SYNTHESIS OF SCHIFF BASE MACROCYCLES UNDER SUPERCRITICAL CO_2 CONDITIONS

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Over the past few years, the research carried out on the synthesis of chiral imine macrocycles has become of growing interest, since these Schiff based symmetric macrocyclic compounds offer an enormous potential in host–guest chemistry and molecular recognition. In traditional chemistry, the preparation of large polyimine meta- and para-macrocycles (shown in the figure below), was successfully achieved using a classic synthetic strategy consisting of a [3+3] cyclocondensation reaction between three units of (1*R*,2*R*)-diaminocyclohexane with three units of an aromatic dialdehyde, either 1,3- or 1,4-diformylbenzene in a standard 0.4 M concentration in dichloromethane (DCM). Here, we present a new methodology for the preparation of these enantiomerically pure imine macrocycles in supercritical CO_2 ($scCO_2$), where $scCO_2$ acts as both solvent and acid catalyst. In this work it was demonstrated that imine bonds can be formed in $scCO_2$ overcoming the reaction between the amine group and the CO_2. This approach opens a new window in the field of imine chemistry preparation under this environment. The use of $scCO_2$ for the preparation of macromolecules as supramolecular hosts presents an additional benefit since in traditional chemistry, organic residual solvents can get entrapped inside the macrocyclic cavity, which can impede the entrance of a potential guest. The use of $scCO_2$ technology appears very promising since the solvent CO_2 gets released after depressurization, leaving the inner macrocyclic cavities unfilled, and thus avoiding the solvent/guest competition for the active sites of the host.

Key words: supramolecular chemistry, amines, macrocycles

INTRODUCTION

Supramolecular chemistry results from the association through intermolecular interaction between two or more molecular species. Intermolecular interactions are the responsible of numerous processes, such as molecular recognition, enzymatic reactions, antigen-antibody, etc [1]. Based in this processes, it is possible to design and construct molecules able to imitate biological processes and even generate new forms of molecular recognition. In order to mimic nature, supramolecular chemists have developed systems where artificial macrocyclic receptors, or “hosts”, are capable of binding strongly and selectively to a substrate, or “guest”, to form “host-guest complexes”. Most of the advances in supramolecular chemistry have been driven by the increased availability of suitable macrocyclic receptors, thus, there have been developed hundreds of macrocycle molecules (crown ethers, porfirines, clalixarenes, cyclodextrines, etc) [2] characterised by their intricate structures resulting from multi-step reactions to simple synthetic procedures.

Regarding the macrocyclic synthetic procedure, there have been established different strategies. For example, in template synthesis, where mainly metals are used as pattern, the size of the macromolecule can be controlled by the size of the metal as well as by the co-ordination geometry that the ions can adopt upon complexation [3]. Another well known approach is called high dilution, which requires, as a general rule, a 1:1 molar concentration of each building block that composes the macrocycle [4]. Here, the higher the concentration of the reactants is, the more likely it is for them to undergo polymerisation, whereas the more diluted, intramolecular condensation is more probable.

One more factor to take into account in supramolecular chemistry is the solvent effect, which is of extreme importance, since a very effective host-guest interaction in one solvent may fail in another [5]. Therefore, the solvent can have a large effect on stability, and can decrease or increase the number of binding sites. On the other hand, the use of solvents can dramatically decrease the interaction with the guest due to the competition of the solvent and guest for the binding sites. Moreover, the solvent used in the synthesis and/or purification of the macrocycle, can get entrapped inside the cavity after isolation, impeding thus the incorporation of the potential guest into the molecule hollow.

Among all the different macrocycles synthesised, a particular example is the research carried out on the synthesis of chiral imine macrocycles that has become of growing interest, since these Schiff based symmetric macrocyclic compounds offer an enormous potential in host–guest chemistry and molecular recognition [6]. Examples of poly-aza-ciclophanes started by Gawronski *et al.* [7], and deeply studied by Kuhnert *et al.* [8-10], are the large polyimine meta- and para-macrocycles, also called trianglimines, that have been successfully achieved using a classic synthetic strategy based on a [3+3] cyclocondensation, where 3 units of (1*R*,2*R*)-diaminocyclohexane reacts with 3 units of an aromatic dialdehyde in dichloromethane (DCM). The preparation of these macrocyles required the use of organic solvents during their synthesis and, in most cases, also in the purification step, which difficult the design of sustainable synthetic routes.

Technology based on $scCO_2$ has been established as an alternative to overcome some of the problems associated with the use of traditional organic solvents, since it has been proven as an environmentally benign medium for the substitution of organic solvents in processes related with preparative chemistry and materials modification. The main objective of this work is to research on the possibilities of using $scCO_2$ as a green solvent for the preparation of triangliminie Schiff base macrocycles. The solvating properties of this fluid can be continuously varied from gas-like to liquid-like values with small changes in the pressure and/or temperature, which can be used to control the thermodynamics of the process. Moreover, the fact that $scCO_2$ is an aprotic solvent is also an advantage in the studied process, because it can not protonate the amine and there are not labile protons interfering in the reaction.

MATERIALS AND METHODS

Materials

(1*R*, 2*R*)- Diaminociclohexane (3) was obtained from the reaction between the racemic mixture (1*RS*, 2*RS*)-diaminociclohexane (1) and L-(+)-tartaric acid (2) (Fig. 1), both purchased from Aldrich following a procedure described elsewhere [11]. 1,3- and 1,4-

diformylbenzene (2 and 3 respectively), were purchased form Fluka. CO_2 (99.995 %) was supplied by Carburos Metálicos S.A., Air Products Group (Spain).

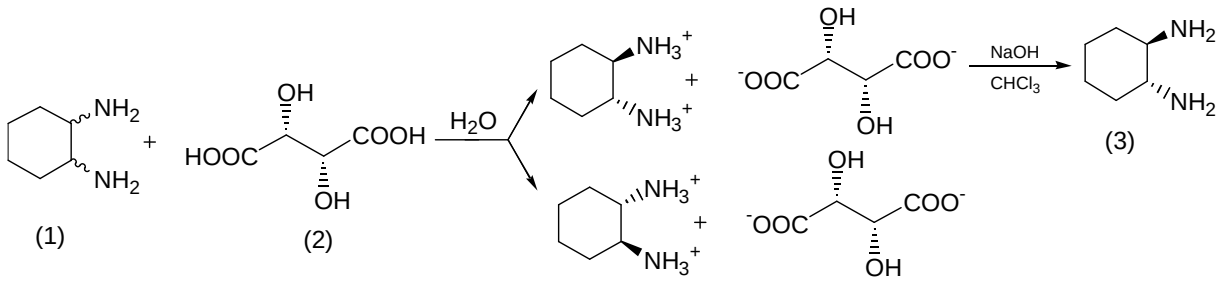

Figure 1: Reaction scheme for the synthesis of (1*R*, 2*R*)-diaminociclohexane [11].

Methods

Cyclocondensation under supercritical conditions was performed using a high pressure autoclave described in Fig. 2. Typically, a 100 mL high-pressure autoclave was charged with 500 mg (4.4 mmol) of (1*R*,2*R*)-diaminocyclohexane and 587 mg (4.4 mmol) of the aromatic dialdehyde, which were placed at the bottom. Compressed CO_2 was then added to the reactor already heated at the working temperature. The system was stirred at 300 rpm during the complete running time. At the end of each experiment, the system was depressurized and let to cool to room temperature. Samples were recovered as white powders.

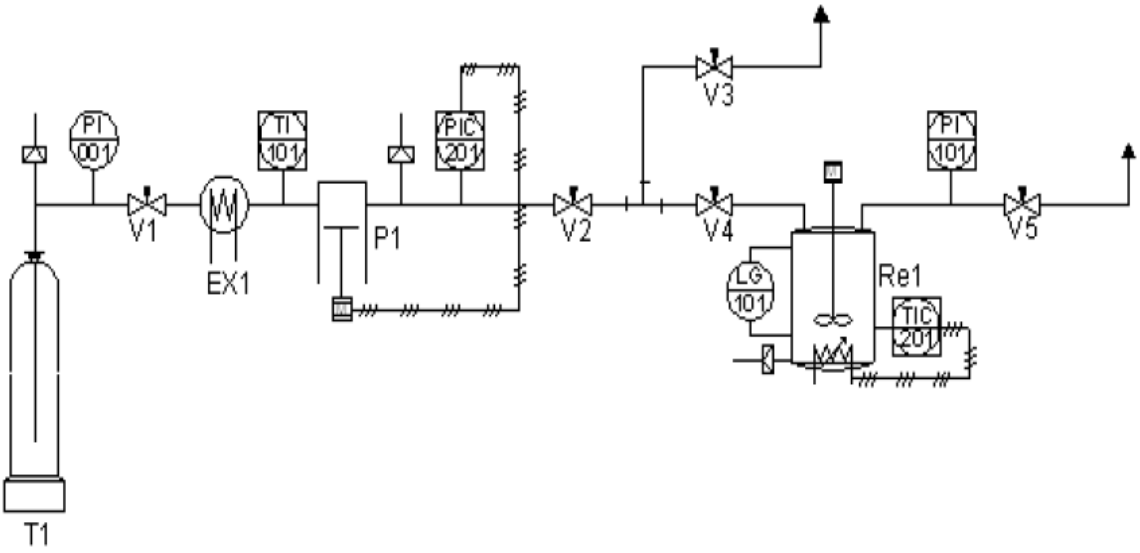

Figure 2: Schematic set-up of the high-pressure equipment where cooled CO_2 (EX1, Lauda Ecoline) is compressed by a syringe pump (P1, ISCO 260D). V1-V3 are valves used to regulate the flow of CO_2.

Characterization

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX 300 MHz spectrometer in deuterated chloroform ($CDCl_3$). δ values were quoted to tetramethylsilane (δ=0.00 ppm) or chloroform δ=7.28 for ^{1}H-NMR. ATR-FTIR spectra were recorded on a Perkin Elmer Spectrum One instrument. The mass spectra (MS) were recorded with a ThermoFinnigan TRACE DSQ.

RESULTS

In order to explore the influence of the chemistry between CO_2 and amines, and the formation of carbamate salts, preliminary experiments were carried out [12]. First, it was study the interaction between $scCO_2$ and the (1*R*,2*R*)-diaminocyclohexane (Fig. 3), since this reaction can slow down the rate of the intended reaction, or even impede it totally. Thus, (1*R*,2*R*)-diaminocyclohexane was treated in a $scCO_2$ atmosphere at 15-20 MPa and 35.5 ºC. The ^{1}H-NMR ($CDCl_3$) spectrum of the recovered sample, displayed only the signals of the diamine that remained unreacted. However, the ATR-FTIR spectrum of the solid sample (Fig. 4a), also showed weak bands corresponding to the amide group (N-C=O) at 1625-1510 cm^{-1}, indicating traces of carbamate ((4) in Fig. 3).

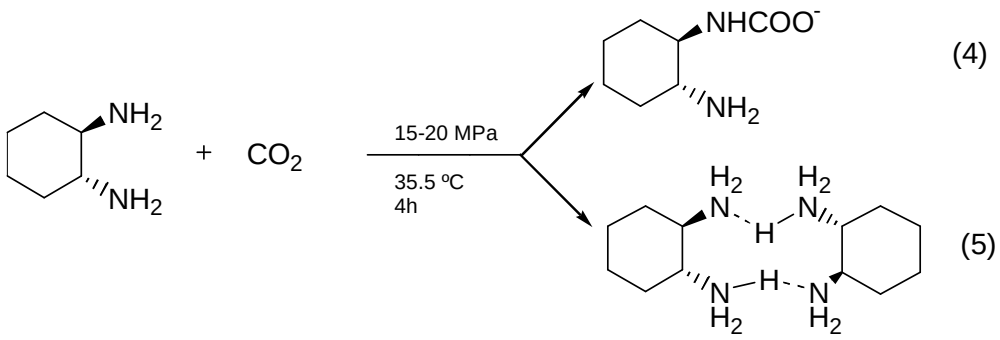

Figure 3: Reaction scheme of (1*R*,2*R*)-diaminocyclohexane with CO_2.

This finding was confirmed by the mass spectroscopy spectrum (Fig. 4(b)), although with a very low intensity. MS revealed the presence of unreacted (1*R*,2*R*)-diaminocyclohexane at *m*/*z* 115 $(M + H)^+$, and two additional minor peaks. The signal at 10% of intensity at *m*/*z* 229 $(M + H)^+$, was attributed to the formation of the diamine dimer (5 in Fig. 3) produced by short contact interactions. The carbamate formation was evidenced by a second minor peak (<5%) at *m*/*z* 157 (M^+).

Under used experimental conditions, the reaction between the amine group and the CO_2 did not occur with a high conversion, and most of the (1*R*,2*R*)-diaminocyclohexane remained unreacted. This lack of reactivity was attributed to the steric hindrance of the amine, since it has been proven that the introduction of a bulky substituent next to the amine group lowers the stability of the carbamate formation [13]. Next, we proceed with the preparation of the macrocycles. Fig. 5 shows the reaction scheme for the synthesis of macrocycle A. The reaction was carried out at a pressure and temperature of 20 MPa and 35.5 ºC, respectively, where the full [3+3]-cyclocondensation took place.

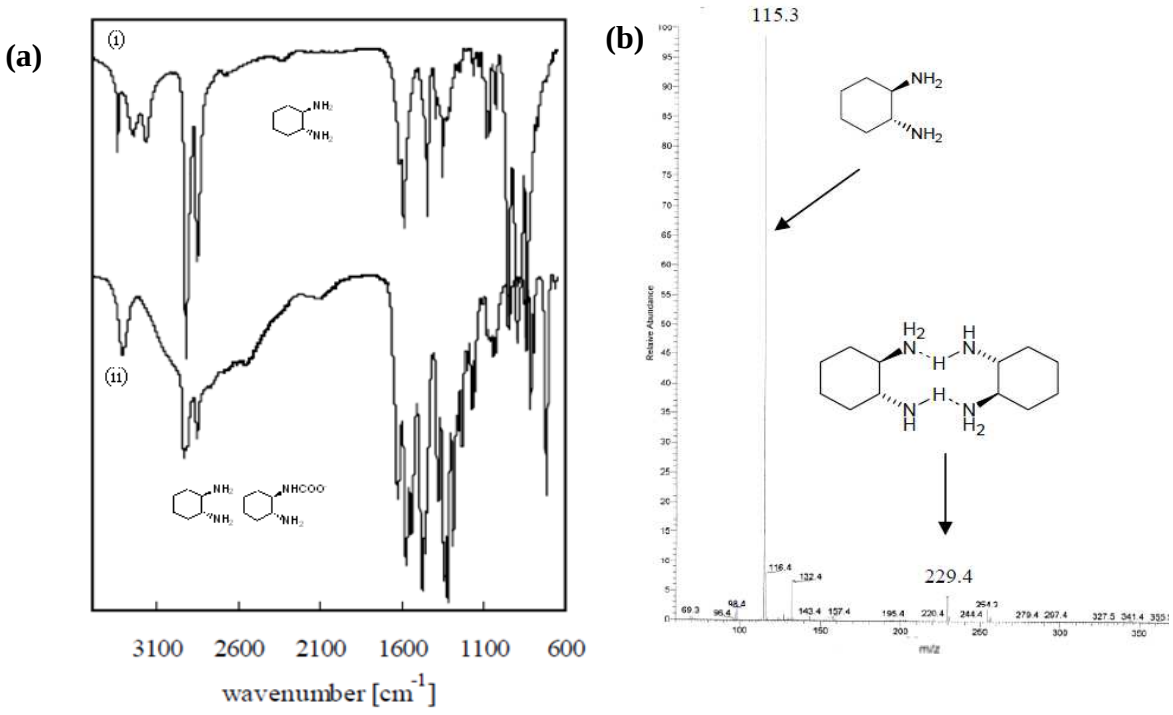

Figure 4: (a) ATR-FTIR spectrum of (i) (1*R*, 2*R*)-diaminocyclohexane and (ii) mixture of (1*R*, 2*R*)-diaminocyclohexane and carbamate; and (b) MS of the mixture of the diamine and the diamine dimer.

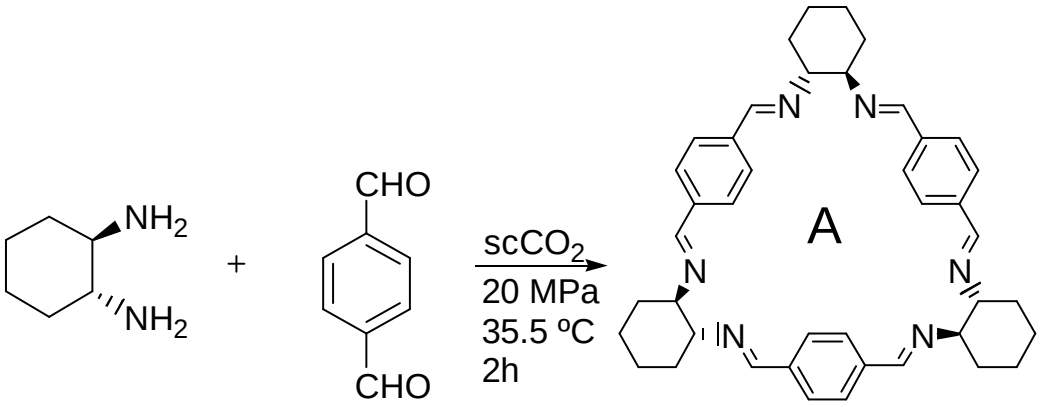

Figure 5: Reaction scheme for the synthesis of macrocycle A.

The high symmetry was observed by ^{1}H-NMR (Fig. 6a), where the spectra showed only one set of signals corresponding to one repeating unit. Thus, there was only one set of signals for the six imine protons at 8.14 ppm, one peak corresponding to the 12 aromatic protons at 7.52 ppm, a broad band at 3.36 ppm for the six protons adjacent to the nitrogens in the ciclohexane ring, and finally two broad bands for the remaining protons of the cyclohexane ring at 1.80 and 1.48 ppm. The ATR-FTIR spectrum (Fig. 6b) clearly indicated the formation of the bond C=N at 1635 cm^{-1}. Further, MS (not shown) revealed the formation of the molecular ion at m/z 637 (M+H) indicating the formation of the

trimeric structure $(C_{14}H_{16}N_2)_3$ [12].

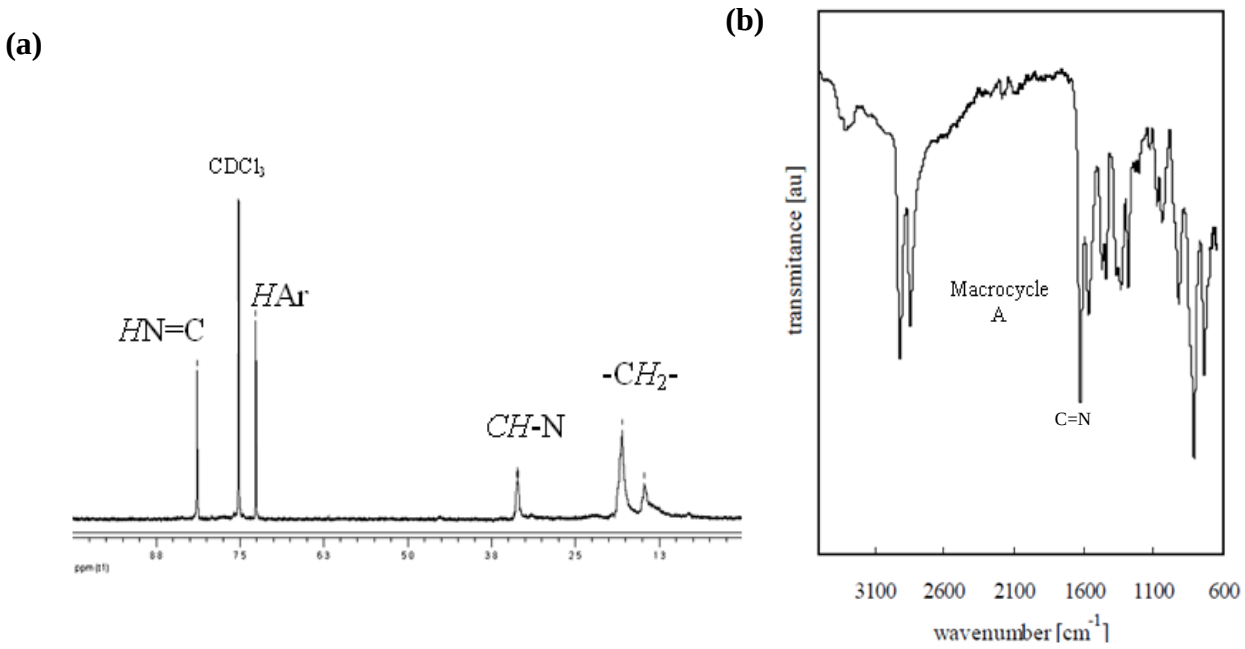

Figure 6: (a) ^{1}H-NMR spectrum of macrocycle A showing only one set of signals, and (b) ATR-FTIR spectrum of macrocycle A.

Following the same experimental conditions as used in the previous experiment, the reaction between (1*R*,2*R*)-diaminocyclohexane and 1,3-diformylbenzene was carried out, as shown in Fig. 7.

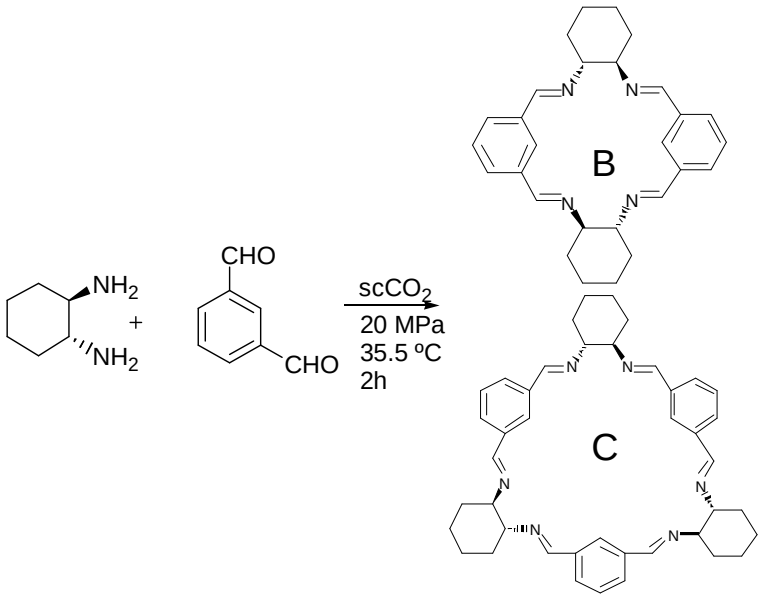

Figure 7: Reaction scheme for the synthesis of macrocycle B and C.

This reaction gave place to the mixture of [2+2] (macrocycle B) and [3+3]-cyclocondensation products (macrocycle C) in a 71:28 molar ratio estimated by ^{1}H-NMR

spectroscopy (not shown) and mass spectroscopy (Fig. 8). ATR-FTIR spectroscopy (not shown) [12] indicated the formation of the C=N bond at 1635 cm^{-1} as in the case of macrocycle A (Fig. 6b). In this case, the appearance of the dimer formed by the [2+2]-cyclocondensation as a major product indicated that thermodynamic control, where the intermediate proceeded via the less activated form, might be responsible of the reaction performed under $scCO_2$ conditions. Hence, the formation of the product with the lowest molecular weight (B), occurred in preference to the [3+3]-condensation product.

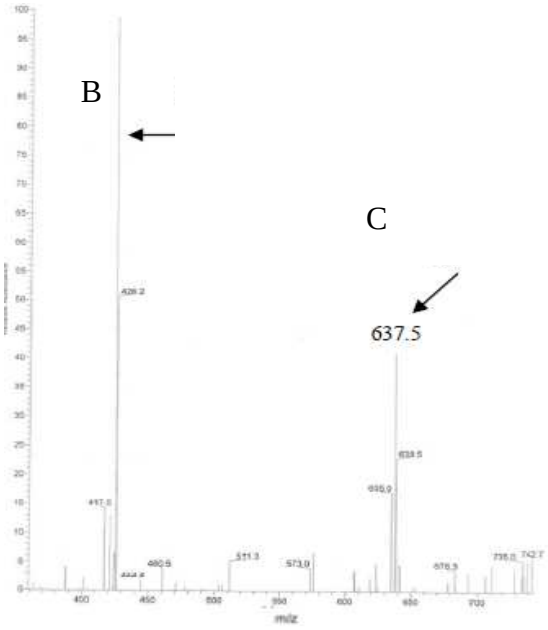

Figure 8: Mass spectrum of the mixtures of macrocycles B and C.

CONCLUSIONS

In this work, we achieved the synthesis of large polyimine macrocycles, with molecular weights ranging from 425 to 637 g/mol, using $scCO_2$ conditions. The designed supercritical route is not only a greener and safer method than the classical procedure, but also a one-stage process, allowing a sustainable use of resources. The synthesised Schiff bases had an empty core, not filled with solvent molecules, since the $scCO_2$ was eliminated as a gas during depressurization. Hence, the supercritically as-synthesized compounds are ready to participate in host-guest chemistry or to act as selective probe materials. These results open a new vision on the use of $scCO_2$ for the preparation of imine containing materials.

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