Towards the synthesis of Schiff base macrocycles under supercritical CO₂ conditions[†]

Ana M. López-Periago,* Carlos A. García-González and Concepción Domingo

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The synthesis of Schiff base macrocycles was achieved using supercritical CO_2 as both solvent and acid catalyst.

Over the past few years, the investigation of the synthesis of chiral imine macrocycles has become of growing interest.¹ These Schiff based symmetric macrocyclic compounds offer an enormous potential in host–guest chemistry and molecular recognition, besides their additional potential applications as ligands and organocatalysts in asymmetric synthesis.^{2–3} The preparation of large polyimine *meta-* and *para-*macrocycles, also called trianglimines, has been successfully achieved using a classic synthetic strategy based on a [3+3] cyclocondensation (Scheme 1),^{4–7} where 3 units of (1*R*,2*R*)-diaminocyclohexane (1a) react with 3 units of an aromatic dialdehyde, either 1,3-(2) or 1,4-diformylbenzene (3), in a standard 0.4 M concentration in dichloromethane (DCM), yielding species 4a or 5a, respectively.

The preparation of these macrocyles required the use of organic solvents during their synthesis and, in most cases, also in the purification step (ethyl acetate), which difficulted the design of sustainable synthetic routes.

Supercritical carbon dioxide (scCO₂) has been proved as an environmentally benign medium for the substitution of organic solvents in processes related with preparative chemistry⁸ and materials modification.9-11 In this work, we report on the possibilities of using scCO₂ as a green solvent for the preparation of Schiff base macrocycles following the classical reaction.⁴[‡] scCO₂ has a number of characteristics that are expected to facilitate the synthesis of these macrocycles. First, the solvating properties of this fluid can be continuously varied from gaslike to liquid-like values with small changes in the pressure and/or temperature, which can be used to control the thermodynamics and kinetics of the process. The additional degree of freedom related to the density of scCO₂, allows simultaneous control of the composition and the structure of the produced materials, and, thus, the design of one-stage processes. Moreover, the fact that $scCO_2$ is an aprotic solvent is also an advantage in the studied process, because it cannot protonate the amine and there are not labile protons interfering in the reaction. On the other hand, compressed CO₂ acts as a Lewis acid,¹² which favours the formation of the acid catalysed imine bond. It should be taken into account that

(1R,2R)-diaminocyclohexane is hygroscopic, and it is the adsorbed water that, when in contact with CO₂, produces the acid medium necessary for the catalysis.

As a major disadvantage of using the scCO₂ synthesis procedure, it must be mentioned that CO₂ can react directly with primary and secondary amines to produce carbamates through the formation of zwitterion intermediates.¹³ In an aqueous amine environment, as the one employed for CO₂ capture, the base that deprotonates the zwitterion can be another amine, H₂O or OH⁻. In dry conditions, the deprotonation occurs with another amine. In the studied process, this side reaction can slow down the rate of the intended reaction. Hence, before proceeding to the preparation of the studied compounds, we first examined the behaviour of the reagent 1a in a scCO₂ atmosphere at a pressure of 15-20 MPa and a temperature of 35.5 °C (Table 1, entry A). This preliminary test was performed to evaluate the extension of the possible reaction between the CO₂ and the amine under used experimental conditions.

The nuclear magnetic resonance (¹H-NMR) spectrum of the recovered sample after scCO₂ treatment of **1a** displayed only the signals of the diamine that remained unreacted (Fig. S1a, ESI†). However, the attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectrum of the solid sample showed, together with the bands of the diamine, the set of bands of the amide group (N–C=O) at 1625–1510 cm⁻¹



Scheme 1 Cyclocondensation reaction and structure of polyimine *para*- (4a) and *meta*- (5a) macrocycles

Instituto de Ciencia de Materiales de Barcelona (ICMAB-CSIC), Campus de la UAB s/n, Bellaterra, Spain.

E-mail: amlopez@icmab.es; Fax: +34935805729;

Tel: + 34935801853

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Entry	Reaction Conditions	Product		¹ H- and ¹³ C-NMR in CDCl ₃ (δ ppm)	ATR-FTIR (ν/cm^{-1})	MS m/z CI
A	P = 15-20 MPa T = 35.5 °C t = 4 h	NHCOO ⁻	1b	¹ H: 2.22 d (2H) 1.81 d (2H) 1.66 d (2H) 1.18 m (4H)	1625–1510 N–C==O	$\begin{array}{l} \textbf{1a } 115 \ (M \ + \ H)^+ \\ (100\%) \\ \textbf{1b } 157 \ (M^+) \ (<5\%) \\ \textbf{1c } 229 \ (M \ + \ H)^+ \\ (10\%) \end{array}$
1a in scCO ₂		H ₂ H N. H N.			3300 NH ₂ 2900–2800 CH	2
			lc		cyclohexane	
B(i)	P = 15 MPa T = 35.5 °C	Nuin		¹ H: 8.14 s (1H,N=CH) 7.53 s (2H,Ar) 3.76 b (2H,CH-N)	1638 C==N	4b 327 (M + H) ⁺ (55%)
1a + 2 in scCO ₂	t = 1.5 h	N' NH ₂	4b	1.59 b (10H,CH ₂)		
B(ii)				¹ H: 8.14 s (6H,N=CH)	1641 C=N	4a 637 (M + H) ⁺ (100%)
1a + 2 in scCO ₂	$P = 20 \text{ MPa}$ $T = 35.5 \degree \text{C}$ $t = 2 \text{ h}$	Macrocycle 4a		7.52 s (12H,Ar) 3.36 b (6H,CH–N) 1.80 b (18H,–CH ₂ –) 1.48 b (6H,–CH ₂ –) ¹³ C: 160.1, 137.7, 128.0, 74.4, 32.7, 24.4		(10070)
С		Macrocycle 5a &		¹ H: 8.18 s (6H,N=CH)	1645 C=N	5a 637 $(M + H)^+$ (45%)
1a + 3 in scCO ₂	P = 20 MPa		7.91 s (3H,Ar) 7.52 b (6H,Ar) 7.26 b (3H,Ar) 3.38 b (6H,CH–N) 1.70 b (30H,–CH ₂ –) ¹ H: 8.31 s (4H,N=CH) 7.98 b (2H,Ar) 7.53 b (4H,Ar) 7.27 b (2H,Ar) 3.40 b (4H,CH–N) 1.70 b (16H,–CH ₂ –)	7.91 s (3H,Ar)		5b 425 $(M + H)^+$ (100%)
	T = 35.5 °C $t = 2 h$					

 Table 1
 Experimental conditions: pressure (P), temperature (T) and time (t); and characterization of prepared compounds

(Fig. S2a, ESI[†]) that indicated the formation of carbamate (**1b**). Moreover, the intensity of the peaks at 800–925 cm⁻¹, attributed to the wagging and twisting of the $-NH_2$ group in the specie **1a**, was considerably reduced in the obtained sample. Mass spectrometry (MS) analysis (Fig. S3a, ESI[†]) revealed the presence of unreacted diamine at m/z 115 (M + H)⁺, and two extra minor peaks that were used two quantified the produced reactions. The first minor peak with a 10% of intensity at m/z 229 (M + H)⁺, was attributed to the formation of the diamine dimer (**1c**) produced by short contact interactions.¹⁴ Carbamate formation was evidenced by a second minor peak (<5%) at m/z 157 (M⁺). Hence, under used experimental conditions, the reaction between the amine group and the CO₂ did not occurred with a high conversion. The used amine is defined as an sterically hindered amine, since the primary

amine group is attached to a tertiary carbon atom. It has been shown that introducing steric hindrance by a bulky substituent adjacent to the amino group lowers the stability of the carbamate formed by CO_2 -amine reaction.¹⁵

Next, reagents **1a** and **2** were reacted under scCO₂ at two different conditions (Table 1, entry B(i) and (ii)). At 15 MPa and 35.5 °C (conditions B(i)), the obtained reaction product was mainly compound **4b**, and not the expected [3+3]-cyclo-condensation product **4a**, as demonstrated by ¹H-NMR (Table 1), ATR-FTIR (Table 1) and MS (Fig. S3b, ESI†) characterization. The isolated product **4b** was an intermediate of the trianglimine **4a**, in which the two $-NH_2$ groups activated the molecule towards an intermediate compound is in good agreement with the computational mechanism

proposed for trianglimine macrocycle formation operating under kinetic control and having the transition state with the lowest energy.⁴ Likely, the solvent power of scCO₂ at the working conditions was not sufficient to allow the complete macrocyclation. Hence, in a further trial, both the system pressure and the reaction time were raised up to 20 MPa and 2 h, respectively (Table 1, entry B(ii)). Under those experimental conditions, [3+3]-cyclocondensation took place and the highly symmetric (D3h) macrocycle 4a was formed with a high yield. The isolated 4a specie was analyzed by both ¹H- (Fig. S1b, ESI[†]) and ¹³C-NMR (Fig. S1c, ESI[†]) spectroscopies, showing the set of signals corresponding to the 4a repeating unit, as quoted by Gawronski et al.⁴ The ATR-FTIR spectrum indicated the formation of the bond $C=N^4$ with a band at ca. 1641 cm⁻¹ (Fig. S2b, ESI[†]). Further, MS analysis (Fig. S3c, ESI[†]) revealed the formation of the molecular ion at m/z 637 (M + H)⁺, indicating the presence of the trimeric structure ($(C_{14}H_{16}N_2)_3$) of the 4a macrocycle

The major divergence with the data published in the literature in regard of the characteristics of the prepared macrocycle was related with the solubility of the precipitated compound. The 4a trianglimine synthesized by the classical route has been described to be very soluble in chloroform, ethyl acetate or even methanol.⁴ However, the macrocyle synthesised following the scCO₂ method was highly insoluble in those organic solvents. This difference in solubility was thought to be caused by the effect of the solvent used in the reaction. Solubility is very dependent on crystal structure and habit, which are influenced by the used solvent.^{16–17} Hence, using scCO₂ instead of and organic solvent could give place to a different crystal structure or crystal habit. Indeed, the crystal structure of specie 4a reported in the literature showed the inclusion of ethyl acetate within the macrocyclic cavity, which could be responsible for the fast dissolution of the trianglimine in organic solvents.4

Finally, the reaction between **1a** and **3** (Table 1, entry C) performed under $scCO_2$ at 20 MPa and 35.5 °C gave a mixture of [3+3]- (compound **5a** with symmetry C3) and [2+2]-(compound **5b**) cyclocondensation products in a *ca.* 28:71 molar ratio estimated by ¹H-NMR spectroscopy and MS (Fig. S3d, ESI†). ATR-FTIR spectroscopy indicated the formation of the C=N bond at *ca.* 1645 cm⁻¹ (Fig. S2c, ESI†). In this case, the appearance of **5b** formed by [2+2]-cyclocondensation as a major product indicated that the thermodynamic control, where the formation of the intermediate proceed *via* the less activated form, might be responsible of the reaction performed under scCO₂ conditions. Hence, the precipitation of the compound with the lowest molecular weight **5b**, occurred in preference to the [3+3]-condensation product **5a**.

To conclude, in this work it was proven that large polyimine macrocycles, with molecular weights ranging from 425 to 637 gmol⁻¹, were formed under $scCO_2$ conditions in the absence or organic solvents. The designed supercritical route

is not only a greener and safer method than the classical procedure, but also a one-stage process that would lead to high yield values, thus, allowing a sustainable use of resources. The synthesized 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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Notes and References

‡ Experimental procedure: Cyclocondensation reaction under supercritical conditions was performed using a high pressure apparatus described elsewhere.¹⁸ Typically, a 100 mL autoclave was charged with 500 mg (4.4 mmol) of **1a** and 587 mg (4.4 mmol) of the aromatic dialdehyde (either **2** or **3**). Compressed CO₂ was then added to the reactor already heated at the working temperature. The system was stirred at 300 rpm. At the end of each experiment, the system was depressurized and let to cool down to room temperature before sample collection.

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