol), 36.5% aqueous formaldehyde (2.0 ml, 26.5 mmol) and triethylamine (0.75 mL, 5.4 mmol) were added to a solution of Cu(CH$_3$COO)$_2$·H$_2$O in methanol (50 mL). The resulting mixture was magnetically stirred and heated at reflux for 24 h. After cooling at room temperature, 65% aqueous HClO$_4$ (20 mL) was added and a pink solid precipitated. It was recovered by filtration and recrystallized from 0.1 M aqueous HClO$_4$. Yield 30%. ESI-MS (MeCN): m/z (%) = 407 (100) [**M** - HCLO$_4$ - ClO$_4^-$]$^+$. FT-IR (solid, ATR): 3525 (m), 3247 (m), 3180 (m), 2970 (w), 2888 (w), 1602 (m), 1504 (m), 1472 (m), 1428 (m), 1052 (vs), 998 (s), 620 (s) cm^{-1}. UV–Vis [H$_2$O; λ_{max}, nm (ε, M^{-1}cm^{-1})]: 500 nm (67).

Synthesis of [2](ClO$_4$)$_2$. A solution of 4-nitrophenylisocyanate (0.27 g, 1.65 mmol) in anhydrous acetonitrile (20 mL) was added dropwise under dinitrogen atmosphere to a round-bottom flask containing a solution of [**4**](ClO$_4$)$_3$ (1 g, 1.65 mmol), triethylamine (0.92 mL, 6.6 mmol) and pyridine (0.53 mL, 6.6 mmol) in anhydrous acetonitrile (30 mL). The resulting mixture was magnetically stirred at room temperature for 5 h. The pink solid precipitated during the reaction was isolated by filtration, washed with cold acetonitrile (10 mL) and dried in vacuo. Yield 71%. ESI-MS (MeCN): m/z (%) = 570 (100) [**M** - ClO$_4^-$]$^+$, 235 (25) [**M** - 2ClO$_4^-$]$^{2+}$. FT-IR (solid, ATR): 3425 (w), 3388 (m), 3230 (m), 2951 (w), 2887 (w), 1700 (s), 1655 (w), 1608 (m), 1594 (m), 1534 (s), 1505 (s), 1485 (s), 1446 (m), 1425 (m), 1365 (w), 1316 (vs), 1295 (s), 1207 (s), 1170 (m), 1154 (m), 1104 (s), 1081 (s), 1071 (s), 1054 (vs), 997 (s), 954 (s), 876 (m),

838 (m), 743 (m), 684 (m), 616 (s) cm^{-1}. UV–Vis [CH$_3$CN; λ_{max}, nm (ε, M^{-1}cm^{-1})]: 335 (17050), 501 (68).

Synthesis of [3](ClO$_4$)$_2$. [5](ClO$_4$)$_4$ (1.00 g 1. 33 mmol), was dissolved in anhydrous acetonitrile (30 mL) under dinitrogen atmosphere, then triethylamine (0.74 mL, 5.32 mmol) and pyridine (0.43 mL, 5.32 mmol) were added to the mixture. A solution of 4-nitrophenylisocyanate (0.44 g, 2.66 mmol) in anhydrous acetonitrile (20 mL) was slowly added and the resulting mixture was stirred for 5 h at room temperature. A pink precipitate was filtered off, washed with cold acetonitrile (10 mL) and dried in vacuo. Yield = 80%. ESI-MS (MeOH): m/z (%): 778 (50) [M - ClO$_4$]$^+$; 339 (100) [**M** - 2ClO$_4$$^-$]$^{2+}$. FT-IR (solid, ATR): 3433 (w), 3394 (m), 3235 (m), 2952 (w), 2885 (w), 1705 (s), 1661 (w), 1613 (m), 1600 (m), 1542 (s), 1510 (s), 1490 (s), 1456 (m), 1431 (m), 1374 (w), 1325 (vs), 1301 (s), 1272 (m), 1213 (s), 1176 (m), 1159 (m), 1109 (s), 1090 (s), 1075 (s), 1059 (vs), 1000 (s), 960 (s), 932 (w), 883 (m), 843 (m), 749 (m), 688 (m), 619 (s) cm^{-1}. UV-vis [CH$_3$CN; λ_{max}, nm (ε, M^{-1}cm^{-1})]: 336 (32800), 498 (69).

Synthesis of N-(4-nitrophenyl)-N'-propyl-urea, 6. A solution of 4-nitrophenylisocianate (0.22 g, 1.33 mmol) in anhydrous acetonitrile (20 mL) is slowly added under a dinitrogen atmosphere to a solution containing propylamine (0.078 g, 1.33 mmol), triethylamine (0.37 mL, 2.66 mmol) and pyridine (0.21 mL, 2.66 mmol) in anhydrous acetonitrile (10 mL). After magnetically stirring for 5h, a yellow precipitate formed. It was separated by filtration, washed with acetonitrile and dried in vacuo. Yield: 82%. ESI-MS: m/z (%) 222 (100) [M - H]$^-$. ^{1}H NMR (300MHz, CDCl$_3$, 25°C, ppm): δ= 0.88 (t, 3H, CH$_3$), 1.45 (m, 2H, CH$_2$), 3.06 (m, 2H, CH$_2$), 6.45 (m, 1H, NH) 7.62 (d, 2H, arom), 8.15 (d, 2H, arom), 9.23 (d, 1H, NH). UV-vis [CH$_3$CN; λ_{max}, nm (ε, M^{-1}cm^{-1})]: 336 (16200).

X-ray crystallographic studies. Diffraction data for [**3**](ClO$_4$)$_2$ (red, 0.35 x 0.22 x 0.12 mm^3) and [**3**](ClO$_4$)$_2$·6DMSO (pale red 0.75 x 0.60 x 0.45 mm^3) have been collected by means of a conventional Enraf-Nonius CAD4 four circle diffractometer. Diffraction data for crystal of succinate-containing complex, 2([**3**]C$_4$H$_4$O$_4$)·4DMF (violet, 0.50 x 0.42 x 0.33 mm^3) have been collected by means of a Bruker-Axs CCD-based three circle diffractometer. Both instruments work at ambient temperature with graphite-monochromatized Mo-Kα X-radiation (λ = 0.71073 Å). Data reductions for intensities collected with the conventional diffractometer were performed with the WinGX package;[51] absorption effects were evaluated with the psi-scan method[52] and absorption correction was applied to the data. Data reduction for frames collected by the CCD-based system were performed with the SAINT software[53]; absorption effects were empirically evaluated by the SADABS software[54] and absorption correction was applied to the data. All crystal structures were solved by direct methods (SIR 97)[55] and refined by full-matrix least-square procedures on F^2 using all reflections (SHELXL 97).[56] Anisotropic displacement parameters were refined for all non-hydrogen atoms. Hydrogens bonded to C atoms were placed at calculated positions with the appropriate AFIX instructions and refined using a riding model; hydrogens bonded to secondary amines were located in the final ΔF maps and their positions were successively refined restraining the N-H distance to be 0.96 ±0.01 Å.
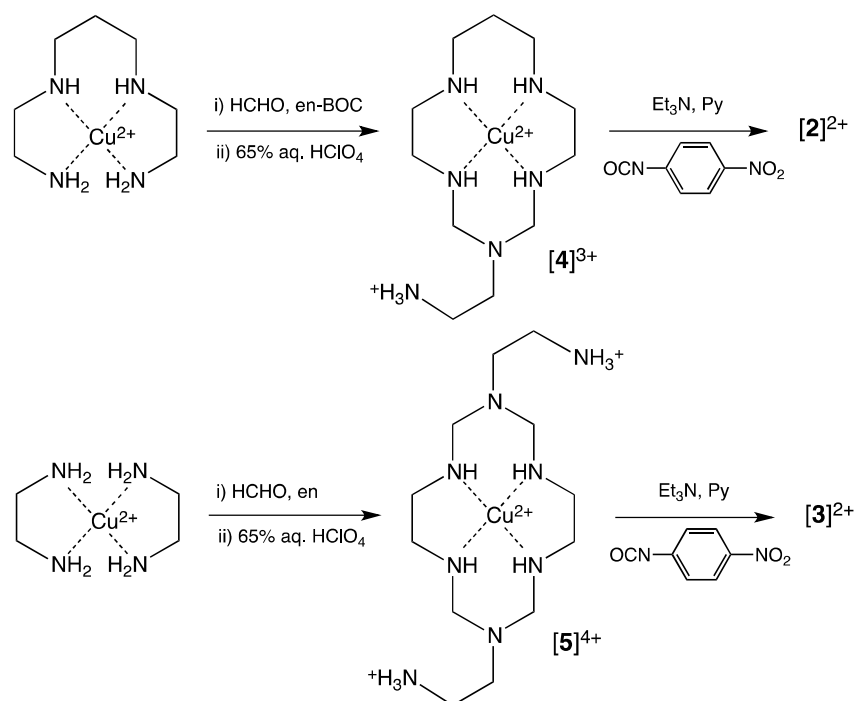
Crystal data for [**3**](ClO$_4$)$_2$: C$_{26}$H$_{40}$Cl$_2$CuN$_{12}$O$_{14}$, M = 879.15, triclinic, P-1 (no. 2), a = 8.153(4), b = 9.129(6), c = 13.618(7) Å, α = 76.59(5), β = 75.01(5), γ = 68.05(4) °, V = 897.7(9) Å^3, Z = 1, 3415 measured reflections, 3162 unique reflections (R_{int} 0.036), 2321 strong data [I$_O$>2σ(I$_O$)], 0.0837 and 0.1185 R1 and wR2 for strong data, 0.1743 and 0.2039 R1 and wR2 for all data.

Crystal data for [**3**](ClO$_4$)$_2$·6DMSO: C$_{38}$H$_{76}$Cl$_2$CuN$_{12}$O$_{20}$S$_6$, M = 1347.98, triclinic, P-1 (no. 2), a = 10.259(3), b = 12.451(3), c = 14.554(4) Å, α = 66.14(2), β = 74.18(2), γ = 70.85(2)°, V = 1584.9(8) Å^3, Z = 1, 7859 measured reflections, 5553 unique reflections (R_{int} 0.021), 3490 strong data [I$_O$>2σ(I$_O$)], 0.0641 and 0.1056 R1 and wR2 for strong data, 0.1669 and 0.1933 R1 and wR2 for all data. Positional disorder affects perchlorate counterions and dimethyl sulfoxide solvent molecules (see the S.I. for details)

Crystal data for 2([**3**]C$_4$H$_4$O$_4$)·4DMF: C$_{72}$H$_{116}$Cu$_2$N$_{28}$O$_{24}$, M = 1885.02, triclinic, P-1 (no. 2), a = 9.329(1), b = 12.550(1), c = 18.982(2) Å, α = 92.63(1), β = 93.56(1), γ = 101.92(1)°, V = 2166.2(4) Å^3, Z = 1, 15742 measured reflections, 7592 unique reflections (R_{int} 0.016), 6306 strong data [I$_O$>2σ(I$_O$)], 0.0380 and 0.0464 R1 and wR2 for strong data, 0.1046 and 0.1117 R1 and wR2 for all data.
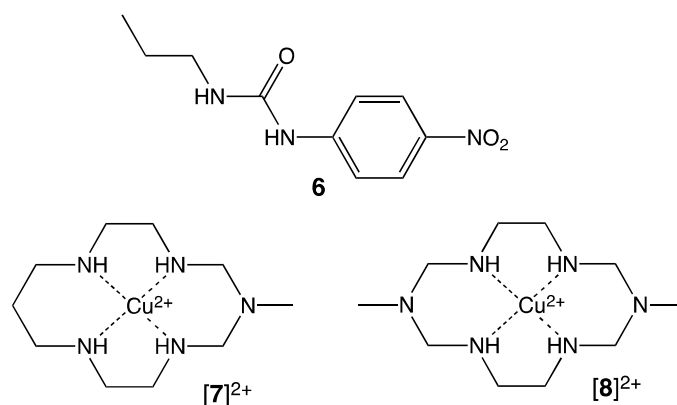
RESULTS AND DISCUSSION

Synthesis and crystal structure of the macrocyclic complexes. The copper complexes [**2**]$^{2+}$ and [**3**]$^{2+}$ were prepared by to a two-step procedure (see Scheme 1) involving (i) the metal templated synthesis of the macrocyclic framework affording the protonated mono- and bis-amino intermediates, [**4**]$^{3+}$ and [**5**]$^{4+}$, respectively, and (ii) the reaction with 4-nitrophenylisocyanate to convert primary amino groups into ureas. Azacyclam complex [**4**]$^{3+}$ was obtained by a template reaction in which the copper(II) complex of an open tetra-amine (2.3.2-tet) is converted into a macrocyclic compound in the presence of formaldehyde and mono-protected ethylenediamine, which behaves as "locking fragment".

Scheme 1. Synthesis of complexes [**2**]$^{2+}$ and [**3**]$^{2+}$.

Diazacyclam complex [**5**]$^{4+}$ was also prepared according to a template method[47] in which ethylenediamine acts both as starting ligand for copper(II) and as locking fragment. Both intermediates [**4**]$^{3+}$ and [**5**]$^{4+}$ were isolated after addition of excess perchloric acid as tri- and tetra-perchlorate salts, respectively, being the primary amino groups protonated. The addition of acid induces at the same time deprotection of primary amino group of mono-pendant arm azacyclam derivative. The reaction with 4-nitrophenylisocyanate was carried out in anhydrous acetonitrile in the presence of pyridine.[57, 58]

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[7]²⁺   [8]²⁺

The mono- and bis-urea derivatives [**2**]²⁺ and [**3**]²⁺ were satisfactorily characterised by FT-IR and ESI-MS spectroscopies. The electronic spectra of complexes [**2**]²⁺-[**5**]⁴⁺ as well as of the reference urea derivative **6** were measured in MeCN. Solutions with different concentrations (about 10^{-5} and 10^{-3} M) of macrocycle/urea conjugates were examined to accurately detect both the intense bands in the UV range and the weak band in the visible range. Absorption data of all the mentioned compounds and of the reference macrocyclic copper complexes of methylazacyclam, [**7**]²⁺, and dimethyldiazacyclam, [**8**]²⁺, are reported in Table 1.

Table 1. UV-vis spectral data for copper(II) aza- and diaza-cyclam complexes and related reference compounds in acetonitrile

compound	λ (nm)	ε ($M^{-1}cm^{-1}$)
[**2**]²⁺	335	17050
	501	68
[**3**]²⁺	336	32800
	498	69
[**4**]³⁺	500	67
	510[a]	76[a]
[**5**]⁴⁺	496	68
6	336	16500
[**7**]²⁺	505	75[a, b]
[**8**]²⁺	498	76[a, c]

[a] in water; [b] ref. 61; [c] ref. 62

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The strong absorption in the UV region (335-336 nm) can be ascribed to a charge-transfer transition due to the nitrophenylurea moieties on the pendant arms of compounds [2]$^{2+}$ and [3]$^{2+}$.[15, 44] This band displays a similar intensity in the spectra of complex [2]$^{2+}$ and of metal-free urea derivative 6, while it is about twofold more intense in the spectrum of [3]$^{2+}$, in accordance with the presence of two nitrophenylurea chromophores appended on the macrocyclic complex.

The weak bands observed in the visible region (around 500 nm) must be considered an envelope of the three possible d–d transitions (xz, yz $\rightarrow$ x^2-y^2, z^2 $\rightarrow$ x^2-y^2 and xy$\rightarrow$x^2 -y^2) in the copper(II)-tetramine chromophore with square-planar coordination geometry.[44, 59] The d-d absorptions in the spectra of [2]$^{2+}$ and [3]$^{2+}$ are comparable to those previously reported for plain copper(II)-azacyclam, [7]$^{2+}$, and diazacyclam, [8]$^{2+}$, complexes[60, 61] and to those exhibited by the mono- and bis-ethylammonium derivatives [4]$^{3+}$ and [5]$^{4+}$.

Red crystals of complexes salt [3](ClO$_4$)$_2$ suitable for X-ray diffraction studies were obtained by slow diffusion of diethyl ether in acetonitrile solution. In a separate experiment, slow diffusion of ethyl acetate in a DMSO solution, provided pale red crystals of [3](ClO$_4$)$_2\cdot$6DMSO, whose structure has been discussed in S.I. (see Figure S1 and S2, and Table S1).

The molecular structure of the copper(II) diazacyclam complex [3]$^{2+}$ determined on a single crystal of its perchlorate salt is shown in Figure 1.

Figure 1. ORTEP view (30% probability level) of the Cu^{II} diazacyclam complex salt [**3**]$(ClO_4)_2$. Selected bond lengths (Å) and angles (deg.): Cu(1)-N(1) 2.009(6) Å, Cu(1)-N(3) 1.999(5) Å, N(1)-Cu(1)-N(3) 94.0(2)°, N(1)-Cu(1)-N(3)' 86.0(2)°; symmetry code (') = -*x*, 1-*y*, 1-*z*. Dashed lines indicate hydrogen bonds.

The molecular structure exhibits C_i symmetry with the metal center placed on a crystallographic center of inversion; the macrocyclic diazacyclam ligand adopts the *trans*-III(*R,R,S,S*) configuration[62] commonly observed in Cu^{II} cyclam metal complexes. The copper(II) center shows a square-planar coordination and lies on the plane defined by the four secondary

amines. The mean Cu^{II}-N distance is 2.00(1) Å and results slightly shorter than the value of 2.03 Å reported for the strain-free Cu-N distance.[63]

The two axial positions corresponding to a rather elongated octahedral coordination for the metal center are occupied by two symmetrically equivalent O(6) atoms of two perchlorate counterions. The observed Cu(1)-O(6) distance of 2.71(1) Å suggests that only very weak coordinative interaction occurs. In particular, each perchlorate counterion profits of this weak interaction and of an additional H-bond interaction provided by the N(3) secondary amine, that acts as H-donor. Features of the N-H···O interaction are: N(3)···O(7) 3.11(1) Å, H(3N) ···O(7) 2.27(5) Å, N(3)-H(3N) ···O(7) 145(4)°.

The tertiary amines show a trigonal-pyramidal geometry with N(2) located at 0.26(1) Å from the basal plane defined by the tree C atoms bonded with nitrogen. This suggests a pronounced sp^3 character for N(2) atom, which is also excluded by any coordinative interaction with the metal center, due to the Cu(1)-N(2) distance of 3.31(1) Å.

The nitrophenyl-urea pendant arms result almost coplanar, with dihedral angles of 9.7(8)° between the urea group and the phenyl ring, and 10.3(19) between the phenyl ring and the terminal nitro group, respectively. The dihedral angle between the urea group and the nitro group is 19.2(15)°.

The NH groups of the urea moieties act as H-donor groups of weak N-H···O interactions (D···A > 3.2 Å) involving the oxygen atoms of perchlorate counterions as H-acceptor species. A complete description of H-bond interactions at the solid state is reported in S.I.

Interaction of [2]$^{2+}$ with oxoanions. Spectrophotometric studies. The behaviour of anion receptors containing binding groups inclined to form hydrogen bonds, such as urea and thiourea,

is usually investigated in aprotic media in order to prevent solvent competition. The present study was performed in acetonitrile, in which system $[2]^{2+}$ (as well as $[3]^{2+}$) displays a reasonable solubility.

In particular, the interaction of the copper complex/urea conjugate with anionic species was investigated by spectrophotometric titration experiments in which solutions of tetrabutylammonium salts of the selected anions (usually about 2×10^{-3} M) were added to a solution of $[2]^{2+}$ (about 5×10^{-5} M).

The urea-anion interaction was monitored by observing the changes in the absorption band corresponding to the charge-transfer transition (335 nm). This transition generates a partial negative charge on the nitro- substituent and a partially positive charge on the NH group belonging to the urea moiety. Therefore, the interaction of a negatively charged species with the urea subunit is expected to stabilise the excited state and, as a consequence to reduce the transition energy. Thus the anion-urea interaction should result in a red-shift of the absorption band: the stronger the interaction, the larger the resulting $\Delta\lambda$.

At first, a common Y-shaped oxoanion such as acetate was considered due to its well-known tendency to interact with urea derivatives. Spectra taken during the titration of a solution of $[2](ClO_4)_2$ with a standard solution of tetrabutylammonium acetate are reported in Figure 2.
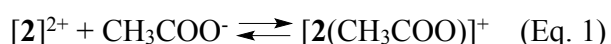
Figure 2. (a) Family of spectra taken in the course of the titration of a 5.4 x 10^{-5} M solution in [**2**](ClO$_4$)$_2$ with a 2.2 x 10^{-3} M solution of [Bu$_4$N]CH$_3$COO at 25 °C (solid bold line: 0 eq; dashed bold line: 4 eq of added acetate). (b) Titration profile at 370 nm indicating the formation of a 1:1 adduct.
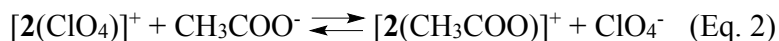
Upon addition of CH$_3$COO$^-$, the band at 335 nm progressively shifts to higher wavelengths up to 353 nm with an increase of molar absorbance from 17050 to 19600 M^{-1}cm^{-1}. The titration profile obtained by plotting absorption intensity at 370 nm vs equivalent ratio (see Figure 2b) indicates a 1:1 stoichiometry for the receptor-acetate interaction.

Non-linear least-square treatment[49] of spectral data allowed the evaluation of the constant (logK = 6.03±0.04) associated to the equilibrium:

$$[\mathbf{2}]^{2+} + CH_3COO^- \rightleftharpoons [\mathbf{2}(CH_3COO)]^+ \quad (Eq. 1)$$

It should be noted that receptor [**2**]$^{2+}$ was isolated as perchlorate salt and, as a consequence, ClO$_4^-$ anions are present in solution when spectrophotometric titration is performed. Therefore,

the receptor-anion association constant determined by the above-described experiment should be related, in principle, to an "exchange" equilibrium:

$$[2(ClO_4)]^+ + CH_3COO^- \rightleftharpoons [2(CH_3COO)]^+ + ClO_4^- \quad \text{(Eq. 2)}$$

At any rate, competition of perchlorate can be considered negligible owing to its extremely poor basic and coordinating properties.

These data showed that the interaction between complex $[2]^{2+}$ and acetate involves the urea pendant arms, as evidenced by the red-shift of the nitrophenylurea CT absorption band. At any rate, no information about a possible cooperative effect of the proximate metal center in the anion binding process can be provided by this titration experiment. In fact, possible changes of the d-d band cannot be clearly observed at low concentration levels due to its low intensity. Therefore the titration experiment was repeated on a more concentrated solution of $[2]^{2+}$ in acetonitrile.

Figure 3 shows d-d spectra taken during the titration of a 10^{-3} M solution of $[2]^{2+}$ with [Bu$_4$N]CH$_3$COO. The band centerd at 501 nm undergoes a shift to higher wavelength (λ= 544 nm) and an intensity increase (up to 102 M^{-1}cm^{-1}), until 1 eq of acetate is added. This behaviour suggests that an interaction between the anion and the metal center also takes place, inducing a change in the coordination geometry and, as a consequence, in the d-d absorption band. In particular, a change from a square-planar geometry to a fivefold coordination, probably with a square-pyramidal geometry, is caused by the first equivalent of added acetate. In fact, approach of a fifth donor atom along the z axis is expected to raise the energy of the d orbitals with a z component, with a consequent decrease in the energy of d-d transitions envelope, and to cause a red-shift of the corresponding band. Moreover, the interaction of an "axial" ligand induces the

loss of the center of symmetry in the azacyclam complex, a circumstance which makes d–d transitions "less" forbidden and increases the absorbance.[44, 64]
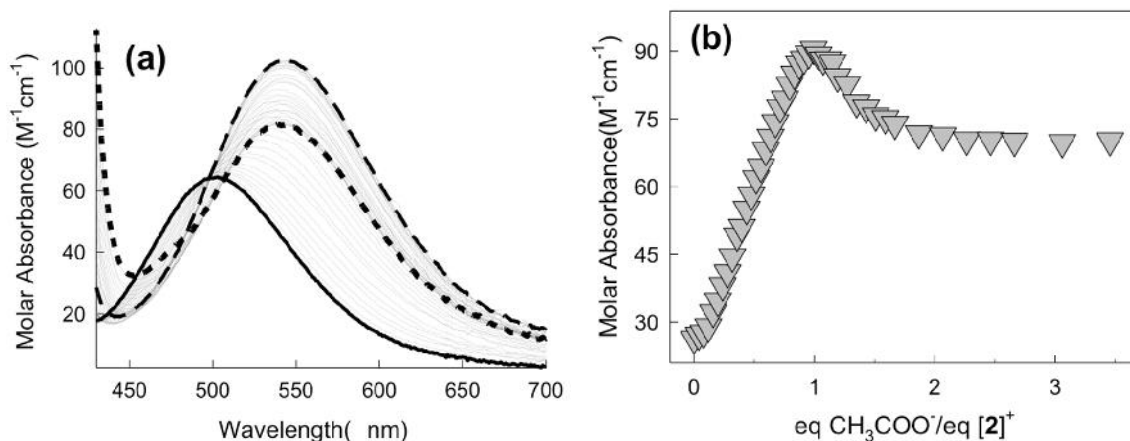

Figure 3. Spectra taken over the course of the titration of a 1.01 x 10^{-3} M solution of the Cu^{II} azacyclam complex [**2**]$^{2+}$ in MeCN with a 2.02 x 10^{-2} M solution of [Bu$_4$N]CH$_3$COO in MeCN (solid bold line: 0 eq; dashed bold line: 1 eq; short-dashed bold line: 3.5 eq of added acetate). b) Titration profile at 570 nm.

The titration profile clearly shows that the band intensity increases until 1 equivalent of acetate has been added, then moderately decreases upon addition of a second equivalent (82 M^{-1}cm^{-1} at 544 nm). This result could be explained by an interaction of a further anion to the metal center with a consequent coordination change from a square-pyramidal to an elongated-octahedral geometry. The partial symmetry recovery results in a moderate intensity decrease of the d-d absorption. At any rate the second equivalent of anion interacts only with the metallo-macrocyclic subunit of receptor [**2**]$^{2+}$, as no detectable variations of the band corresponding to the urea subunit were observed after the addition of the first equivalent of [Bu$_4$N]CH$_3$COO.
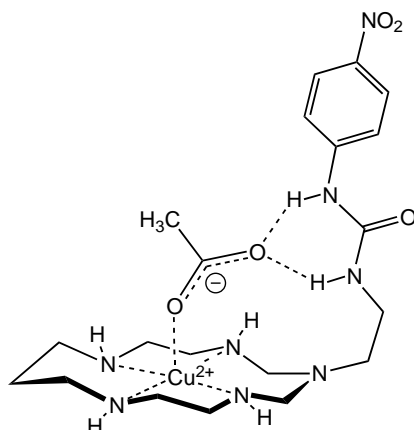
Therefore, UV-vis titration experiments performed at different concentrations indicate that acetate interacts at the same time with both the urea and the metallo-macrocyclic subunits of receptor $[2]^{2+}$. The presence of a metal ion close to the urea groups may favour the binding process not only for electrostatic reasons but also because of the active part played in the recognition process, by establishing coordinative interactions with the anionic substrate.

An analogous investigation was performed on model compound **6** in order to assess the anion binding properties of 4-nitrophenylurea subunit in the absence of any possible cooperative effect due to presence of the metal center. Figure S4 reports the spectra taken during the titration of a solution of **6** with a standard solution of $[Bu_4N]CH_3COO$ and the corresponding titration profiles.

The reference system also interacts with acetate as shown by the red shift of the CT band (from 336 to 364 nm) observed during the addition of the anion solution. The isosbestic point observed along the titration experiment at 344 nm, suggests that only two species are present at the equilibrium (**6** and $[6 \cdot CH_3COO]^-$). Best fitting of spectrophotometric titration data with non-linear least-squares procedure[49] over the interval 290-390 nm was obtained by assuming a 1:1 equilibrium with a logK= 3.92±0.01.

Comparison of stability constant values determined for $[6 \cdot CH_3COO]^-$ and $[2(CH_3COO)]^+$ adducts clearly indicates that the proximity of Cu^{2+}/macrocycle subunit connected to the urea group distinctly increases its binding properties towards acetate.

Spectral data suggest that carboxylate group interacts at the same time with metal ion and urea pendant arm and a scorpionate-like[43, 65, 66] structure could be assumed for the $[2(CH_3COO)]^+$ complex as sketched in Scheme 2.

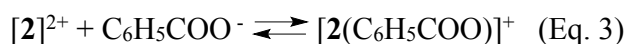**Scheme 2.** Sketch of hypothesized structure of $[2(CH_3COO)]^+$ complex.

It should be noted that carboxylate group interacts with receptor $[2]^{2+}$ according to a "bridged" mode while it is expected to behave as a "Y-shaped" anion in the interaction with plain urea. At any rate, the existence of a dynamic equilibrium between different species containing acetate interacting via bridged- and Y-fashioned modes cannot be ruled out in solution.

Analogous investigations were carried out with a variety oxoanions ($C_6H_5COO^-$, NO_3^-, HSO_4^-, $H_2PO_4^-$, $HP_2O_7^{3-}$).

Addition of tetrabutylammonium benzoate to a MeCN solution of $[2]^{2+}$ induced spectral changes very similar to those observed during the titration experiment with acetate. In particular, the maximum of the band at 335 nm underwent a red shift of 15 nm and an isosbestic point at 336 nm was observed (Figure S5).

LogK value (5.14 ± 0.01) determined for the equilibrium:

$$[2]^{2+} + C_6H_5COO^- \rightleftharpoons [2(C_6H_5COO)]^+ \quad (Eq.\ 3)$$

by non-linear least-square treatment of spectral data is slightly lower than that obtained from titration with acetate. It can be ascribed to the lower basicity of benzoate and its consequent lower tendency to accept H-bond if compared with acetate.[15, 29]

The adduct formed by benzoate with receptor $[2]^{2+}$ is considerably more stable than the adduct formed with model compound **6** (logK = 4.10 ± 0.01), as already observed in the case of acetate. This confirms that the proximity of a metal center to the urea subunit increases the stability of the receptor/anion adduct.

Less basic (and, therefore, poorly coordinating) anions such as nitrate and hydrogen sulphate, affected to a lower extent the spectral properties of receptor $[2]^{2+}$ than carboxylate anions. As an example, Figure S6 displays the spectra obtained on titration with hydrogen sulphate. The band at 335 nm underwent a very small red shift along the titrations with $[Bu_4N]NO_3$ and $[Bu_4N]HSO_4$ (by 4 and 7 nm, respectively) suggesting that only a weak interaction of anionic substrates with the 4-nitrophenylurea subunit takes place (receptor-anion association constants lower than 2 log units). Moreover the d-d band at 501 nm, monitored during analogous titration experiments on more concentrated solutions of the receptor, did not show any significant red shift. The small intensity increase may be ascribed to a precipitation process as suggested by the baseline increase (Figure S6b).

Titration with dihydrogen phosphate induced considerable changes in the absorption spectrum of $[2]^{2+}$. In particular, the band at 335 nm underwent a red shift (to 348 nm) and a progressive intensity decrease, while a simultaneous increase of the baseline was observed, (signalling incipient precipitation) which prevented from completion of the titration experiment (figure S7). The shift of the CT band to higher wavelength suggests that an interaction of the anion with the nitrophenylurea subunit takes place, as already observed in the case of acetate and benzoate. On

the other hand, absorption intensity decrease and spectrum baseline increase are usually consistent with the formation of a poorly soluble species during the titration (for instance the 1:2 neutral complex). The precipitation lowers the complex concentration and absorption intensity, and generates turbidity and baseline change. At any rate, spectral data obtained by this titration experiment did not allow an accurate determination of the adduct stoichiometry and of the corresponding stability constant value. Any attempts to perform similar experiment at lower concentration levels did not provide better results.

In order to have a better insight on the affinity of $[2]^{2+}$ towards anions of the phosphate family, the receptor's behaviour in solution was also investigated in the presence of pyrophosphate. Moreover, di- and poly-phosphate anions, which participate in several bio-energetic and metabolic processes,[5, 67] represent relevant targets in anion recognition and sensing. Spectra collected during the titration experiment with $[Bu_4N]_3HP_2O_7$ and the corresponding titration profile are reported in Figure 4.
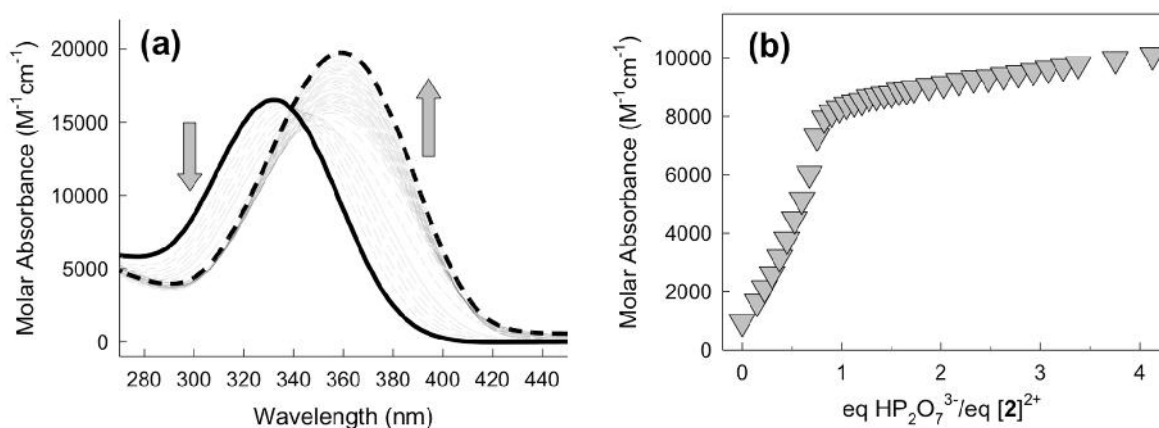

Figure 4. (a) Family of spectra taken in the course of the titration of a solution of $[2](ClO_4)_2$ (5.5 x 10^{-5} M) in MeCN with a standard solution (2.1 x 10^{-3} M) of $[Bu_4N]_3HP_2O_7$ at 25 °C (solid

bold line: 0 eq; dashed bold line: 4.1 eq of added hydrogenpyrophosphate). (b) Titration profile at 390 nm.

In this case too, the band at 335 nm was shifted to higher wavelengths (λ_{max}=360 nm) and its intensity increased (ε_{max}=19700), suggesting a strong interaction of the oxoanion with the urea moiety.

The molar absorbance vs equivalent ratio plot clearly indicate that complex $[2]^{2+}$ interacts with pyrophosphate according to a 1:1 stoichiometry even if no isosbestic point is observed in the absorption spectra during the titration experiment. The presence of more than one complex species in solution can be explained with the structural features of the dimeric phosphate anion, which could interact in an intermolecular fashion with two binding sites (namely urea and metal center) located on different receptor molecules at the same time. Therefore the formation of receptor/anion adducts with different stoichiometric ratios (e.g. 2:1 or 3:2) could be expected at low concentration of anion (receptor/anion molar ratio >1), as also suggested by the titration profile displaying an inflection point at an anion/receptor molar ratio close to 0.5 . At any rate, the best fitting of titration data was obtained by assuming the formation of 1:1 species and the logK value for $[2(HP_2O_7)]^-$ adduct was 5.36±0.02.

An analogous titration experiment performed on the model compound **6** showed that pyrophosphate interacts with nitrophenylurea according to 1:1 stoichiometry (see Figure S8) with logK=4.27±0.01. The $[6 \cdot HP_2O_7]^{3-}$ adduct is distinctly less stable than the 1:1 complex formed by $[2]^{2+}$ with pyrophosphate, confirming again the relevant contribution of the proximal metal center to the anion recognition process.

Titration with $[Bu_4N]_3HP_2O_7$ was performed also on a more concentrated MeCN solution of $[2]^{2+}$ in order to monitor the changes experienced by d-d band and to assess the interaction of

pyrophosphate with the metal center. The band centerd at 501 nm underwent a red-shift ($\Delta\lambda = 35$ nm) and an intensity increase in the course of the titration (ε_{max}=106 $M^{-1}cm^{-1}$ at 536 nm after addition of 1 eq anion), as shown in figure 5a. The titration profile suggests that an interaction according to an 1:1 stoichiometry takes place, although a precipitation process, which occurs in the presence of excess anion, does not allow to determine the corresponding equilibrium constant (see Figure 5b). Variations of the d-d band are consistent with a change of the copper(II) coordination geometry from square-planar to square-pyramidal and clearly indicate that metal ion is directly involved in the recognition process.

Figure 5. Spectra taken over the course of the titration of a 1.13 x 10^{-3} M solution of complex $[\mathbf{2}]^{2+}$ in MeCN with a 2.1 x 10^{-2} M solution of $[Bu_4N]_3HP_2O_7$ in MeCN (solid bold line: 0 eq; dashed bold line: 1.4 eq of added hydrogenpyrophosphate). b) Titration profile at 550 nm.

Changes of both CT and d-d band observed during titration experiments suggest that one anion interacts at the same time with the nitrophenylurea group and the metallo-macrocyclic subunit. Therefore it may be assumed that pyrophosphate is bound according to a "bridged mode", providing a scorpionate-like structure. Unfortunately, although several attempts to isolate the

adduct in crystalline form, no crystal suitable for X-ray crystallographic studies were obtained and the hypothesis of the scorpionate adducts formed by $[2]^{2+}$ cannot be supported by structural data directly concerning this complex.

Interaction of $[3]^{2+}$ with oxoanions. Titration experiments in MeCN analogous to those described in the previous section were also performed to investigate the solution behaviour of bis-urea pendant-arm complex $[3]^{2+}$ in the presence of different oxo-anions.

The addition of acetate considerably affected the absorption spectrum of the complex: the strong absorption band at 336 nm undergoes a red-shift ($\Delta\lambda= 25$ nm) and an intensity increase (ν from 32800 to 38900 $M^{-1}cm^{-1}$) in the course of the titration (See Figure 6a). The spectral changes are observed until 2 equivalents of anion were added to the complex solution. The 1:2 (receptor/anion) stoichiometry of the final adduct was confirmed by the titration profiles reported in Figure 6b.
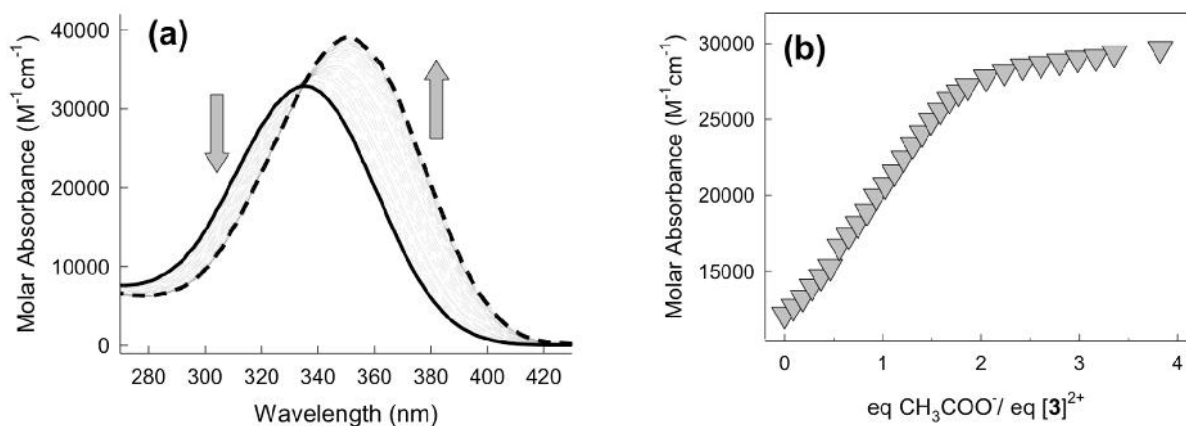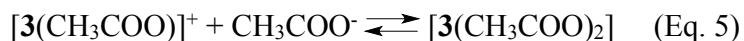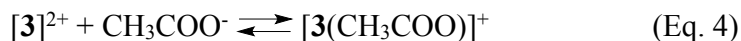

Figure 6. (a) Family of spectra taken in the course of the titration of a 2.5 x 10^{-5} M MeCN solution in $[3](ClO_4)_2$ with a 2.0 x 10^{-3} M MeCN solution of $[Bu_4N]CH_3COO$ at 25 °C (solid bold line: 0 eq; dashed bold line: 5.2 eq of added acetate). (b) Titration profile at 370 nm.

Moreover best fitting of titration data was obtained by assuming the formation of 1:1 and 1:2 complex species according to two stepwise processes:

$$[3]^{2+} + CH_3COO^- \rightleftharpoons [3(CH_3COO)]^+ \qquad \text{(Eq. 4)}$$

$$[3(CH_3COO)]^+ + CH_3COO^- \rightleftharpoons [3(CH_3COO)_2] \qquad \text{(Eq. 5)}$$

LogK values determined for these equilibria are 6.47±0.09 and 5.24±0.09, respectively.

The interaction with acetate also modifies the d-d absorption band as shown by the titration experiment performed on a more concentrated (10^{-3}M) solution of $[3]^{2+}$. The band at 498 nm undergoes a red shift and an intensity increase as already observed for the mono urea-functionalised complex (see Figure S9). At any rate, a precipitation process occurs even during the addition of the first equivalent of anion, preventing completion of the titration experiment.

The behaviour of $[3]^{2+}$ in the presence of benzoate is quite similar to that observed with acetate. Spectral changes registered during the titration experiments indicate that the overall receptor-anion interaction can be described also in this case by a stepwise process analogous to that described by Eqs. 4 and 5, but the corresponding association constants are smaller ($\log K_1 = 5.25\pm0.04$; $\log K_2 = 4.71\pm0.01$) if compared to those obtained for acetate, as expected on the basis of the lower intrinsic basicity of benzoate.[15, 29]

The spectrophotometric titration experiments performed with acetate and benzoate indicate that complex $[3]^{2+}$ interacts in solution with one or two equivalent of carboxylate, depending on its concentration. Each carboxylate group establishes both H-bonds with urea groups on the pendant arms and coordinative interactions at the apical positions of the metal center. These simultaneous interactions should induce the folding of the pendant arm(s), generating

scorpionate-like structures analogous to the one proposed for [2(CH$_3$COO)]$^+$ and sketched in Scheme 2. In particular mono- or bis-scorpionate structures could be expected for 1:1 and 1:2 adducts, respectively.

The poorly coordinating and not basic anions NO$_3^-$ and HSO$_4^-$ did not significantly affect the CT and d-d absorption bands of receptor [3]$^{2+}$, confirming their low tendency to interact with both the nitrophenylurea moiety and copper(II) macrocyclic complex subunit, as already observed for the mono-pendant arm analogue [2]$^{2+}$.

Addition of dihydrogen phosphate induced a progressive precipitation with a consequent absorbance decrease and baseline raising; therefore titration experiment could not be completed (see Figure S10). At any rate, a change of the CT band can be observed before the complete precipitation indicating that H-bond interaction with urea subunits takes place. The poor quality of spectral data did not allow to assess the stoichiometry of the receptor/anion adduct nor the accurate determination of the corresponding association constant(s).

Differently from H$_2$PO$_4^-$, pyrophosphate did not induce precipitation at low concentration levels of complex (< 10^{-4} M) and titration experiments were successfully performed in order to monitor CT band.

The distinct red-shift of the band at 336 nm ($\Delta\lambda$ = 27 nm) again supports H-bond interactions involving the nitrophenylurea pendant arms (Figure 7). The changes of the d-d band at 498 nm cannot be completely monitored due to a progressive precipitation during the titration experiment performed on a more concentrated solution of [3]$^{2+}$. Nevertheless the variations observed after the first additions of anion (intensity increase and shift to higher wavelength) indicate that the coordinative environment of copper(II) undergoes a drastic change due to pyrophosphate coordination.
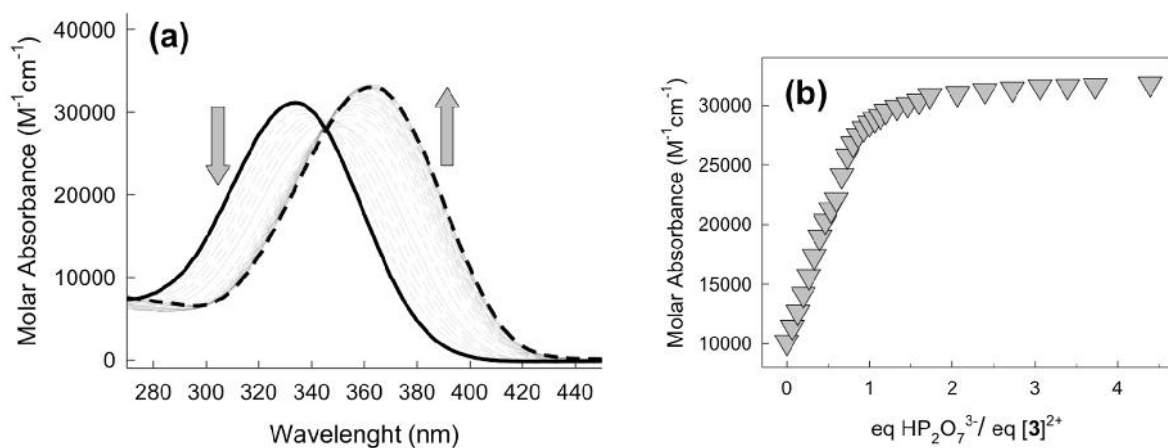
Figure 7. (a) Family of spectra taken in the course of the titration of a 2.5 x 10^{-5} M solution of [**3**](ClO$_4$)$_2$ in MeCN with a standard solution (2.1 x 10^{-3} M) of [Bu$_4$N]$_3$HP$_2$O$_7$ at 25 °C (solid bold line: 0 eq; dashed bold line: 5.2 eq of added anion). (b) Titration profile at 370.

Quite surprisingly the titration profiles determined at different wavelength values seem to indicate that a 1:1 adduct is formed in solution. In addition, best fitting of spectral data was obtained when the formation of only 1:1 adduct was assumed. The corresponding logK value was 7.43±0.06. This behavior can be explained by assuming that the formation of the 1:2 species might be prevented by an electrostatic repulsion due to the high negative charge (3$^-$) on each pyrophosphate anion.

Interaction of [3]$^{2+}$ with dicarboxylates. Spectrophotometric titration experiments performed on [**2**]$^{2+}$ and [**3**]$^{2+}$ clearly indicate that carboxylate and phosphate anions interact with both complexes by establishing at the same time a coordinative bond with the metal ion and H-bonds with the urea subunit(s) on the pendant arm(s). On the basis of the spectrophotometric studies in solution we can assume that carboxylate as well as phosphate groups behave as ditopic species and interact according to a bridging mode, as sketched in Scheme 2. At any rate, other

interaction modes cannot be ruled out particularly in the case of bis-urea derivative $[\textbf{3}]^{2+}$ and, in principle, several equilibria involving different species could take place in solution.

In order to investigate the behaviour of $[\textbf{3}]^{2+}$ in the presence of genuine ditopic anionic species, titration experiments with selected dicarboxylate compounds were performed. In particular spectrophotometric titrations were carried out with malonate, $CH_2(COO^-)_2$, succinate, $(CH_2)_2(COO^-)_2$, and glutarate, $(CH_2)_3(COO^-)_2$.

The addition of dicarboxylate to the solution of the bis-urea pendant arm macrocyclic complex induce a progressive shift of the band at 335 to higher wavelengths, as already observed in titration experiment with acetate. Similar families of spectra were obtained for the three anionic species, with large $\Delta\lambda$ values (24, 25, and 24 nm for malonate, succinate and glutarate, respectively) and moderate intensity increase. Figure 8a reports the spectra taken during the titration with succinate, while Figure S11 and S12 display the families of spectra obtained on titration with malonate and glutarate, respectively.
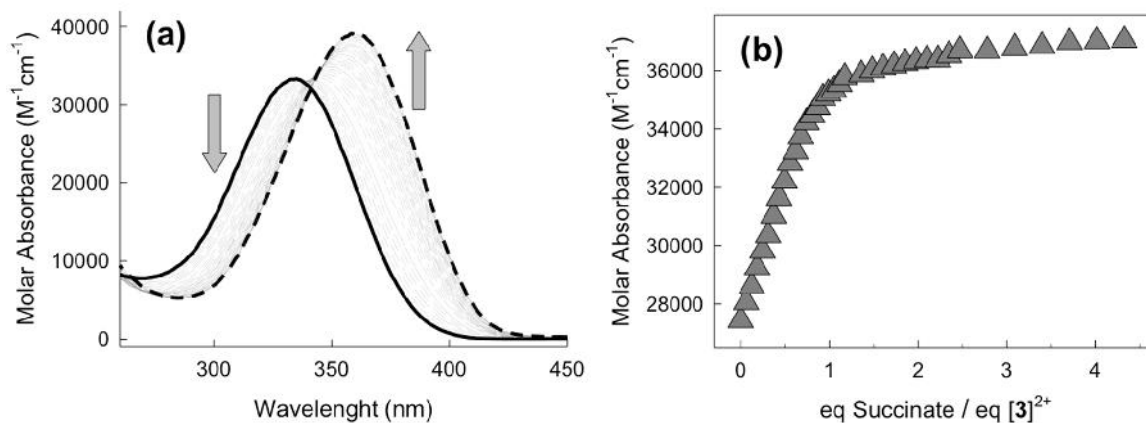

Figure 8. (a) Spectra taken over the course of the titration of a MeCN solution of $[\textbf{3}](ClO_4)_2$ (2.5 x 10^{-5} M) with a standard solution (2.0 x 10^{-3} M) of $[Bu_4N]_2$(succinate) at 25 °C (solid bold line: 0 eq; dashed bold line: 4.4 eq of added anion). (b) Titration profile at 350.

Plots of molar absorbance vs equivalent ratio at significant wavelengths indicate that interaction of $[3]^{2+}$ with all the considered dicarboxylate occurs according to a 1:1 stoichiometry. In Figure 8b the plot obtained for succinate at 350 nm is reported as an example.

Although the titration experiments suggest that a 1:1 adducts are formed in solution, non-linear least square treatment of spectral data do not allow calculating accurate values of association constants. This should be due to a rather large number of equilibria that can take place in solution, since different interaction modes involving at the same time two carboxylate groups (from the anion side) and three binding sites (metal center and two urea subunits from the receptor side) can be hypothesized. Titration experiments performed at higher concentration (1.0 x 10^{-3} M) in order to monitor the d-d band variations induced by dicarboxylate addition could not be completed because a precipitation process occurred in all cases before the first equivalent of anion was added. At any rate, red-shift and intensity increase of the band centerd at 498 nm, which were observed before precipitation occurrence, suggest again that the metal center directly contributes to the interaction with anionic species by establishing axial coordinative bond(s) (see Figure S13).

More information about the structure of dicarboxylate/$[3]^{2+}$ adducts was provided by crystallographic studies. In fact, on slow diffusion of diethyl ether into a DMF/MeCN solution (1:1 by volume) containing equimolar amounts of $[Bu_4N]_2$(succinate) and $[3](ClO_4)_2$, violet crystals of the resulting 1:1 adduct, suitable for X-ray diffraction studies, were obtained.
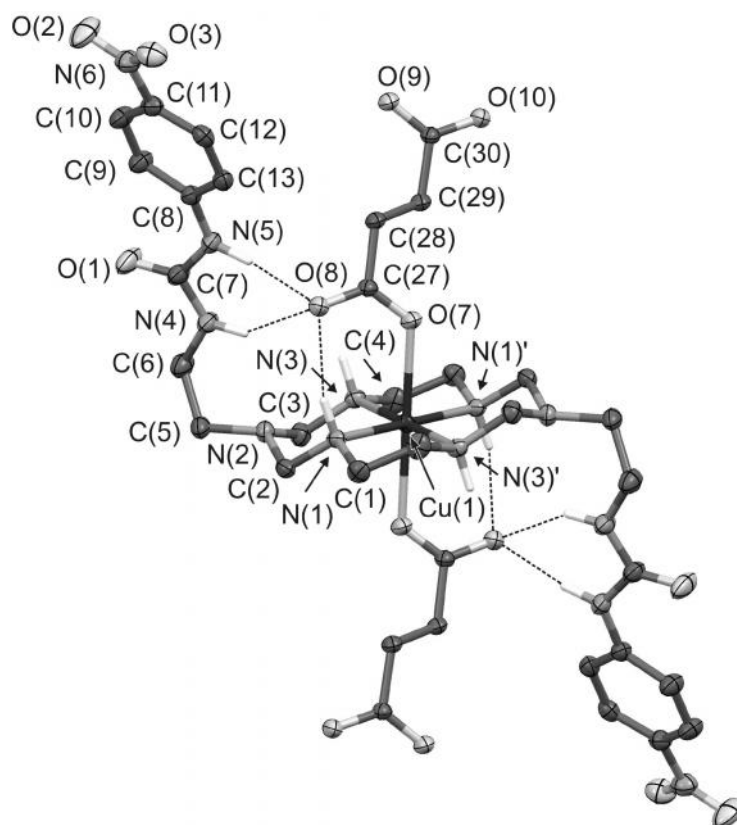
Figure 9. ORTEP view (30% probability level) of one [**3**]$^{2+}$ molecular cations interacting with succinate oxoanions. Selected bond lengths (Å) and angles (deg.): Cu(1)-N(1) 2.008(2) Å, Cu(1)-N(3) 2.032(2) Å, Cu(1)-O(7) 2.425(2) Å, N(1)-Cu(1)-N(3) 93.7(1)°, N(1)-Cu(1)-N(3) ' 86.3(1)° , N(1)-Cu(1)-O(7) 91.2(1)° , N(3)-Cu(1)-O(7) 89.8(1)°, symmetry code (') = 1-*x*, 1-*y*, 1-*z*. Dashed lines indicate hydrogen bonds.

The crystal contains two simmetrically independent [Cu^{II}(**3**)]$^{2+}$ molecular cations, each interacting with two succinate anions and four additional dimethylformamide solvent molecules: 2([**3**]C$_4$H$_4$O$_4$) · 4 DMF (C$_4$H$_4$O$_4$ = succinate). One of the two very similar but not-symmetrically equivalent [**3**]$^{2+}$ molecular cations and the interacting oxoanions are shown in Figure 9 (see Figure S14 for the ORTEP view of the other molecular cation). Both not symmetrically equivalent Cu^{II}-diazacyclam subunits exhibit *C*$_i$ symmetry: the two Cu^{II} metal centers are placed

on two crystallographic centers of inversion and both coppers lie in the plane of the four amines donor set. Both diazacyclam ligands adopt the *trans*-III(*R,R,S,S*) configuration. The mean values for the Cu-N bonds are slightly longer than observed in the structure of $[3]^{2+}$ (without oxoanions): the mean value of 2.02(1) for both Cu(1) and Cu(2) centers in the succinate adduct should be compared to the mean value of 2.00(1) Å observed in the structure shown in Figure 1.

Very interestingly, each carboxylate group of succinate ions interacts with receptor $[3]^{2+}$ according to a "bridged" mode: one O atom of –COO$^-$ is located on an axial position of the elongated octahedral coordination exhibited by the Cu^{II} center while the other O atom acts as H-acceptor of three hydrogen bonds, two of which are provided by the two NH groups of urea.

The direct interaction of carboxylates with the metal center are very similar for the two not-equivalent Cu^{II} centers: the observed distances are Cu(1)-O(7) 2.43(1) Å and Cu(2)-O(9) 2.44(1) Å.

The "bridged" interaction mode of each carboxylic group is determined by two asymmetric N-H···O bonds provided by the urea group on a pendant arm and by a single N-H···O bond provided by a secondary amine of the macrocycle. The two asymmetric H···O distances for the H-bonds involving urea NH groups are 1.90(2) and 2.16(2) Å, and 1.83(2) and 2.29(2) Å for the two independent molecular complexes, respectively, the shortest H···O distance being provided by the urea NH group close to the terminal nitrophenyl group. The H···O distances of the single N-H···O bond provided by the secondary amine of the macrocycle are 2.13(1) and 2.09(1) Å for the two independent molecular complexes, respectively. These values are intermediate between those observed for the urea NH groups.

As each succinate ion interacts at the same time with the metal centers of two not-symmetically equivalent adjacent molecules, molecular chains extending along the **c**-axis

direction are originated in the solid state. A portion of a molecular chain is shown in figure 10 and the geometrical features of the H-bond interactions are reported in Table 2.

Table 2. Features of H-bonds in the $2([Cu^{II}(\mathbf{3})](C_4H_4O_4))\cdot 4$ DMF crystal.

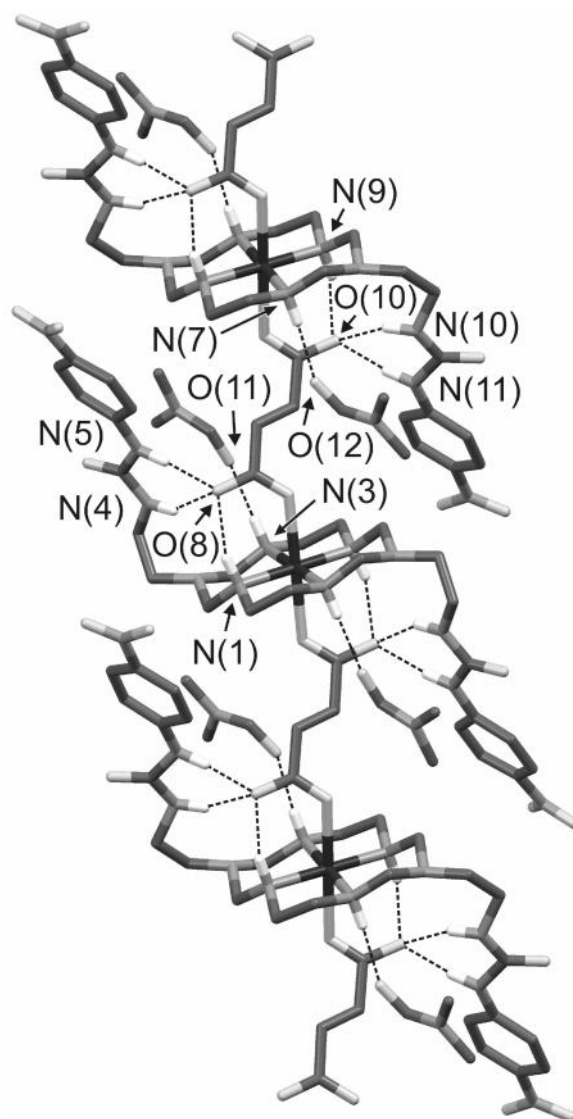| Donor group D	D⋯A (Å)	H⋯A (Å)	D-H⋯A (°)	acceptor atom A
N(1)-H(1N)	3.01(1)	2.13(1)	156(1)	O(8)
N(4)-H(4N)	3.02(1)	2.16(2)	148(2)	O(8)
N(5)-H(5N)	2.83(1)	1.90(2)	166(2)	O(8)
N(3)-H(3N)	3.17(1)	2.45(2)	133(1)	O(11)
N(9)-H(9N)	2.98(1)	2.09(1)	159(1)	O(10)
N(10)-H(10N)	3.13(1)	2.29(2)	147(2)	O(10)
N(11)-H(11N)	2.77(1)	1.83(2)	173(2)	O(10)
N(7)-H(7N)	2.92(1)	2.13(2)	141(1)	O(12)

Figure 10. A simplified sketch of the hydrogen bonds in 2([**3**]C$_4$H$_4$O$_4$)·4 DMF crystal. Atom names identify the independent H-bond interactions.

Crystallographic studies performed on the [**3**]$^{2+}$/succinate adduct show that ditopic anions such as aliphatic dicarboxylates preferentially establish "intermolecular" interactions with the investigated macrocyclic systems. However, the structure represented in Figure 10 describes the

most stable (or one of the most stable) molecular arrangement in the solid state and other different structures could be hypothesized in solution.

On the other hand, it is important to point out that the simultaneous interaction of carboxylate species with the copper(II) ion and the urea group belonging to the same macrocyclic complex is structurally allowed. In particular, urea-containing pendant arms can be folded in order to establish the bifurcated H-bonds with the -COO$^-$ moiety, as foreseen by the scorpionate-like structure hypothesized in Scheme 2. This conformation can be adopted by complexes [**3**]$^{2+}$, and similarly by [**2**]$^{2+}$, even in the recognition in solution of simpler anionic species such as acetate and related monocarboxylates.

CONCLUSIONS

This paper has shown that macrocyclic complexes represent useful platforms in the design of synthetic receptors for anions. Aza- and diaza-cyclam complexes can be easily prepared by template syntheses and functionalised with different groups. The introduction of one or more urea subunits on the macrocyclic framework provides multicomponent systems that can interact with anionic substrates by both coordinative interactions (metal center) and H-bonds (urea subunits).

The investigated copper(II) complexes $[2]^{2+}$ and $[3]^{2+}$ carrying one and two urea pendant arms respectively recognise anionic species displaying coordinating tendency towards copper(II) and good affinity towards urea subunits at the same time, namely carboxylates and phosphates.

In particular, $[2]^{2+}$ forms 1:1 adducts with acetate, benzoate, hydrogendiphosphate, and dihydrogenphosphate, although in the latter case an insoluble product is obtained. Stability constants of the adducts are considerably higher than the ones determined for the interaction of the same anions with plain urea reference compound, confirming the synergistic action of metallo-macrocyclic and urea subunits. Complex $[3]^{2+}$ interacts with the same anions according to 1:1 and 1:2 stoichiometries with the exception of hydrogendiphosphate, which forms just the 1:1 adduct with a distinctly high association constant (logK > 7).

Spectrophotometric investigations suggest that oxo-anionic species interact according to a "bridged" mode, inducing the macrocyclic systems to adopt a scorpionate-like conformation, which is confirmed by crystallographic studies performed on the $[3]^{2+}$/succinate adduct. Although different binding modes, for instance "intermolecular" ones, cannot be ruled out in solution, it should be considered that "intramolecular" interactions should prevail at low concentration level.

Other common anions such as chloride, hydrogensulfate, and nitrate interact only to a poorly significant extent with both investigated complexes.

The macrocyclic systems studied in this work are scarcely soluble in water. This represents a drawback as they cannot be used in aqueous solutions in which receptors for anion usually find practical applications. Moreover, they do not display a very high selectivity toward a specific substrate, but toward two classes of compounds. Nevertheless, the investigation about their behaviour with carboxylate and phosphate derivatives could relevantly contribute to develop novel and more effective systems for anion recognition involving metal-ligand interactions. In particular, the following interesting features should be considered:

(i) owing to their high kinetic resistance to demetallation, aza- and diaza-cyclam macrocyclic complexes are stable even in particular conditions, for instance in the presence of a large excess of anions or in strongly acidic media;

(ii) solubility in water can be improved by introducing more hydrophilic group on the pendant arms;

(iii) macrocyclic complex/urea conjugates could be easily employed to prepare functionalised solid phases.

Incorporation of macrocyclic complex/urea conjugate structures, similar to $[\mathbf{2}]^{2+}$ and $[\mathbf{3}]^{2+}$, into polymeric materials as well as their embedding into solid phase are currently under investigation. The resulting product will be tested to selectively remove selected anionic species from aqueous solutions or to pre-concentrate them before chromatographic analyses.

ASSOCIATED CONTENT

Supporting Information. Comment to crystal structure of [**3**](ClO$_4$)$_2$·6 DMSO, Figures S1-S14, Tables S1-S2. This material is available free of charge via the Internet at http://pubs.acs.org.

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SYNOPSIS

Macrocyclicic copper complexes containing one or two urea-pendant arm(s) recognise anionic species displaying coordinating tendency towards copper(II) and good affinity towards urea subunits at the same time, namely carboxylates and phosphates. Oxo-anionic species interact according to a "bridged" mode, inducing macrocyclic systems to adopt a scorpionate-like conformation.