Drug-containing coordination and hydrogen bonding networks obtained mechanochemically†‡

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In this communication we describe the solid-state preparation and structural characterization of the coordination and hydrogen bonding networks formed by the antibiotic 4-aminosalicylic acid and the nootropic drug piracetam with silver and nickel cations, respectively; the silver complex formed *via* solid-state reaction is anhydrous, while from solution its hydrated phase is obtained.

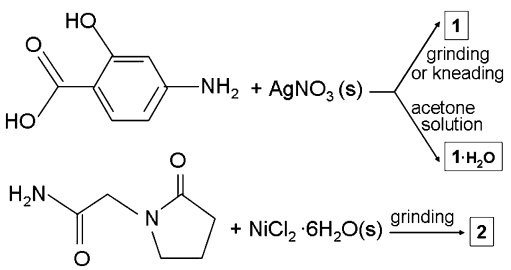
The use of coordination complexes of active pharmaceutical ingredients (API) may open up new routes to the delivery of drugs at biological level because of the foreseeable differences in stability, solubility and bioavailability of the free with respect to the coordinated drug. Recently,[1] we have shown that coordination compounds of the neuroleptic drug gabapentin with zinc and copper can be obtained easily and quantitatively by mechanical co-grinding of solid gabapentin and of the inorganic salts $ZnCl_2$ and $CuCl_2 \cdot 2H_2O$. Beside the potentials in pharmaceutical studies, the use of active ingredients offers the possibility of employing a wide range of readily available new ligands for the construction of coordination networks and complexes, *i.e.* for crystal engineering[2] as well as for coordination chemistry studies. In this communication we show that the mechanical mixing of reactants does not only yield molecular complexes but can also be used to prepare extended coordination as well as hydrogen bonded networks. In this study, the active pharmaceutical ingredients (API) of choice are 4-aminosalicylic acid and piracetam. The 4-aminosalicylic acid (ASA in the following) is an antibiotic that has been used since the 1940s in the treatment of tuberculosis; it has also been shown to be safe and effective in the treatment of inflammatory bowel diseases, namely distal ulcerative colitis[3] and Crohn's disease.[4] Piracetam is a nootropic drug used to improve cognitive abilities. We have used both molecules as ligands in mechanochemical solid-state reactions, as shown in Scheme 1.

It is worth recalling that co-grinding and co-milling of solid reactants have long been known to be viable routes to the synthesis of molecular compounds and of molecular crystals.[5] Early work dates back to the pioneering investigations of Etter,[6] Rastogi[7] and Curtin and Paul.[8] Recently, mechanochemical methods have begun to be successfully applied also in the field of molecular crystal engineering[9] for solvent-free preparation of supramolecular aggregates,[10] co-crystals and coordination networks.[11] Importantly, crystalline materials formed by co-grinding in the absence of liquid can be different from those obtained from solutions or melts as it is the case of the reaction of ASA and $AgNO_3$ (see below).

Compounds **1** and **1·H₂O** have different stoichiometries, the former being anhydrous, while the latter is a mono-hydrate. Interestingly, crystals of the hydrated form **1·H₂O** can be obtained when the complex is prepared in an acetone solution,§ while only the anhydrous form **1** is obtained by manual grinding or kneading[12] (with water or acetone) of ASA and $AgNO_3$ in a 1 : 1 stoichiometric ratio,§ even if the complex is then recrystallized from acetone. This must be due to a "seeding effect", *i.e.* dissolution of a solid material in the minimum amount of solvent actually leaves unaltered small grains, on which crystal growth subsequently occurs.[13] Correspondence between bulk and single crystal structure was ascertained for **1** by comparison of the experimental X-ray powder pattern¶ and that calculated on the basis of single crystal data (see Fig. 1), although the presence of amorphous material and traces of byproducts cannot be excluded. DSC and TGA of complex **1** show that it is stable up to *ca.* 130 °C, temperature at which decomposition is observed. No calorimetric measurements could be performed on complex **1·H₂O**, due to the insufficient quantity obtained.

In crystalline **1**‖ the nitrate ions bridge adjacent silver cations, thus forming a 1D coordination network along the *b*-axis [Ag···O bonds 2.462(9), 2.494(10) Å] (see Fig. 2, top). The nitrate ion and the silver cation all lie on a crystallographic mirror plane; in this way the carboxylic group of each ASA molecule is hydrogen bonded, *via* $R_2^2(8)$ rings [O(H)···O 2.617(8) Å], to a second carboxylic group belonging to a different complex, thus linking the 1D coordination networks to each other (see Fig. 2, bottom). The intramolecular hydrogen-bond observed in the pure ASA structure (refcode AMSALA01) is maintained in complex **1** [O1(H)···O 2.619(7) Å].

In crystalline **1·H₂O**‖ the situation is markedly different. Complex **1·H₂O** contains one silver atom bound to two ASA molecules



Scheme 1 Preparation of the two crystal phases of the silver complex with ASA (top) and of the nickel complex with piracetam (bottom).

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† CCDC reference numbers 723417–723419]. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b913433f

‡ All starting materials were purchased from Aldrich and used without further purification. Reagent grade solvents and bidistilled water were used.

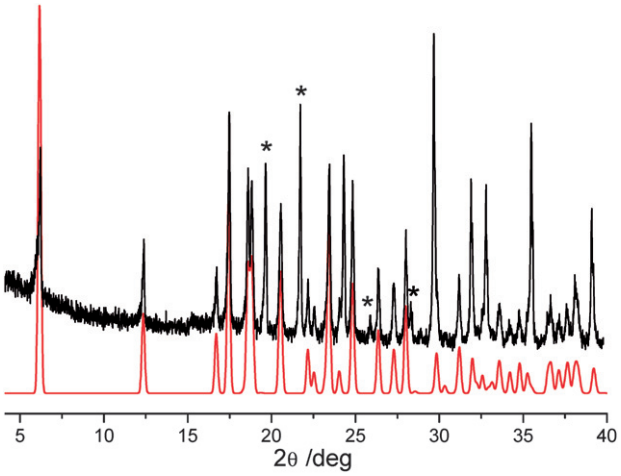

Fig. 1 Complex **1**: Comparison of the XRPD patterns calculated (red) on the basis of single crystal data and measured (black) on the powder obtained *via* kneading with water. Stars indicate the presence of unreacted $AgNO_3$.

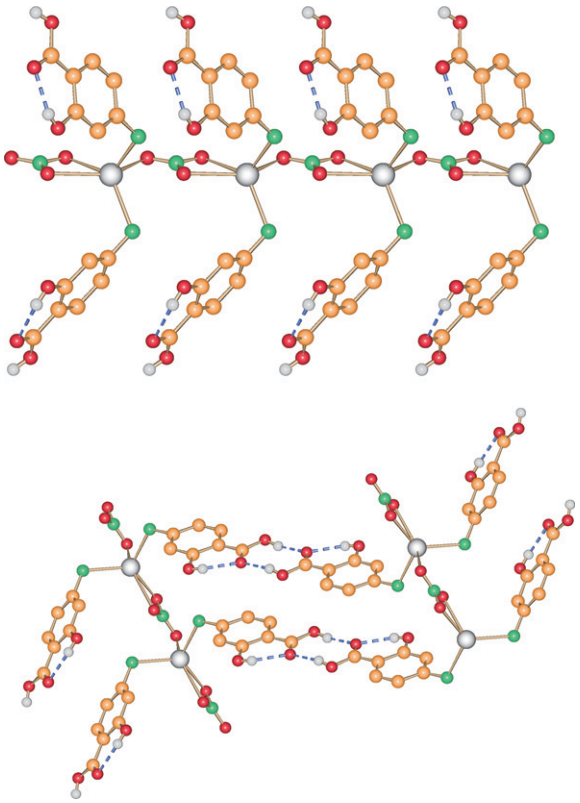

Fig. 2 Crystal packing of complex **1** showing (top) the 1-D network formed by the bridging nitrate anions and (bottom) the 2-D network formed *via* hydrogen bonded rings between ASA carboxylic groups. (No H_C atoms shown for clarity; H_{amino} atoms could not be located).

$[N_{ASA}\cdots Ag$ 2.376(10), 2.413(9) Å], a nitrate anion $[O_{nitrate}\cdots Ag$ 2.635(14) Å] and a water molecule $[O_{water}\cdots Ag$ 2.620(9), 2.625(9) Å]; because of the inversion centre, this unit is doubled and the water molecules bridge two silver cations, thus forming a dimer (see Fig. 3, top). The coordination sphere of each silver atom is completed in an

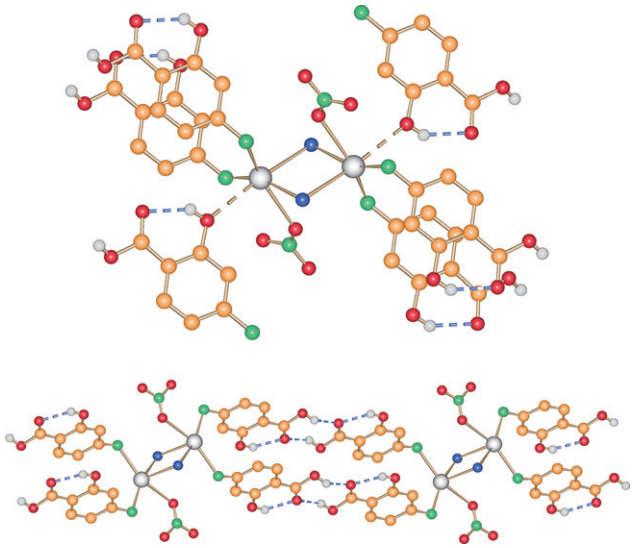

Fig. 3 The dimer (top) formed in **1·H₂O** *via* water molecules (blue spheres) bridging two silver cations, and the long Ag···O contact completing the metal coordination sphere; (bottom) the main packing element of crystalline **1·H₂O**, showing the twin hydrogen bonded rings forming the extended network (compare with Fig. 2, bottom). (No H_C atoms shown for clarity; H_{amino} and H_{water} atoms could not be located).

octahedral fashion by a long Ag···O interaction [2.824(8) Å] with the oxygen atom of an ASA molecule belonging to a different dimer (Fig. 3, top). The intramolecular hydrogen bond present in pure ASA and in complex **1** is maintained here $[O(H)_{OH}\cdots O_{CO}$ 2.64(1) and 2.62(1) Å]. The dimeric units are then linked in an extended 1D-network *via* a twin system of classical $R_2^2(8)$ hydrogen-bonded rings, involving the carboxylic groups of adjacent ASA molecules $[O(H)_{COOH}\cdots O_{CO}$ 2.62(1) and 2.63(1) Å] (see Fig. 3, bottom).

Fig. 4 shows a comparison of the experimental X-ray powder pattern¶ measured on the bulk recovered from crystallization in acetone at −4 °C and those calculated on the basis of single crystal data for **1** and **1·H₂O**. It can be seen that, although some peaks are in

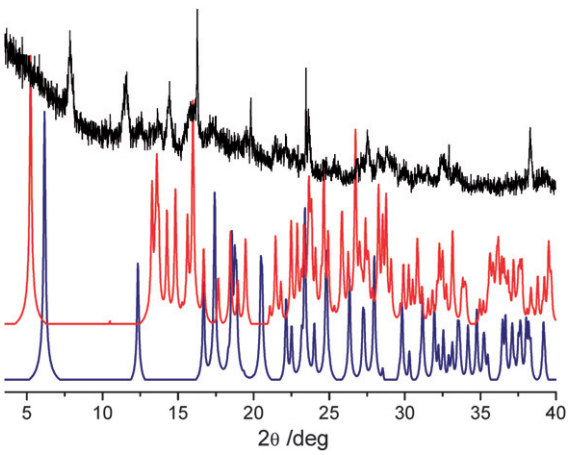

Fig. 4 Comparison of the XRPD patterns calculated on the basis of single crystal data for **1·H₂O** (red) and **1·H₂O** (blue), and the one measured (black) on the powder obtained from reaction in acetone followed by recrystallization at −4 °C.

common, between the experimental and the calculated one, the experimental pattern does not much very well the calculated one for **1·H₂O**. At the same time, no peaks are detected that could be attributed to complex **1** or pure reagents. The crystallization process from acetone at low temperature, therefore, yields a mixture of the hydrated compound and of some unidentified product.

Complex **2** was also obtained *via* a solid-state reaction,§ *i.e.* by grinding piracetam and $NiCl_2 \cdot 6H_2O$ in a 1 : 2 molar ratio. The product was first obtained as a green oil, which took a few days to dry. Recrystallization of the dry product from acetone allowed to obtain single crystals suitable for X-ray diffraction (see Fig. 5).

Fig. 6 shows how crystalline **2**‖ consists of a polymeric network based on a repeating tetrameric unit comprising a pair of piracetam molecules and two metal atoms. The nickel ion lies on a centre of inversion; the asymmetric unit contains two water molecules, one of which is coordinated to the metal centre. Both the chloride ion and the "free" water molecule interact *via* hydrogen bonds with the NH_2 group of the piracetam molecule [N(H)···Cl 3.335(8) Å, N(H)···$O_{W,free}$ 2.97(1) Å] and to the water molecule bound to the metal atom [$O_{W,bound}$(H)···Cl 3.094(7) Å, $O_{W,free}$(H)···$O_{W,bound}$ 2.747(9) Å], and are also bound to each other [$O_{W,free}$(H)···Cl 3.110(8) and 3.222(8) Å].

DSC and TGA measurements show that this compound is stable only up to *ca.* 80 °C.

In summary, we have been able to exploit simple mechanochemical methods of preparation to obtain new coordination and hydrogen bonding networks. The combination of solid state and solution methods has allowed the characterization of these compounds both in the bulk and as single crystals. It is worth stressing that only the knowledge of the single-crystal structures obtained by conventional solution methods has allowed full rationalization of the structures. The successful use of pharmaceutically active molecules as ligands may indeed be a way worth exploring in the quest for new drugs or new drug delivery methods; silver has for example been employed in the form of a triclosan salt,[14] due to its antimicrobial properties.

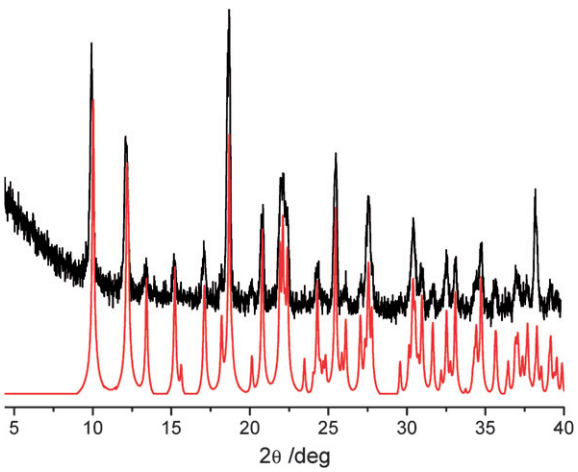

Fig. 5 Complex **2**: Comparison of the XRPD patterns calculated (red) on the basis of single crystal data and measured¶ (black), after drying, on the powder obtained *via* grinding.

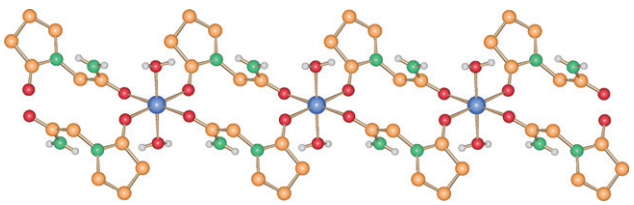

Fig. 6 The 1-D coordination network in crystalline **2**, with the nickel complex constituting the repeating unit and the piracetam molecules bridging two adjacent metal cations.

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Notes and references

§ *Solid-state synthesis of* **1** *and* **2**. A stoichiometric 1 : 1 mixture of ASA : $AgNO_3$ was manually ground in an agate mortar for 5 min and subjected to an X-ray powder diffraction measurement. Similarly, a stoichiometric 1 : 2 mixture of Piracetam : $NiCl_2 \cdot 6H_2O$ was ground to obtain complex **2**. Single crystals of **1**, **1·H₂O**, and **2** were obtained by dissolving the products of the solid-state reactions in the minimum amount of acetone. The solutions were allowed to evaporate slowly at room temperature yielding colourless (for M = Ag) or green (for M = Ni) prismatic crystals.

Synthesis of **1·H₂**. ASA and ASA : $AgNO_3$ in stoichiometric ratio 1 : 1 were dissolved in acetone and the solution was left to evaporate at −4 °C, yielding colourless crystals of **1·H₂O**. All our attempts to obtain the hydrate complex in different conditions failed. Therefore, it seems that the hydrate is a metastable form with respect to the anydrous one.

¶ *Powder data* were collected with a Panalytical X'Pert Pro equipped with X'Celerator detector. A Cu anode was used as X-ray source at 40 kV and 40 mA. The program PowderCell 2.2[15d] was used for calculation of the X-ray powder patterns.

‖ *Crystal structure determination.* Crystal data for **1**, **1·H₂O** and **2** were collected at rt with an X'Calibur Oxford diffractometer equipped with a graphite monochromator (Mo Ka radiation, λ = 0.71073 Å). **1**: $C_{14}H_{12}AgN_3O_9$, M = 474.14, orthorhombic *Pmcn* (non-standard version of space group *Pnma*), a = 28.665(3), b =, 5.402(7), c = 10.882(1) Å, V = 1685(2) Å^3, Z = 4, D_c = 1.869 g cm^{-3}, R_1 (wR_2) 0.0697 (0.0972) for 1835 observed independent reflections, R(int) = 0.0894. **1·H₂O**: $C_{28}H_{28}Ag_2N_6O_{20}$: M = 984.30, triclinic *P*-1, a = 7.580(5), b = 7.627(5), c = 17.111(5) Å, α = 92.062(5), β = 97.578(5), γ = 118.434(5)°, V = 856.7(8) Å^3, Z = 1, D_c = 1.908 g cm^{-3}, R_1 (wR_2) 0.0569 (0.1149) for 2872 observed independent reflections, R(int) = 0.1647. **2**: $C_{12}H_{28}Cl_2N_4NiO_8$, M = 485.97, monoclinic $P2_1/c$, a = 9.6316(7), b = 7.3983(5), c = 15.873(1) Å, β = 113.769(6)°, V = 1035.1(1) Å^3, Z = 1, D_c = 1.559 g cm^{-3}, R_1 (wR_2) 0.0695 (0.2429) for 1817 observed independent reflections, R(int) = 0.0759. SHELXL-97[15a] used for structure solution and refinement based on F^2. Non-hydrogen atoms refined anisotropically, with the exception of carbon atoms in **1·H₂O**, for which data of only moderate quality could be obtained. H atoms were added in calculated positions and refined riding on their respective atoms in complexes **1** and **1·H₂O**, while they were found and refined in **2**; H_{amino} atoms in **1** and **1·H₂O** and H_{water} atoms in **1·H₂O** could not be located. SCHAKAL99[15b] used for molecular representations. PLATON[15c] used to calculate hydrogen bonds.

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