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Production and Characterization of a new Copper(II) Propanoate-Isonicotinamide Adduct obtained via Slow Evaporation and using Supercritical CO₂ as an Antisolvent

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ABSTRACT

A new adduct of isonicotinamide (INA) with copper (II) propanoate $[Cu(C_3)_2]$ was prepared $[Cu_2(C_3)_4(INA)_4]$ using two different methods. This type of compounds shows high fungicidal activity. Solvent evaporation from ethanol rendered crystals suitable for single crystal X-ray diffraction (SCXRD). Furthermore, a new semicontinuous method capable of the simultaneous crystallization and micronization of the adduct using supercritical CO_2 , the supercritical antisolvent technique (SAS), was also assessed. Crystals were characterized using powder X-ray diffraction (PXRD), infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) coupled with mass spectrometry, scanning electron microscopy (SEM) and micro-elemental analysis. In the adduct, two copper(II) ions are coordinated through two bridging and two chelating carboxylates to the propanoate anions forming approximately a plane. Each metal ion is then coordinated with the pyridine nitrogen of two different INA molecules that behave as monodentate ligands. The amide groups of the INA form H-bonds with other amide and carboxylate groups forming a molecular crystal with a 3D H-bond arrangement of the binuclear units. Using the SAS technique, crystals 100 folds smaller than those obtained by slow evaporation were obtained, proving SAS as a suitable method for mixed-ligand complexes preparation with reduced particle size and therefore expected bioavailability enhancement.

1. INTRODUCTION

 The synthesis and behavior of copper (II) alkanoates has been widely studied during the last decades.¹⁻⁹ The paddle-wheel configuration in which the carboxylate ligands bond both copper (II) atoms with a bridging ligand confers these compounds interesting features. They present monotropic polymorphism and mesomorphism, as a hexagonal columnar discotic liquid crystal.¹⁰ Recent research has explored the thermal behavior and structure of the copper(II) alkanoate series in both crystal and liquid crystal phases where the dimeric complex molecular units are present.⁵ Important applications of the copper (II) alkanoates result from their magnetic properties,^{11, 12} and their potential use in the production of nanoreactors.¹³⁻¹⁶ Special interest arises from their biological activity as they have proven pharmaceutical activity in diverse fields such as antiinflammatory, antirheumatic and antitumoral¹⁷⁻²⁶ as well as fungicidal activity²⁷⁻³¹ for which they have been extensively studied as wood preservatives. Dimeric complexes involving bridging carboxylate groups, like the Copper(II) propanoate (Cu(C₃₎₂,

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hereafter), are of special interest for their fungicidal properties.²⁷ Pyridine-4carboxamide, or isonicotinamide (INA, hereafter), is a pharmaceutical coformer of common use in the co-crystal production as it possesses antitumoral, antipyretic, thrombolytic and antibacterial properties.³² It is also known to behave as a high-yielding supramolecularreagent.³³ The nitrogen atom present in the pyridine readily acts as a hydrogen bond acceptor when faced with hydrogen bond donors such as carboxylic acids³⁴ and can even coordinate directly to the copper.³³ The activity of the metal ions increases with the addition of some already biologically active substances, therefore a large number of adducts and complexes of copper(II) carboxylates with N donor ligands such as urea, nicotinamide, papaverine, 3-hydroxypyridine, 2-aminopyridine... have already been produced and their crystal structure solved.^{28, 29, 31, 35-37}

In this communication we report the preparation of the new adduct formed by $Cu(C_3)_2$ and INA. Single crystals were obtained by slow evaporation from an ethanol solution, which allowed the resolution of the crystal structure. On the other hand, this method presents several drawbacks for the production of crystals at industrial scale. Cooling crystallizers require temperature to have a considerable effect on solubility. Furthermore, the slow crystal growth rate in slow evaporative crystallizers, and therefore the long periods of time required to obtain the product, as well as the use of large amounts of organic solvents, can make the scaling up of the process practically or economically non-viable. Other evaporative crystallizers (APV Kestner, Swenson or Oslo-Krystal) can present tube-scaling problems and may require a washing process after crystallization. The utilization of supercritical CO₂ as a solvent in the production of several metal organic frameworks with different organic ligands in a batch reactive crystallization process³⁸ has been investigated by López-Periago and coworkers.^{39, 40} More information on the

processing of metal-organic frameworks using supercritical fluids as reaction medium or drying agents can be found in a recent review.⁴¹

As an alternative to these processes, we investigate the feasibility of using the supercritical CO₂ anti-solvent technique (SAS) in the precipitation and production of metal adducts with N donor ligands. The SAS technique has been previously employed in the production of several co-crystals (multicomponent system connected by non-covalent interactions)⁴²⁻⁴⁴ and presents the added advantage of the production of solvent-free precipitates with smaller particle size (thus increasing even more the bioavailability of the new copper adducts) in a semicontinuous process.

Carbon dioxide presents major advantages as a supercritical fluid because it is innocuous, non-flammable and its critical point is relatively easy to reach (304 K and 7.4 MPa). It is also considered a green solvent,⁴⁵ thus carbon dioxide is the most commonly used supercritical fluid. Its use in the anti-solvent technique is due to the good miscibility with many organic solvents. Carbon dioxide diffuses in the organic solvent in which the solutes to precipitate have been previously dissolved reducing the solvation power of the solvent and generating supersaturation. The properties of supercritical fluids are intermediate between those of gases and liquids and can be easily modified with slight changes in temperature or pressure enabling the control of particle size and/or morphology.⁴³ The solubility of the target solutes to precipitate in carbon dioxide should be very low. The solubility values of several copper complexes in supercritical CO₂ have already been measured⁴⁶⁻⁵⁰ as well as the solubility of the INA isomer nicotinamide,⁵¹ which has already been processed by SAS processing. Neither copper (II) alkanoates nor INA have been processed by SAS before. The aim of this paper is to explore the

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 crystal structure of the $Cu(C_3)_2$ -INA adduct and to study the feasibility of the SAS technique to produce the mentioned adduct.

2. EXPERIMENTAL SECTION

2.1. Materials. INA ($C_6H_6N_2O$) 99% was purchased from Sigma-Aldrich in its polymorph form I. Cu(C_3)₂ ($C_6H_{10}CuO_4$) was prepared in our laboratory by direct reaction of copper (II) oxide (Merck pro analysis >99%) with propanoic acid (Fluka puriss. >99.5%) in a small amount of ethanol heated under reflux at 333 K for several hours as described elsewhere⁷. Absolute ethanol was purchased from Fisher Scientific. All reactants were used with no further purification. Compressed CO₂ (99.998%) was supplied by Contse S.A. (Spain).

2.2 Adduct preparation Two different methods were used to obtain adducts of $Cu(C_3)_2$ -INA: Slow evaporation from solution and supercritical antisolvent precipitation.

2.2.1 Crystallization from solution (slow evaporation)

This procedure consisted in the grinding of $Cu(C_3)_2$ and INA in a 1:2 molar ratio respectively (1.2 mmol of $Cu(C_3)_2$) assisted with a few drops of ethanol. The powder obtained by grinding was dissolved in approximately 175 mL of ethanol at 333 K and then filtered twice. After cooling, the obtained solution was covered with perforated parafilm and left to slowly evaporate. A change of color from cyan to lighter blue was observed. Crystals suitable for single crystal X-ray diffraction were obtained after several weeks.

2.2.2 Supercritical procedure

The supercritical fluid antisolvent (SAS) technique was also used. A complete description of the high-pressure equipment employed can be found elsewhere.⁴² A typical experiment is described here. Compressed CO₂ was cooled to 272 K in a chiller and pumped into the system using a high pressure pump (Thar-SCF high pressure Pump P-50) at a rate of 20 g/min. The CO₂ passed through a heat exchanger, where temperature was raised to 313 K, before entering a 500 mL precipitation chamber. A back pressure regulator (BPR) situated at the exit of the chamber kept the pressure in the chamber at 10 MPa throughout the experiment. When steady conditions were reached in the precipitation chamber a 1:2 molar ratio solution in ethanol of $Cu(C_3)_2$ (3.3 mg/mL) and INA was injected using an high-performance liquid chromatography (HPLC) pump (labAlliance series III pump) into the precipitation chamber through a 100 µm nozzle at a flow rate of 1 mL/min. The precipitation chamber was equipped with a heating jacket to ensure that the experiment occurs at the desired temperature of 313 K. Inside the chamber a basket with a filter (frit, $2 \mu m$) was placed in order to collect the microparticles obtained. The effluent exiting the BPR was directed to a cyclone separator where CO₂ was separated from the waste. After spraying approximately 30 mL of solution the HPLC pump was stopped and 1.5 L of CO₂ at the same precipitation conditions were allowed to flow through the chamber at 20 g/min to ensure that the product was free of ethanol. A schematic representation of the process is illustrated in Figure 1.

Experiments were performed at 298 and 313 K and pressures of 8, 10 and 25 MPa using ethanol as a solvent and a 1:2 molar ratio of $Cu(C_3)_2$ to INA. Further experiments were conducted at 313 K and 10 MPa using methanol. An additional experiment at 313 K and 10 MPa using ethanol and a 1:1 molar ratio of $Cu(C_3)_2$ to INA (excess of $Cu(C_3)_2$) was also performed.

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Solubility of Cu(C₃) and INA was studied in a mixture of CO₂ and ethanol at the precipitation conditions using a high-pressure view cell available at our laboratory and following the procedure previously described.⁵² As required for a successful SAS precipitation, solubility of these compounds was very low, below 2×10^{-5} in mole fraction.



Figure 1. Schematic representation of the SAS equipment and process. T: temperature control and measurement; P: pressure measurement; BPR: back pressure regulator.

2.3 Adduct characterization. Single Crystal X-ray Diffraction (SCXRD) experiments were performed with a wavelength λ = 0.8000 Å, at 100 and 320 K at the 911-3 beamline of Max II (Max IV Laboratory, Lund, Sweden) using a MAR225 CCD area-detector, making *phi* scans while collecting the data. The oscillation range ($\Delta \varphi$) used for each image was one degree. The structure was solved and refined using the SHELXS-97 and SHELXL-97 programs.⁵³

 Powder X-ray Diffraction data (PXRD) for most of the compounds were collected on reflection mode in a Panalytical X'Pert MPD X-ray diffractometer with vertical goniometer θ -2 θ . A Cu anode X-ray tube was powered at 40 kV and 40 mA (K_{a1} 1.54056 Å). Scans were measured between 5° and 60° 2 θ with a step size of 0.016° 2 θ and a continuing time of 5 s per step.

The adduct obtained by slow evaporation was measured at room temperature (RT) in transmission mode in 0.5 mm spinning capillaries at the I711 beamline of the Max II synchrotron (MAX IV Laboratory, Lund, Sweden), with a wavelength of 0.9940 Å, and using a Newport diffractometer equipped with a Pilatus 100 K area detector mounted 76.5 cm from the sample. The detector was scanned continuously, from 2 to 70°, in approx. 6 min, recording 125 images per ° (step size 0.008°) for each measurement. The true 20 position of each pixel was recalculated, yielding an average number of 100.000 pixels contributing to each 20 value. Integration, applying no corrections for the tilt of the detector, provided full width at half maximum (FWHM) values of 0.03–0.08° from 0 to 120°.

The Rietveld refinement was performed with the FullProf program,^{54, 55} introducing the atomic coordinates previously obtained from the single crystal data in each case.

Fourier Transform Infrared (FTIR) spectra of the samples were obtained using the spectrum 100 Fourier-transform infrared spectrometer from Perkin Elmer with the universal attenuated total reflection (ATR) sampling accessory at a resolution of 4 cm⁻¹. Samples were measured in the 4000-650 cm⁻¹ range.

Differential scanning calorimetry (DSC) thermograms were measured using a TA Instruments Q 20 modulated DSC connected to a refrigerating cooling system (RCS), at a heating rate of 5 K/min and a dry nitrogen flow of 50 mL/min. Samples were confined

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in sealed aluminum volatile pans and weighed using a MT5 Mettler microbalance (error of ± 0.001 mg). Temperature and enthalpy of the calorimeter were previously calibrated using standard samples of In (purity > 99.999%), Sn (>99.9%) and benzoic acid (>99.97%). Thermogravimetric analysis (TGA) and decomposition mechanisms were studied with a TA Instruments Q500 thermobalance equipped with an evolved gas analysis (EGA) oven connected to a ThermoStar Omnistar GSD 301 O/301T mass spectrometer. Samples were placed in Pt containers and heated at 10 K/min under a 100 mL/min N₂ flow from room temperature to 773 K. Uncertainty in the temperature was ± 0.1 and ± 0.5 K in the DSC and TGA measurements, respectively.

Particle size and morphology of samples were examined by Scanning Electron Microscopy (SEM) using a JEOL 6335F JSM microscope. Samples were coated with gold in a Q150RS Rotary-Pumped Sputter Coater. SEM images were taken with an accelerating voltage of the electron beam of 10, 15 or 20 kV.

Micro-elemental analysis of the samples was performed in a LECO CHNS-932. Uncertainty in the measurements was ± 0.3 % for N and H and ± 0.35 % for C.

3. RESULTS AND DISCUSSION

3.1. Crystal Structure. Large crystals of the adduct $Cu_2(C_3)_4(INA)_4$ with single crystal quality were obtained through slow solvent evaporation. The experimental parameters, crystal sizes, and main crystallographic information obtained from the SCXRD data at 100 K (structure II) and 320 K (structure I) are shown in Table 1.

Table 1. Crystallographic Data and Structure Refinement Parameters of $Cu(C_3)_2$ -INA adduct

	$Cu(C_3)_2$ -(INA) ₂
chemical formula	$CuC_{18}H_{22}N_4O_6$
formula weight (g/mol)	453.94
crystal system	monoclinic
space group	$P 2_{l}/c$

crystal size (mm)	$0.060\times0.040\times0.030$		
λ (Å)	0.8000(1)		
temperature (K) / structure	100 / II	320 / I	
a (Å)	10.572 (2)	10.812 (2)	
b (Å)	11.612 (2)	12.367 (3)	
c (Å)	15.779 (3)	15.467 (3)	
α (°)	90	90	
β (°)	103.,93 (3)	103.46 (3)	
γ (°)	90	90	
$V(A^3)$	1880.1(7)	2011.3(7)	
Ζ	4	4	
D_{calc} (g/cm ³)	1.604	1.499	
$\mu (mm^{-1})$	1.207	1.128	
absorption correction	none	none	
reflection collected	3844	4659	
reflections with $I > 2\sigma(I)$	3624	3441	
parameters refined/restraints	276/0	280/0	
hydrogen treatment	mixed	mixed	
R-factor	0.0403	0.0427	
wR ₂ -factor	0.1052	0.1056	
goodness of fit	1.074	1.046	
CCDC no	1846632	1846633	

Figures 2a and 2b show the structures of $Cu(C_3)_2$ and the $Cu_2(C_3)_4(INA)_4$ adduct obtained at 100 K. The colour change from the original cyan of the $Cu(C_3)_2$ to a lighter blue can be attributed to the change in the coordination of the copper from 5 (square pyramidal) in the alkanoate to 6 (distorted octahedral) in the adduct. The paddle-wheel structure of $Cu(C_3)_2$ is constructed by four bridging carboxylate ligands (μ_3) which form *catenae* in a one dimensional (1D) coordination polymer arrangement (Fig. 2a), typical of all the Cu(II) alkanoates.¹⁻⁹ The paddle-wheels, and therefore the *catenae*, disappear in the new complex where two-metal units are coordinated by two bridging (μ_2) and two chelating carboxylates (μ_2) from the propionate anions, and four N atoms from INA molecules. Each Cu ion in the binuclear unit is coordinated by four O atoms (two of them from two different bridging carboxylates, and the other two from the chelating carboxylate), in the plane approximately, while the N atoms are in the apical vertices of the distorted octahedron (see Figure 2b). The INA behaves as a monodentate ligand

coordinating to the copper ions through the pyridine nitrogen atom, and leaving the amide group towards the outside of the complex, where H-bonds are then formed with other amide and carboxylate groups. The amide-amide synthons grow linearly in the direction of the apical vertices of the Cu octahedron. The H-bonds between the amide groups and the chelating carboxylates are similar to those previous reported for complexes of Cu(II) and INA^{33, 56} and grow perpendicular to the ones of amide-amide synthons, and laterally with respect to the chelating carboxylate, joining different di-copper units (see Figure 2c). Thus, the final structure results in a molecular crystal of isolated binuclear complexes joined by H-bonds in a 3D arrangement (see Figure 2c). Hydrogen-bond interactions and distances are summarized in Table 2.

Table 2. Hydrogen-bond intermolecular distances for the $Cu(C_3)_2$ - INA adduct at 320 K.

Amide-Amide Synthon	Distance (Å)
O(6)H(2N1)	2.179 (4)
O(5)H(4N2)	2.086 (4)
Amide-Carboxyl	
O(3)H(2N2)	2.148 (4)
O(4)H(4N1)	2.164 (4)

The complex crystallizes in the monoclinic system group ($P 2_1/c$), centrosymmetric, and it is worth noting that the inversion center is in the middle of the di-copper units, so the asymmetric unit contains half of those aforementioned parts: one Cu, two propionates and two INA molecules. Small distortions are observed in the structures at 100 and at 320 K, mainly in the chelating carboxylate and the expected higher thermal displacement in the alkyl chain of the propionates.



Figure 2. a) *Catena* of a Cu(II) alkanoate (1D coordination polymer of double coordination bond of paddle wheels), showing the square pyramidal coordination of the Cu atoms; b) binuclear unit of the Cu(C₃)₂-INA adduct, measured at 100 K, with 50% probability ellipsoids and showing the distorted octahedric coordination around the Cu atoms; the semi-transparent atoms have been generated by symmetry operations; c) 3D arrangement of the units showing the H-bonds of the amide-amide and the amide-carboxylic synthons.

The synthesis of the adduct was also attempted by the SAS technique using supercritical CO_2 . Experiments were performed at different temperatures and pressures,

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solvents and $Cu(C_3)_2$ to INA molar ratios. Both pressure and temperature had a significant effect in the adduct formation by SAS. PXRD of the different samples prepared by SAS only fit the pattern of the adduct prepared by evaporation in the experiments performed at 313 K and 10 MPa using ethanol or methanol as solvents and the 2:1 molar ratio of $Cu(C_3)_2$ to INA. At the remaining conditions, complex PXRD patterns which do not match those of the pure compounds or the adduct previously described were obtained. PXRD of all the samples precipitated by SAS are given as supplementary material (Figure S1).

Figure 3 compares the patterns of the products obtained by SAS at 313 K and 10 MPa for a 2:1 Cu(C₃)₂ to INA molar ratio using ethanol as solvent and that of the sample prepared by slow evaporation (by grinding some crystals). The pattern from the grinded crystals was fitted by Rietveld refinement using the model obtained by SCXRD. On the other hand, the adduct prepared by SAS showed the most intense peaks of the former sample, but clearly with much lower crystallinity. PXRD of this sample was also refined using the Rietveld method. Similar cell parameters were obtained for the samples prepared by SAS in ethanol and by evaporation. The fittings and data of the Rietveld refinements for both samples are given as Supporting Information (Figure S2). For the SAS sample, the microstructure was also studied. The average crystal domain corresponded to a platelet, which was extremely narrow in the direction (010) (see Table S1 in supplementary material). No sign of other crystalline phases (reactants, or new phases) was observed by PXRD.



Figure 3. Comparison of the diffraction patterns observed for the adduct obtained by: a) SAS using ethanol at 313 K, 10 MPa and a 1:2 molar ratio of $Cu(C_3)_2$ to INA, b) slow evaporation and c) calculation from the Rietveld refinement at room temperature.

SEM images of the precipitated adducts, commercial and SAS processed INA, $Cu(C_3)_2$ prepared at our laboratory and SAS processed $Cu(C_3)_2$ are shown in Figure 4. In every case, ethanol was used as a solvent. $Cu(C_3)_2$ prepared at our laboratory presented a ribbon-like morphology with heterogeneous crystal sizes that can vary from 1 µm in width and length up to 50 µm. After processing $Cu(C_3)_2$ by SAS, size was reduced to small spheres of 70 nm diameter. Commercial INA presented prismatic crystals of polydisperse size and rough surface that vary from 20 to 100 µm in thickness and 60 to 400 µm in length. SAS processed INA showed a platelet morphology with thickness of around 7 µm and surfaces up to several 100 µm². Adduct crystals obtained by slow evaporation presented sizes up to 150 µm wide and lengths close to 1 mm (although crystals were crashed and fragmented and show therefore an heterogeneous size distribution).



Figure 4. SEM images of: a) $Cu(C_3)_2$ prepared at our laboratory; b) commercial INA; c) $Cu_2(C_3)_4(INA)_4$ formed by slow evaporation; d) $Cu(C_3)_2$ processed by SAS; e) INA processed by SAS; f) adduct formed by SAS employing a 1:2 molar ratio of $Cu(C_3)_2$ to INA. SAS experiments were performed at 313 K and 10MPa using ethanol. Images b), c) and e) are at 100x magnification; images a) and f) at 1000x and d) at 1500x magnification.

As it can be observed, the production of the adduct crystals by SAS generated much smaller crystals (up to 100 times smaller). Supercritical CO₂ combines liquid-like densities with gas-like diffusion coefficients allowing a very rapid mixture of the liquid and supercritical phase in the precipitation chamber. This leads to a fast supersaturation of the solution and the precipitation of the solute. As at 313 K and 10 MPa we operate over the critical point of the mixture CO₂-ethanol^{57, 58} we can expect gas-like mixing in the precipitation chamber,⁵⁹ thus, many crystal nuclei are produced and crystal growth is hindered. However, the small adduct particles precipitated by SAS exhibited a mixture of different morphologies. Whilst most particles were around 3µm wide and 30 to 50 µm long, nano-fibers and small conglomerates were also present. SEM images for the sample precipitated from the methanol solution are given in the supporting information (Figure S3). Morphology of the sample in this case was similar but particles were even smaller than those precipitated from the ethanol solution. Although the only crystalline phase

observed by PXRD was that of the adduct, the different morphologies observed in the SAS samples by SEM could indicate the presence of amorphous impurities. The results obtained from the microstructural analysis by XRD of the sample precipitated by SAS using ethanol show a platelet domain (see Supporting Information), compatible with the main particle morphology but with an average crystal domain much smaller than the observed particle size.

3.2. FTIR Spectroscopy. Figure 5 shows FTIR spectra of the samples. Table 3. displays the absorption peak assignments of INA, 7 Cu(C₃) $_{2}^{60, 61}$ and the adduct formed by both techniques. One of the most significant bands is the carbonyl amide stretching band at 1708 cm⁻¹. In pure INA the carbonyl group is bonded through H-bonds to two amide groups of different INA molecules (distances of 2.076 and 2.088 Å), the vibration frequency of this stretching band is at 1655 cm⁻¹. In the adduct though, this carbonyl group of the INA is bonded to only one amide group forming the amide-amide synthon shown in Figure 2 (distances of 2.179 and 2.086 Å) and consequently the frequency of this vibration blue shifts to 1708 cm⁻¹. The presence of this synthon also shifts the asymmetric and symmetric stretchings of the NH₂ group from 3361 cm⁻¹ and 3177 cm⁻¹ in the pure INA that red shift to 3296 cm⁻¹ and 3149 cm⁻¹ in the adduct respectively. These shifts show that in the adduct a different H-bond net is present. In the $Cu(C_3)_2$ the carboxylate asymmetric and symmetric stretchings have a frequency of 1585 cm⁻¹ and 1420 cm⁻¹ respectively. The wavenumber difference between these stretching bands (Δv = 165 cm⁻¹) is in accordance with the bridging bidentate structure of the Cu(C₃)₂⁶². In the adduct, the asymmetric stretching of the carboxylate was observed at 1583cm⁻¹ and two different symmetric stretching were observed at frequencies of 1420 cm⁻¹ and 1393 cm⁻¹.

Although a smaller distance between the asymmetric and symmetric stretchings of the carboxylate with the chelating bidentate could be expected⁶³ the intramolecular

forces between the chelating ligand and the amide group red shift the symmetric band to 1393 cm⁻¹ in the adduct. Other important aspect that can be observed in the spectra is the shift in the vibration frequency of the pyridine ring breathing motion, present in the INA at 994 cm⁻¹ and in the adduct at 1029 cm⁻¹, due to the monodentate coordination of the pyridine ring with the Cu (II).

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Table 3. Infrared	peaks (cm ⁻¹) and a	assignments of INA,	$Cu(C_3)_2$ and the add	$\operatorname{duct} \operatorname{Cu}(\operatorname{C}_3)_2$ -
INA: v stretching	; δ bending; γ tors	ion; ω wagging; tw t	wisting; p rocking.	
ΙΝΑ	$Cu(C_2)_2$	$C_{11}(C_{2})_{2}$ INA		Assignment

INA	$Cu(C_3)_2$	$Cu(C_3)_2$ -INA	Assignment
3361 s		3296 s	v_{asv} (NH ₂)
3177 s		3149 s	$v_{\rm sym}$ (NH ₂)
	2974 m	2986 w	v_{asy} (CH ₃)
	2944 m	2964 sh	V _{sym} (CH ₃)
	2922 w	2936 w	V (CH ₂)
	2922 w 2879 w	2950 w 2879 w	v _{sym} (CH ₂)
1655 m	2077 W	1708 g	$v_{asy}(CH2)$
1633 III 1631 m		1/00 S	Vasy (C=O) allide
1021 m	1505 -	1040 m 1592 -	NH_2 deformation amide
1506	1585 S	1583 S	V _{asy} (COO ⁻)
1586 s		1583 s	v pyridine ring
1551 s		1555 w	v pyridine ring
	1511 m		δ_{asy} (CH ₃)
	1473 w		δ_{asy} (CH ₃)
	1459 w	1460 m	δ_{asv} (CH ₃)
1466 w			v pyridine ring
	1420 s	1420 sh	$v_{\rm sym}(\rm COO^{-})$
1415 s		1420 sh	v pyridine (CC)
1110 5		1 120 511	in plane pyridine (CH)
	1383 w	1393 s	$\frac{\delta}{\delta} $
	1505 W	1375 S	U_{sym} (COO-)
	1271	1393 8	V _{sym} (COO)
1011	13/1 m	1309 W	O_{sym} (CH ₃)
1311 W	1000	1304 sh	v pyridine (CC)
	1299 s	1289 w	ω (CH ₂)
		1278 m	ω (CH ₂)
	1243 m	1229 m	tw (CH_2)
1219 m		1219 w	v pyridine (CC)
1148 w		1151 m	$\rho_{asv}(NH_2)$
1122 m		1119 m	C-CONH ₂ amide
1087 w		1077 w	δ pyridine (CH)
	1087 w	1077 w	ν (CC _a)
	1072 s	1066 s	γ (CH ₂)
1065 m	1072 5	1066 s	δ CCC ring
1005 111	1015 w	1000 s	
	1015 W	1009 w	γ (CII ₃)
004	998 W	1000 sn	V(CC)
994 m	000	1029 m	ring breatning pyridine
	893 s	884 W	$v(C_{\alpha}CO)$
852 s		861 m	breathing pyridine
	811 s	809 s	$\gamma (C_{\alpha}H_2)$
795 m			out of plane pyridine (CH)
776 m			ring breathing pyridine(CC)
754 m		764 w	out of plane ring deformation
	754 m	764 w	γ (CH ₂)
721 m			out of plane ring deformation
	699 w		δ (COO-)
668 m	077 W		$\delta ring (CCC)$
000 111	665 m		$\frac{1}{8} (COO-)$
	003 111		0(000)

FTIR spectra of the adducts obtained by SAS (in ethanol at 313 K, 10 MPa and a 1:2 molar ratio of $Cu(C_3)_2$ to INA) and slow evaporation are nearly identical as can be expected from the PXRD patterns. Nevertheless, SAS spectrum shows a broadening of the absorption bands at 1460 and 1393 cm⁻¹ and two new peaks at 1321 and 839 cm⁻¹ (none of them present in the FTIR spectra of pure INA or $Cu(C_3)_2$ which suggest the presence of impurities in the SAS precipitate.



Figure 5. FTIR spectra: a) adduct obtained by slow evaporation; b) adduct obtained by SAS using ethanol at 313 K, 10 MPa and a 1:2 molar ratio of $Cu(C_3)_2$ to INA; c) $Cu(C_3)_2$; d) INA.

3.2. Thermal behavior. DSC and TGA experiments were carried out to study the thermal behavior of the adducts obtained by SAS and slow evaporation.

Thermal analysis by DSC of the adduct obtained by evaporation after cooling at 10 K/min is shown in Figure 6. DSC shows in the first heating a phase transition at 235.7 K associated to the conversion of structure II obtained from SCXRD at 100 K to structure I obtained at 320 K. Furthermore, a small change in the heat capacity of the sample at

219.7 K was also observed. This change could be related to the rotation of the pyridine rings in the adduct. Isostructural phase transitions are common in mixed ligand complexes or in coordination polymers.^{64, 65} In fact, small changes in the coordination environment can affect drastically some of the properties of these materials, such as those related to the magnetic and electrical properties of transition metals.

In contrast, no phase transition was detected at low temperature in the sample prepared by SAS, which could be possibly related to the much smaller particle size of this sample. The reduction of the phase transition temperature with particle size and film thickness has been previously reported.^{66, 67}



Figure 6. DSC of the adduct obtained by slow evaporation. Sample was cooled down from room temperature at 10 K/min up to 183 K and then heated at 10 K/min up to 360 K.

Thermogravimetric data of the adducts prepared by evaporation and SAS are given in Figure 7. The adduct obtained by slow evaporation had an onset temperature on melting of 482 K. The enthalpy of fusion could not be determined using DSC because there is a mass loss associated to the fusion process (see Figure 7a) indicating a decomposition, possibly due to an incongruent fusion and the presence of a peritectic

point in the binary $Cu(C_3)_2$ -INA phase diagram, breaking the coordination and liberating the two components, INA and copper(II). The INA thus sublimed/evaporated producing the observed loss of mass. This melting temperature was intermediate between the sublimation/evaporation temperature of commercial INA (429 K), and the decomposition temperature reported for $Cu(C_3)_2$ (503 K).⁷ On the other hand, the adduct obtained via SAS in ethanol at 313 K and 10 MPa with a molar ratio 1:2 $Cu(C_3)_2$ to INA had a more complex thermal behavior. It firstly showed an endothermic event with onset at 394 K followed by an exothermic event. This endo-exo event had associated a loss of mass of ca. 25% (measured using TGA).



Figure 7. Thermal analysis data: a) TGA and DSC (5 K/min) of the adduct obtained by slow evaporation; b) TGA and DSC (5 K/min) of the adduct obtained by SAS in ethanol at 313 K, 10 MPa and a 1:2 molar ratio $Cu(C_3)_2$ to INA ; c) TGA (10 K/min) and mass spectroscopy results for 44 m/z (red), 77 m/z (green) and 104 m/z (blue) of the adduct obtained by slow evaporation; d) TGA (10 K/min) and mass spectroscopy results for 44 m/z (red), 77 m/z (green) and 104 m/z (blue) of the adduct adduct obtained by SAS in ethanol at 313 K, 10 MPa and a 1:2 molar ratio $Cu(C_3)_2$ to INA.

Decomposition behavior in N2 of the crystals prepared by slow evaporation was studied using mass spectrometry. Short after melting (429 K) commercial INA sublimed/evaporated and mass loss could be observed in the TGA. In the adduct, however, INA was stabilized and there was no mass loss until the melting temperature of the adduct was reached at 482K. INA evaporated at this temperature and the characteristic mass to charge ratios (m/z) of the INA at 77 m/z and 104 m/z could be clearly observed along with other decomposition molecules suggesting the liberation of INA from the adduct and the same pyrolysis mechanism for the $Cu(C_3)_2$ as suggested elsewhere.¹³ The mechanism involved a self-redox reaction with the formation of metallic copper and radicals of the carboxylic acid, that break into CO2 gas and fragments of alkyl chains when heated. The decomposition behavior of the adduct obtained by SAS showed the formation of mainly CO₂ as mass loss starts. Although the release of INA starts at 429 K (sublimation of INA), the highest concentration of INA was reached after the 482 K (melting onset of the adduct), suggesting that most of the INA in the SAS precipitate was in the adduct structure. The different thermal behavior of the sample prepared by SAS seems to be related to the much smaller particle size which seems to prompt adduct decomposition at a much lower temperature. Similar finding have been previously reported.68

Micro-elemental analysis of the SAS samples are given as supplementary material (Table S2). Whilst a 4.5 C:N molar ratio was obtained in the adduct prepared by evaporation, slightly smaller ratios close to 4 were obtained in the samples precipitated by SAS. The lower carbon content suggests partial decomposition of the sample. Additionally the SAS experiment performed at a 1:1 molar ratio of $Cu(C_3)_2$ to INA (with large $Cu(C_3)_2$ excess) also yielded the same C:N ratio.

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All these data suggest that the samples obtained by both techniques have the same crystal structure but, in the compound processed by SAS, the adduct may be mixed with other non-crystalline phase(s). DSC and TGA analysis point in the same direction indicating the presence of more than one compound in the precipitate obtained by SAS. The thermal behavior of $Cu(C_3)_2$ processed by SAS also showed that decomposition and mass loss started much earlier than expected. In this case, micro-elemental analysis showed that the carbon content of the $Cu(C_3)_2$ sample processed by SAS was also lower than the theoretical one. The partial decomposition of the alkyl chain in $Cu(C_3)_2$ during the SAS process yielding Cu or CuO nanoparticles cannot be ruled out. The very small size of these nanoparticles would make very difficult their detection. We are currently studying the preparation of Cu nanoparticles from the pyrolysis of other copper alkanoates. Experimental data seems to indicate that the SAS process leads to a mixture of phases where the adduct is the major component.

4. CONCLUSION

The preparation of a mixed-ligand complex or adduct with $Cu(C_3)_2$ and isonicotinamide has been carried out by two very different synthetic routes: a conventional one (slow evaporation) and a novel one which involves the use of supercritical CO₂ as an antisolvent. By slow solvent evaporation large crystals were prepared, whilst the SAS method rendered nanocrystals of the same adduct and noncrystalline impurities, as seen by the different characterization techniques.

The complex was thoroughly characterized by SCXRD, PXRD, DSC, TGA, microanalysis and FTIR. The structure, solved by XRD, shows that the molecules of INA in this mixed ligand copper complex, coordinating the metal centers, act like capping agents breaking the *catenae*, typical from copper (II) carboxylates. On the other hand, the amide groups of INA form a net of H-bonds between the isolated binuclear complexes.

DSC and TGA data show the stability of INA in the adduct at temperatures up to 482 K. Mass spectroscopy indicates the sublimation and decomposition of INA around this temperature.

Finally, the use of SAS appears as a suitable method to synthesize mixed-ligand complexes or adducts. Furthermore, these materials are solvent-free precipitates obtained through a single-step process. The reduction in the particle size that would lead to an enhanced bioavailability of the adduct and the semicontinuos nature of the process are clear advantages of the SAS method in comparison to other more conventional methods. The reduction in particle seems to shift the phase diagram to lower temperature and leads to a much lower decomposition temperature. Further purification strategies should be implemented in order to remove the impurities of the SAS product. Our work opens up the path to the study of similar metal adducts using the SAS technique.

ASSOCIATED CONTENT

Supporting Information. Crystallographic information files (cif) of Cu₂(C3)₄INA₄: CCDC-1846632 (at 100 K), and CCDC-1846633, at 320 K, solved by SCXRD, and CCDC-1848049 (at 298 K) solved by PXRD.

In the Supporting information file: *1)* PXRD patterns of the samples precipitated by SAS at the different conditions (Figure S1). *2)* High Resolution Powder Diffraction (HRPD) and Rietveld refinements (Figure S2); *3)* Experimental parameters and structure refinement data from PXRD for the adducts obtained by slow evaporation and SAS (Table S1). *4)* SEM images of the sample prepared by SAS at 313 K and 10 MPa using methanol as a solvent (Figure S3). *5)* Microelemental analysis of the samples prepared by evaporation and SAS at the different conditions (Table S2). This information is available free of charge via the Internet at http://pubs.acs.org/.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Production and Characterization of a new Copper(II) Propanoate-Isonicotinamide Adduct obtained via Slow Evaporation and using Supercritical CO₂ as an Antisolvent

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TOC graphic



TOC SYNOPSIS

A new adduct of isonicotinamide (INA) with copper (II) propanoate $[Cu(C_3)_2]$ was prepared $[Cu_2(C_3)_4(INA)_4]$ using two different methods: solvent evaporation from ethanol and micronization from the ethanol solution using supercritical CO₂ as antisolvent (SAS). Solvent evaporation rendered crystals suitable for single crystal X-ray diffraction while SAS gave nanocrystals with improved bioavailability in a semicontinuous process.