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Chemical sensors based on new polyamides bio-based on (Z) octadec-9-enedioic acid and β-cyclodextrin[a]

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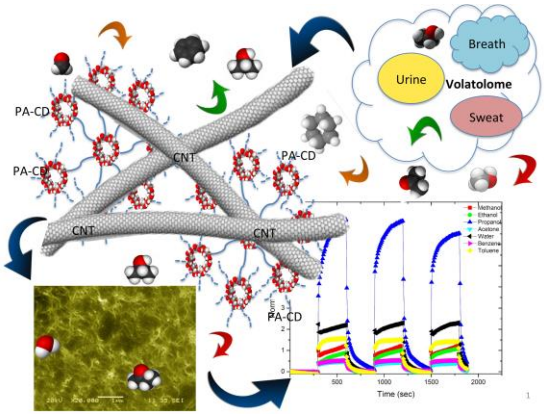
The synthesis of new biobased polyamides from different β-cyclodextrin monomers and the (Z) octadec-9-enedioic acid is investigated. The aim of this study is to design different sensors, having different sensibilities and selectivities to a set of various volatile organic compounds (VOC) relevant in the early detection of lung cancer. The sensors are obtained from the synthesized polyamides, using multi walled carbon nanotubes as conductive nanofillers and a layer by layer process. The Conductive Polymer nanoComposites (CPC) designed from the heptakis-6-amino β-cyclodextrin and 6^A,6^D diamino β-cyclodextrin have a high affinity for polar

[a] **Supporting Information** is available online from the Wiley Online Library or from the author.

protic solvents, while the CPC having a matrix based on 6^{A},6^{D} diamino 2^{A-G},3^{A-G},6^{B},6^{C},6^{E},6^{F},6^{G} nonadeca-O-benzyl-β-cyclodextrin develops hydrophobic interactions with non-polar solvents. Due to a higher accessibility of cyclodextrin, the chemo-resistive response of the hydrophilic linear polyamide CPC is larger than one of the hydrophilic branched polyamide CPC. As required, the VOC diffusion/desorption phenomenon is reversible for all the sensors.



1. Introduction

The planned depletion of fossil resources and environmental issues urge researchers to find alternatives to replace petroleum based fuel, chemicals and organic materials. Biomass has been suggested as the alternative solution[1-10]. In particular, vegetable oils have been extensively studied for the production of green materials[5,9]. However, the competition with human feeding as well as economic and environmental aspects have to be considered to guarantee the feasibility of conventional plastics being replaced by bioplastics[3,10,11]. The fossil-based polymer industry is a mature market, which limits the growing bioplastic industry due to the required cost-effectiveness of bio-based chemicals. However, if high value applications are considered, the polymer price is no longer the main selection criterion. In a prospective report concerning the

industrial material development for the 21rd century, Wirth[12] highlighted the need for new specialized performance polymers which address not only the cost, but also environmental issues and innovative gain. The field of specialized polymers from renewable resources is at its early beginning, witnessed by the few launched industrial applications[13]. The drug delivery applications have also drawn large interest thanks to the biodegradability of some polymers issued from biomass[14,15]. Polymers from renewable resources have also been used to prepare shape memory materials and to improve performances of foams, coating and adhesives[9], thanks to the dispersion of nanoparticles allowing the design of new materials with new properties. Furthermore, biopolymers nanocomposites have recently been used for the design of new artificial nose (e-nose)[16,17]. Indeed, the metabolomics analysis of patient versus healthy person was suggested to provide an anticipated diagnosis of various diseases, in particular cancers[18-24]. Therefore, the volatile organic compounds (VOC) from breath, urine, skin, saliva, nasal mucus, called the volatolome[25], could witness the human health condition[26-28]. For the exhaled breath, several hundreds of VOC have to be discriminated and detected from the ppm to the ppb level[26,27]. The VOC detection also suffers from a high water concentration (more 80%) making the diagnostic difficult. VOC are commonly analyzed by GC-MS, IR, flow tube MS and optical spectroscopy, however, various drawbacks such as a high cost, low portability and low sensitivity have been reported[29]. On the other hand, e-noses were presented as a non-invasive, quick and portable technique and offering the option of a time recording. This technology provides the opportunity of large-scale patients monitoring, a useful advantage for the early detection of diseases. Among the various e-nose designs, Quantum Resistive Sensors (QRS) offer numerous advantages such as possible use at room temperature, poor water sensitivity [30], improved sensitivity and selectivity[29]. They are obtained by the structuring of conductive nanofillers, such as carbon nanotubes or graphene sheets[29,31,32], embedded in an insulating polymer matrix. The

polymer subjected to VOC modifies the junction gap of the percolated nanofillers, playing thus the role of a transducer, whose selectivity is adjusted by the chemical nature of the polymer matrix. The large amount of VOC to detect in order to build a patient fingerprint requires the design of a miniaturized array composed of an assembly of various transducers, different by their polymer chemical nature. Pattern recognition algorithms have to be used for discrimination of a cancerous patient among a healthy population. Most of synthetic polymers-based transducers suffer from a low selectivity due to the hydrophobic matrix. Except for some papers[30,33,34], polar VOC are poorly detected with existing QRS, suggesting the need for a polymer library that covers the entire range of polarity of VOC to be detected.

Biomass offers a large diversity of synthons allowing the design of polymers spreading the whole range of required polarity of exhaled VOC. The saccharide family provides numerous hydrophilic derivatives, while hydrophobicity can be ensured by oil-based derivatives, such as the (Z) octadec-9-enedioic acid (D18:1). This natural unsaturated fatty diacid is produced by a fungus fermentation of the oleic acid[35]. Cyclodextrins (CDs), compounds derived from starch, are cyclic oligosaccharides and possess a very specific structure (truncated conical shape) that creates a hydrophobic interior and hydrophilic exterior[36,37]. Their internal cavity is able to accommodate one or two guest molecules depending on size and chemical structure of the CD[38-40]; these characteristics make CD an ultimate candidate for smart material, when incorporated in matrix of conductive polymer composites[41]. During the past decades, CDs have successfully been used as drug carriers to improve solubility, chemical stability, dissolution and bioavailability or decrease unfavourable side-effects of drugs. Thus, these host molecules found vast applications as artificial enzymes, drug carriers, nanopores, catalyst, chemo-sensors, to name but a few[29,42-46]...

Most of CD-based polymers are star polymers with a CD core[47-50] or linear polymer with dangling CD grafted on a macromolecular backbone[51-53]. However, these strategies involved

monomers from fossil resources. To fulfil the bioplastic requirements for an e-nose application, new design of polymers must be provided. The A2+B2 polycondensation with CD monomers is an obvious solution to access to CD-based polymers from renewable resources only. However, the high number of hydroxyl functions of the CDs makes their selective modification to provide a difunctional CD that could react with a co-monomer potentially very tedious. However, one of us developed a strategy allowing the differentiation of up to six functions located on the C6 carbons of the CD [54,55]. It is hence possible to synthesize a CD with two diametrically opposed functions through the deprotection of a fully benzyl-protected β-CD using diisobutylaluminium hydride (DIBAL-H). This reaction affords a 6^A,6^D-diol in high yields, [54,55] allowing the design of new difunctional CDs useful for polycondensation.

The aim of this work is to develop new matrixes of fully bio-based polymers for quantum resistive sensors, using multi walled carbon nanotubes as conductive nanofillers. These nanocomposites are then expected to have an electrical response upon the application of a voltage. The incorporation of CD units in the polymer forming the matrix of a Conductive Polymer nanoComposite (CPC) will provide specific interactions with VOC of various polarity, thanks to the free hydrophobic cavity and the large number of hydroxyl functions of the CD. The condensation of different β-CD derivatives with the (Z) octadec-9-enedioic acid (D18:1) will be investigated to provide the base of a CD-based library of polymers. The D18:1 unit is expected to favour interactions between the matrix and the nanofillers. To synthesize linear CD-based polymer by a A2+B2 polycondensation, difunctional CDs will be synthesized. However, an easily accessible heptafunctional-CD will also be used as monomer to synthesize hyperbranched polymers, in order to investigate the polymer architecture upon the matrix performances. Indeed, the architecture of the polymers used for the coatings of the carbon nanotubes was found to affect the solubilisation of the fillers, and the properties of nanocomposites [56].

The sensors will be obtained using a layer by layer process, which allows building the transducers from the nanoscale to the macroscale and controlling the 3 dimensions architecture of the conductive network[16,57]. The resulting network was thus sensitive to diffusing molecules due to the modification of the conductive junctions during the molecules diffusion.

2. Experimental Section

2.1. Materials

All reagents used in the synthesis, if not specified, were purchased from Aldrich Chemical Co. THF, toluene and dichloromethane used in all experiments were purified according to conventional methods. The (Z) octadec-9-enedioic acid (D18:1) (COGNIS) was recrystallized from dichloromethane and β-cyclodextrin (Roquette, France) was recrystallized from distilled water then lyophilized. Benzyl chloride, sodium hydride (60 % dispersion in mineral oil, Fluka), diisobutylaluminium hydride, triethylamine (Alfa Aesar), methanesulfonyl chloride, palladium on activated carbon (1% in weight) (Alfa Aesar), celite 545 (treated with sodium carbonate), sodium azide, Lindlar palladium (palladium on calcium carbonate), tributylphosphine (PBu_3, Jammsen Chemica), triphenylphosphine (Alfa Aesar), diiode, sodium methoxide (Fluka), ammonium hydroxide solution (20%), N-hydroxysuccinimide (Alfa Aesar), N,N'-dicyclohexylcarbodiimide and 4-pyrrolidinopyridine were used without further purification. Anhydrous dimethylsulfoxide and anhydrous dimethylformamide were used as received. Multi-walled carbon nanotubes (CNT), provided by Nanocyl® (Belgium), were produced by CVD process with a purity of 90%, with a mean diameter of 10 nm and an average length of 1.5 μm. CNT were dried under vacuum at 60 °C for 24 h prior to solution preparation. All volatile organic compounds (propanol, acetone, benzene, cyclohexane, butanone, water, methanol, ethanol and

toluene) were grade used for analytical and high-pressure liquid chromatography (HPLC).

2.2. Monomers synthesis

The heptakis-6-amino β-cyclodextrin, the 6^A, 6^D diamino β-cyclodextrin and the 6^A,6^D, diamino, 2^{A-G},3^{A-G},6^B,6^C,6^E,6^F,6^G nonadeca-O-benzyl-β-cyclodextrin were synthesized as already reported[29,49,54]. The synthesis procedures are described in the supporting information. The synthesis of (Z) octadec-9-enedioic-N-hydroxysuccinimide ester was conducted by reacting D18:1 (3 g, 9.61 mmol) with N-hydroxysuccinimide (2.21 g, 19.22 mmol) in presence of N,N'-dicyclohexylcarbodiimide (3.96 g, 19.22 mmol) and 4-pyrrolidinopyridine (0.28 g, 1.92 mmol) in dried methylene chloride. The solution was stirred at room temperature for 24 hours, then filtered and concentrated. In order to eliminate the dicyclohexylurea (DCU) produced during the reaction, the previous step was repeated after dissolution of the residue in fresh CH_2Cl_2. An extraction CH_2Cl_2 / acetic acid solution was then realized and the organic layer was washed several times with water, dried over $MgSO_4$ and concentrated. The DCU release was improved by conducting a new precipitation in freeze acetone. A part of inactivated D18:1 was eliminated by precipitation in ether, then the residue was purified by silica gel chromatography eluting with a pentane/EtOAc mixture (1:1). The (Z) octadec-9-enedioic-N-hydroxysuccinimide ester was obtained with a 10% yield. The NMR characterizations showed the quantitative formation of the new terminal functions of the compound, concurrently to the disappearance of the acidic functions (**Figure S20 and S21**).

2.3. Synthesis of linear polyamides

The 6^A, 6^D diamino β-cyclodextrin based polyamide was synthesized using equimolar amounts of 6^A,6^D diamino β-cyclodextrin (0.037 g, $3.26.10^{-5}$ mol) and (Z) octadec-9-enedioic-N-hydroxysuccinimide ester (0.017 g, $3.26.10^{-5}$ mol) in 1 ml of DMSO. The polycondensation was

conducted at 90 °C for 20 h. The crude product was then dried under vacuum to remove the solvent prior the characterization.

In the same way, the second linear polyamide was synthesized using the $6^{A},6^{D}$, diamino, 2^{A}-^{G},3^{A}-^{G},6^{B},6^{C},6^{E},6^{F},6^{G} nonadeca-O-benzyl-β-cyclodextrin (0.277 g, $9.74.10^{-5}$ mol) and the (Z)-octadec-9-enedioic-N-hydroxysuccinimide ester (0.049 g, $9.74.10^{-5}$ mol) in DMSO (0.6 mL) at 90 °C for 20 h. The crude product was recovered as previously described.

2.4. Synthesis of hyperbranched polyamides

The hyperbranched polyamide was synthesized from the heptakis-6-amino-β-cyclodextrin (0.25 g, $2.28.10^{-4}$ mol) and the (Z) octadec-9-enedioic-N-hydroxysuccinimide ester (0.033 g, $6.52.10^{-5}$ mol) in DMSO (1 mL). The molar ratio of amine functions to the acid functions was set to 1.5. The reaction mixture was heated at 90 °C during 20 h and stopped prior cross-linking. The crude product was recovered as above.

2.5. Characterisation

NMR Experiments: NMR experiments were carried out in DMSO using an Avance 300 MHz Bruker instrument. For the diffusion-ordered spectroscopy (DOSY) experiments, the maximum field gradient strength, calibrated using a previously reported procedure, was 56.8 $G.cm^{-1}$[42]. The DOSY experiments were carried out using the stegp1s pulse sequence with a linear gradient of 16 steps between 2% and 95%. Before each diffusion experiment, the proton relaxation times were determined in order to correctly set the D1 parameter of the DOSY sequence, and the length of the gradient δ and the diffusion time Δ were optimized for each analysed product. All the DOSY experiments were realized at 25°C in DMSO-d6.

Size exclusion chromatography (SEC): SEC was performed with a WATER system composed of a HPLC 515 pump, a standard injector, UV detector and a refractometer with a set of WATER styragel columns (HR 4E). The samples were prepared at a 3 $mg.mL^{-1}$ concentration. The SEC

was calibrated using polystyrene or poly(methyl methacrylate) standards.

2.6. Preparation of conductive polymer nanocomposites (CPC)

The CPC sensors were obtained by dispersing a solution of carbon nanotubes in various polymer matrices to obtain a percolated network CNT. First, 200 mg of CNT were dispersed in 20 cm^3 of chloroform and 50 to 100 mg of polymer were dissolved in 5 cm^3 of DMSO. The dispersion is obtained using ultrasound generated by a Branson 3510 sonicator (100 W, 40 kHz) for 6 h at 60 °C (in a temperature controlled bath) to get a homogeneous solution. A spray layer by layer deposition of the two solutions on interdigitated electrodes (25%Ag/75%Pd) with a 15 µm gap inserted in a ceramic holder[58]. The number of layers was set in order to obtain an initial resistance of about 5 kΩ for the various CPC.

2.7. Chemo-resistive behaviour of transducers

The chemo-resistive behaviour of sensors was investigated by exposing the various CPC to VOC vapours. The resistance changes were recorded at room temperature under alternative exposition to nitrogen and VOC (5 min. sequences). The experiments were conducted at saturated concentration of VOC in nitrogen, unless specified. The results were converted into relative amplitude, calculated from Equation 1, which allows quantifying the sensors performances more easily, as it is a more sensitive and normalized parameter.

$$Ar = \frac{R_v - R_{ini}}{R_{ini} C_{VOC}}$$

Equation 1

R_v is the resistance of sensors when exposed to vapour, while R_{ini} correspond to the initial resistance in dry nitrogen at room temperature and C_{VOC} is the saturated vapour concentration of VOC in nitrogen expressed in ppm[58].

3. Results and Discussion

3.1. Monomers and polymers synthesis

CDs composed of 6 to 8 glucopyranose units linked by of α (1,4) bonds display a high level of symmetry. The three hydroxyl functions respectively in the position 2, 3 and 6 of a pyranose ring can be distinguished through their different stereoelectronic properties (nucleophilicity and basicity), but among the different glucopyranose units, each of hydroxyl group (2, 3 or 6) are chemically equivalent. Therefore the regioselective differentiation of two, three or more of them remains a difficult but important task[40]. When two or more sites need to be transformed, then the number of possibilities implies sophisticated techniques of purification or judicious strategies of synthesis. For the synthesis of diametrically opposed diamine, Davis[59] proposed a pathway requiring the synthesis of a capped β-CD synthesized according to a modified procedure of Tabushi[60]. The reported yield is 12% for a three steps procedure, improvement of this result had to be considered for our purpose. Some of us developed a strategy to access difunctional CDs by unprotecting a fully benzyl-protected CD with DIBAL-H [54,55,61-64]. In the present work, we used this strategy to synthesize the $6^A,6^D$ diamino β-cyclodextrin (β-$CD(OH)_{19}(NH_2)_2$) in 55% yield and the $6^A,6^D$ diamino $2^{A-G},3^{A-G},6^B,6^C,6^E,6^F,6^G$ nonadeca-O-benzyl-β-cyclodextrin (β-$CD(OBn)_{19}(NH_2)_2$) in 59% yield as precursors of linear polyamides. The high yield of the second strategy is in agreement with previous works[61-63], a requirement for polymer synthesis applications of such compounds. These bifunctional monomers of different chemical nature were synthesized in order to design linear polymers able to develop different affinities with a set of selected COV, when incorporated in quantum resistive sensors. In order to study the influence of the polymer architecture, the heptakis-6-amino β-CD (β-$CD(OH)_{14}(NH_2)_7$) was also

synthesized as precursor of hyperbranched polyamide. All the monomers were successfully synthesized using already published procedures[29,49,54]. The procedures, as well as characterizations, are given in supporting informations.

The (Z) octadec-9-enedioic acid (D18:1) was used as comonomer to condensate each CD-based monomer. Only few examples of polyamides obtained by polycondensation of octadec-9-enedioic acid with aliphatic or cycloaliphatic diamines[65-67] or benzylic diamines[66] are described in the literature. In this work, the polyamides were synthesized by a coupling reaction between amine functions and the activated D18:1 by the N-hydroxysuccinimide (NHS) [68-70], to prevent from ester functions formation[68].

The expected polymer structures are presented in **Figure 1**. First, two different linear polyamides were synthesized using equimolar amounts of β-CD$(OH)_{19}(NH_2)_2$ or β-CD$(OBn)_{19}(NH_2)_2$ and (Z) octadec-9-enedioic-N-hydroxysuccinimide ester. While polycondensations were usually conducted in bulk, the polycondensations realized in this study were conducted in solution, due to lack of CD melting point at moderate temperature. The influence of temperature, concentration, time and nature of the solvent was examined.

It was observed concerning the β-CD$(OH)_{19}(NH_2)_2$ based polymers, that the highest molar mass polycondensates were more soluble in DMSO than in DMF. Thus, this solvent was chosen to realize the polymerizations described below. The CD monomer concentration was set to be as high as possible ($[NH_2]$=0.0326 mol.L^{-1}) to favour the reaction and the polymerization medium was heated at 90°C for 20h. The formation of polycondensates was shown by ^{13}C NMR and confirmed by DOSY NMR determining the diffusion coefficient of each monomer unit. The ^{13}C NMR spectrum (**Figure 2**) evidenced the disappearance of the signal of the methylene carbons linked to the activated acid functions at 30.12 ppm and the formation of a new peak at 35.24 ppm assigned to the same methylene carbons, when bonded to CD units through an amide function. It

is worth noting that the carbons C6 linked to OH groups were still observed at 59.65 ppm, indicating that no reaction occurred on these groups. Therefore the synthesized polymers were linear and not branched. From DOSY analysis, only one diffusion coefficient was observed when polymerizing β-CD$(OH)_{19}(NH_2)_2$ and the activated D18:1 (**Figure 3**; run 2 **Table 1**). In this experiment whatever the considered peak, the diffusion coefficient was equal to $(9.23\pm0.1).10^{-11}$ $m^2.s^{-1}$. For comparison, the values of the corresponding CD and D18:1 monomers are respectively $(1.02\pm0.1).10^{-10}$ $m^2.s^{-1}$ and $(1.80\pm0.05).10^{-10}$ $m^2.s^{-1}$. The lowest value obtained for the polymer demonstrates its highest hydrodynamic volume. Besides, the standard deviation determined from different polymer peaks was low, suggesting a well-defined structure of the polymer. This result is consistent with the absence of reaction between the CD hydroxyl functions and the activated acid functions of D18:1 observed in ^{13}C NMR. This absence of reaction was confirmed by an attempted polymerization between the activated D18:1 and a $6^A,6^D$ diol $2^{A-G},3^{A-G},6^B,6^C,6^E,6^F,6^G$ nonadeca-O-benzyl-β-CD (run 4, **Table 1**), for which no polymer was formed, in agreement with Morpurgo *et al.* [68]. In this experiment, the DOSY NMR analysis of the crude product provides two different diffusion coefficients, from the CD and D18:1 peaks, equal to values of the diffusion coefficients previously determined for each monomer (**Figure S17**).

The linear polyamide based on β-CD$(OBn)_{19}(NH_2)_2$ exhibited a solubility totally different from that of polyamides synthesized from β-CD$(OH)_{19}(NH_2)_2$, allowing the determination of the polymer molar mass by SEC in tetrahydrofuran. Thus, the molecular weight of the synthesized polymer was estimated to 12800 g mol^{-1} or 14600 g mol^{-1}, when considering either a PS calibration or a PMMA calibration, with a dispersity of about 2. The DOSY NMR experiment showed a single diffusion coefficient equal to $(3.14\pm0.3).10^{-11}$ $m^2.s^{-1}$, much lower than the coefficient of the β-CD$(OBn)_{19}(NH_2)_2$ monomer ($D=(9.37\pm0.1).10^{-11}$ $m^2.s^{-1}$). This observation

confirmed the formation of polymer. The appearance of a new peak at 35.30 ppm on the ^{13}C NMR spectrum witnesses the formation of amid bonds (**Figure S18**).

Finally, a branched polyamide was synthesized from the heptakis-6-amino-β-CD and the activated D18:1, using a molar ratio between the amino and acid functions equal to 1.5. The polycondensation was carried out in DMSO at 90°C and stopped prior to gelation of the system. The polyamide formation was evidenced by DOSY NMR, providing a single diffusion coefficient equal to $(6.19\pm0.6).10^{-11}$ $m^2.s^{-1}$, a typical value for polymers. The standard deviation was slightly higher in this case, suggesting a branched structure of the polymer.

Unlike linear polyamide based on β-$CD(OBn)_{19}(NH_2)_2$, the polymers synthesized from β-$CD(OH)_{19}(NH_2)_2$ or β-$CD(OH)_{14}(NH_2)_7$ could not be characterized by SEC in THF, since they were not soluble in this solvent. For this reason, we tried to determine the molar mass of all the polymers from their DOSY diffusion coefficient. Indeed, DOSY NMR as SEC characterization relies on the hydrodynamic volume of particles. Therefore, a calibration with polyethylene glycols of various molar mass was realized in DMSO at 25°C; the linear correlation is presented in **Figure S19**. The molar masses determined either by DOSY or by SEC are listed in **Table 1**. It was observed that the DOSY values were quite low, probably due to the fact that the polyamides hydrodynamic volumes are different from those of the POE ones, because of their different chemical natures and structures, while having the same molar mass. To determine the molar mass of these polymers, end functions analysis has been considered. The ^{1}H NMR spectrum does not allow the titration of the remaining functions, due to overlapped low signals intensities. To conclude, it is difficult to determine accurately this parameter.

3.2. Properties of the Conductive Polymer nanoComposites

The linear and branched polyamides previously described were used to design quantum resistive chemo-sensors (QRS) using multi walled carbon nanotubes (CNT) as conductive nanofillers.

They were built on interdigitated electrodes according a spray layer by layer process[16,57]. The chemo-resistive behaviour of sensors was then estimated by exposing the various CPC to a set of VOC, which were relevant in the early detection of lung cancer and thus could be considered as biomarker of this disease. Different alcohols, aromatic and aliphatic alkanes, ketones were thus investigated. Water was also considered, since it is the main VOC of the exhaled breath. The resistance of sensors was monitored during alternative exposition to VOC and dry nitrogen for 5 minutes periods (3 times). For the aimed application, it is important to check the sensibility and selectivity of the systems, as well as the reversibility of the phenomenon (VOC diffusion inside the matrix, followed by its desorption when the VOC flow is stopped).

The chemo-resistive responses of the two linear polyamides to different solvents (methanol, ethanol, water, cyclohexane, toluene, benzene, acetone and propanol) are shown in **Figure 4** and **5**. All sensors are detecting the set of VOC but with different sensitivities (function of selective interactions between analytes and sensors) and the phenomenon was found reversible after each nitrogen pulse, as suggested by Ar values close to 0 obtained after nitrogen washing. However, the chemo-resistive responses' (Ar) recovery was sometimes slow, indicating a slow desorption of the diffusing molecules during this step, particularly for some sensors based on β-$CD(OBn)_{19}(NH_2)_2$. In the same way, thermodynamic equilibrium was not completely reached after 5 min of VOC flow for all systems. It means that the diffusion kinetics vary according the studied VOC/CPC combinations. It was observed that the sensor whose polyamide was synthesized from β-$CD(NH_2)_2(OH)_{19}$ has a large Ar_5 (value of Ar recorded after 5 min of VOC flow), when exposed to methanol vapours. This polymer has a strong hydrophilic character thanks in part to the 19 hydroxyl functions that generate many hydrogen bonds with polar protic solvents, such as methanol. It exhibited also a good affinity for ethanol, propanol and water but to a lesser extent. In contrast, benzylated polyamide, due to the presence of benzyl groups in the

polymer chain, is found more selective to non-polar solvents such as toluene (van der Waals interactions as London dispersion force). Acetone has a particular behavior, probably due to interactions between permanent dipoles (Keesom force) of polymer amide groups, these interactions being stronger than the interactions induced by two induced dipoles (London dispersion force). Finally, the chemo-resitive finger prints of these two kinds of sensors demonstrate that an appropriate functionnalization of CD allows to taylor their selectivity to either polar-protic or non-polar VOC.

The CPC composed of branched polyamide (whose synthesis was conducted from the heptafunctional β-CD$(OH)_{14}(NH_2)_7$) was also exposed to various VOC considered as biomarkers of lung tumour. The results are shown in **Figure 6**. As for the CPC based on linear hydrophilic polyamide, this CPC was found highly sensitive to polar-protic analytes such as propanol and developed little interaction with non-polar VOC. However, branched polyamide based sensors exhibited smaller responses than their linear homologues, which was assigned to a lower accessibility of CD[71].

4. Conclusions

New biobased linear and branched polyamides were synthesized from bifunctional and heptafunctional β-CD monomers and (Z) octadec-9-enedioic-N-hydroxysuccinimide ester, in order to bring additional chemical selectivity to CPC with a CNT conducting architecture. The spray layer by layer (sLbL) process proved to be effective, to achieve the additive building of a conductive network sensible to either polar or non-polar VOC. Polyamide-CD functionalized CPC proved to be able to reversibly detect some VOC biomarkers of lung cancer with different sensitivities. The level of detection is expected to get down to ppb concentration, which is the

relevant resolution for breath biomarkers discrimination.

The input of the sensors developed in this work, in a whole, more than the amplitude of chemo-resistive responses that did not reach those of previous CPC formulations, was to provide a new and versatile CPC functionalization process leading to a good balance between sensitivity and reversibility of chemo-resistive responses. Additionally, polyamide-CDs are found to be very selective towards propanol which is valuable in the prospect of the integration of such sensor into an e-nose to improve its discrimination capability to a series of alcohols.

To get closer from a biomedical application, the next step of this study will be to implement these different CPC, into an array with complementary QRS, to investigate the discrimination of the resulting e-nose towards a blend of VOC biomarkers at ppm concentration and in the presence of a large amount of water molecules as in real breath.

5. Abbreviations

Ar	relative amplitude
CD	Cyclodextrin
CNT	Multi walled carbon nanotubes
CPC	Conductive Polymer nanoComposites
CVD	Chemical Vapor Deposition
C_{VOC}	saturated vapour concentration of VOC in nitrogen
D18:1	(Z) octadec-9-enedioic acid
DCU	Dicyclohexylurea
DIBAL-H	Diisobutylaluminium hydride
DMF	*N*,*N*-dimethylformamide

DMSO	Dimethyl sulfoxyde
DOSY	Diffusion-Ordered SpectroscopY
EtOAc	Ethyl acetate
PMMA	poly(methyl methacrylate)
PS	polystyrene
QRS	Quantum Resistive Sensors
R_v	Resistance of sensors when exposed to vapour
R_{ini}	initial resistance of sensors in dry nitrogen
sLbL	spray layer by layer
THF	Tetrahydrofuran
VOC	Volatile Organic Compounds
β-CD$(OH)_{14}(NH_2)_7$	heptakis-6-amino β-cyclodextrin
β-CD$(OH)_{19}(NH_2)_2$	6^A,6^D diamino β-cyclodextrin
β-CD$(OBn)_{19}(NH_2)_2$	6^A,6^D diamino 2^{A-G},3^{A-G},6^B,6^C,6^E,6^F,6^G nonadeca-O-benzyl-β-CD

Keywords : renewable resources, Cyclodextrin based polymer, CNT, Cancer biomarker detection, Electronic nose

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Figure captions

Figure 1: Expected structures of the different investigated polyamides

Figure 2: ^{13}C NMR of the polycondensate synthesized from the (Z) octadec-9-enedioic-N-hydroxysuccinimide ester and β-CD$(NH_2)_2(OH)_{19}$ in DMSO at 25°C.

Figure 3: DOSY NMR spectrum of the polycondensate synthesized from the (Z) octadec-9-enedioic-N-hydroxysuccinimide ester and β-CD$(NH_2)_2(OH)_{19}$ in DMSO at 25°C.

Figure 4. Effect of flow rate of different vapours on the amplitude *A*r of linear polyamide based on β-CD$(OH)_{19}(NH_2)_2$-CNT sensor.

Figure 5. Effect of flow rate of different vapours on the amplitude *A*r of linear polyamide based on β-CD$(OBn)_{19}(NH_2)_2$-CNT sensor.

Figure 6. Effect of flow rate of different vapours on the amplitude *A*r of branched polyamide based on β-CD$(OH)_{14}(NH_2)_7$-CNT sensor.

Table

Run	Monomer	Polymer structure	D[1)] ($m^2.s^{-1}$)	$\overline{M_w}$[1)] (g/mol)	$\overline{M_n}$[2)] (g/mol)	Đ[2)]
1	$\beta CD(NH_2)_7(OH)_{14}$	branched	$(6.19\pm0.6).10^{-11}$	2850	-	-
2	$\beta CD(NH_2)_2(OH)_{19}$	linear	$(9.23\pm0.1).10^{-11}$	1500	-	-
3	$\beta CD(NH_2)_2(OBn)_{19}$	linear	$(3.14\pm0.3).10^{-11}$	8500	12760* 14640**	1.96* 2.05**
4	$\beta CD(OH)_2(OBn)_{19}$	monomers	$(1.80\pm0.05).10^{-10}$ $(9.70\pm0.05).10^{-11}$	-	-	-

[1)] determined from DOSY NMR

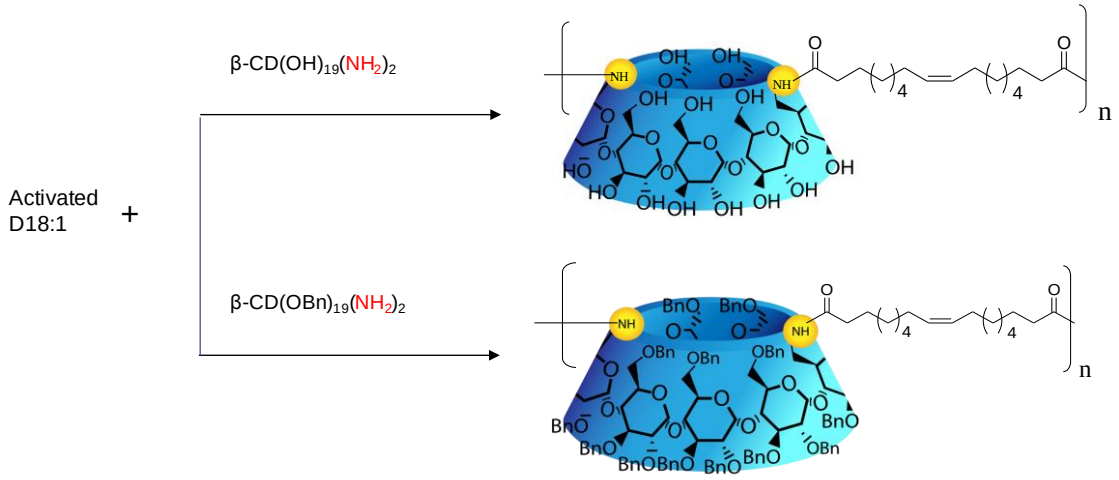
[2)] determined from SEC

* PS calibration

** PMMA calibration

Table 1: Determination of the polyamides molar mass

Linear polyamides :



Branched polyamide :

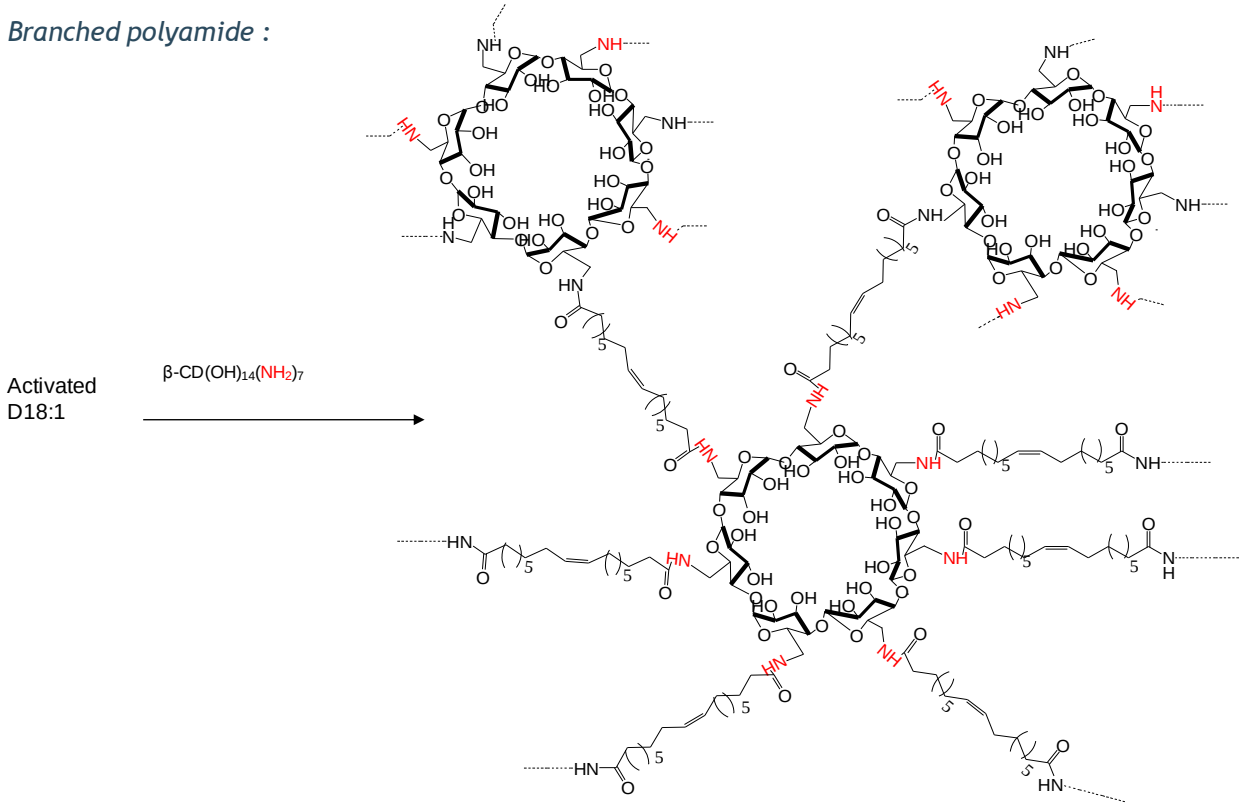


Figure 1: Expected structures of the different investigated polyamides

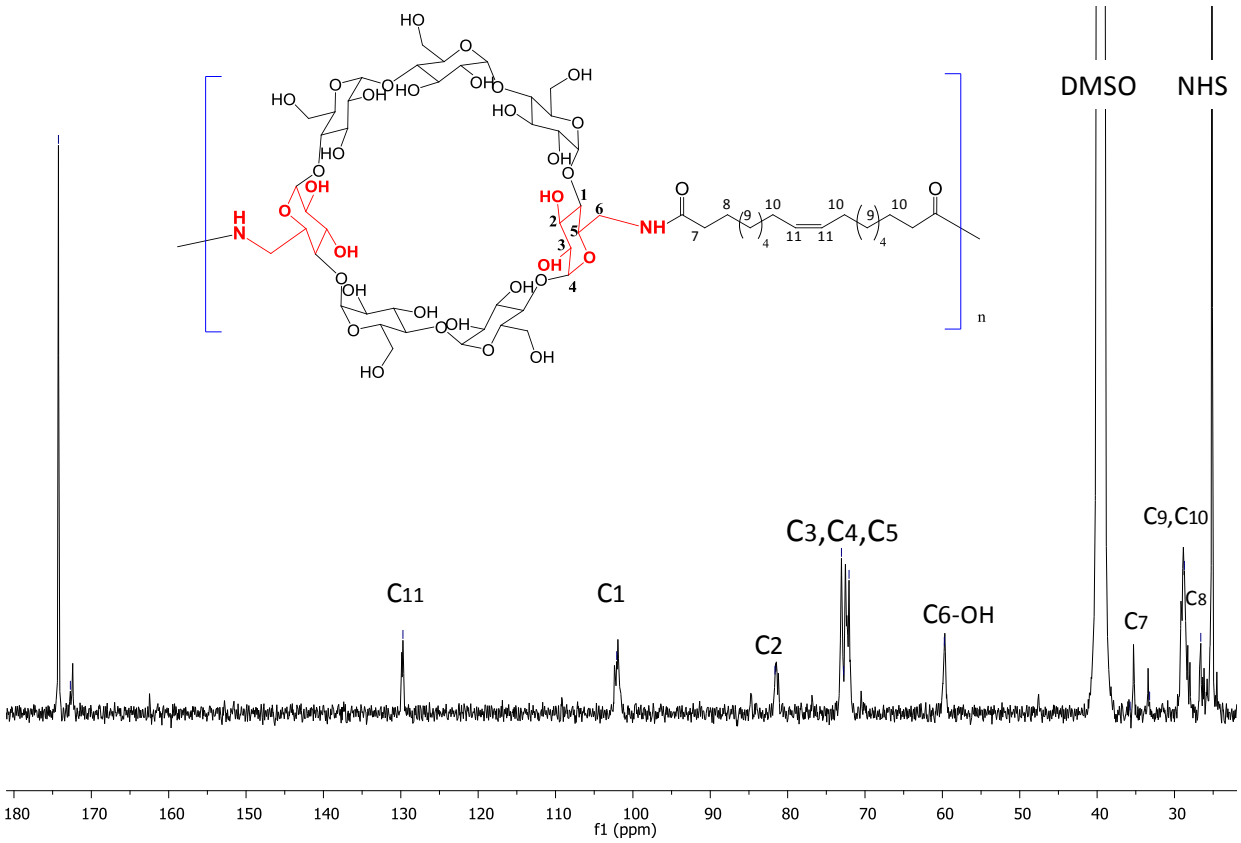
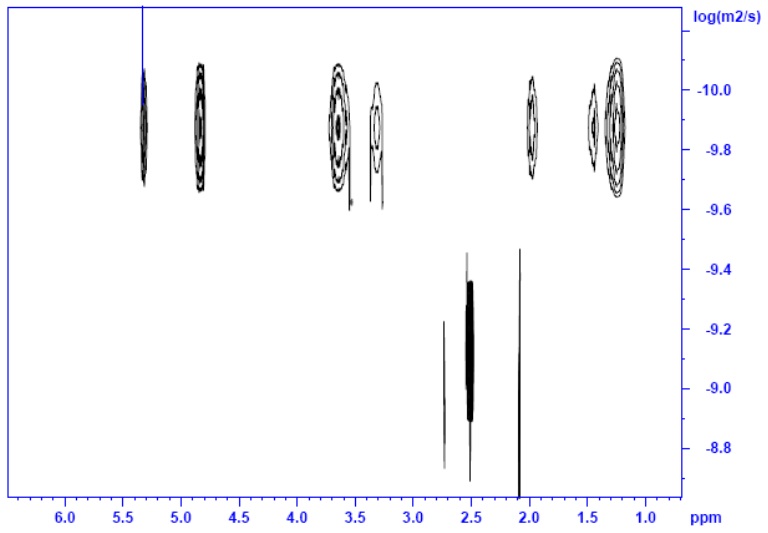


Figure 2: ^{13}C NMR of the polycondensate synthesized from the (Z) octadec-9-enedioic-N-hydroxysuccinimide ester and β-CD$(NH_2)_2(OH)_{19}$ in DMSO at 25°C.



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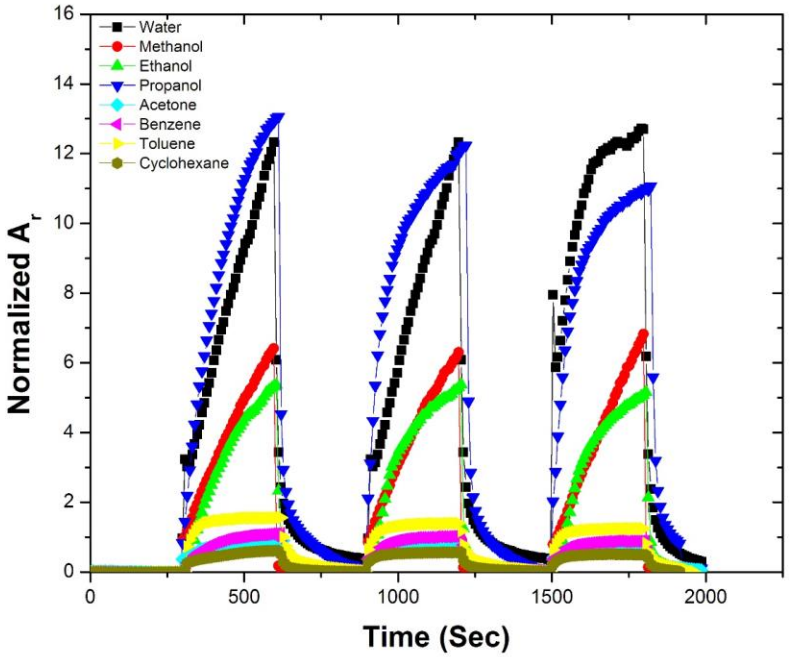


Figure 4. Effect of flow rate of different vapours on the amplitude *A*r of linear polyamide based on β-CD$(OH)_{19}(NH_2)_2$-CNT sensor.

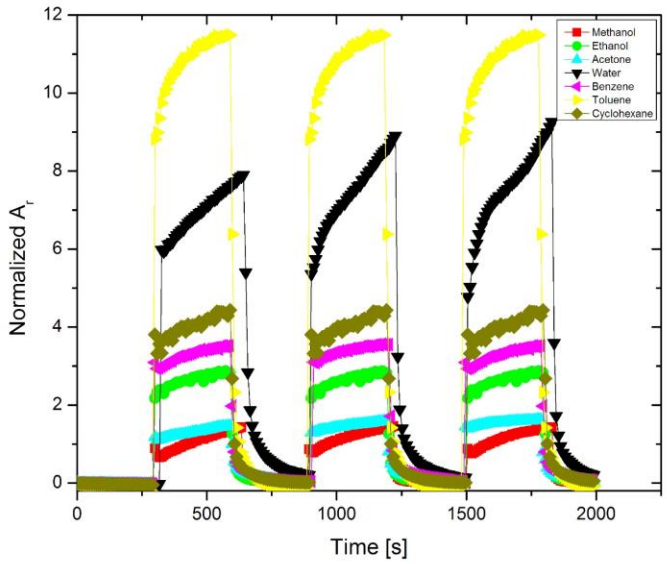


Figure 5. Effect of flow rate of different vapours on the amplitude *A*r of linear polyamide based on β-CD(OBn)$_{19}$(NH$_2$)$_2$-CNT sensor.

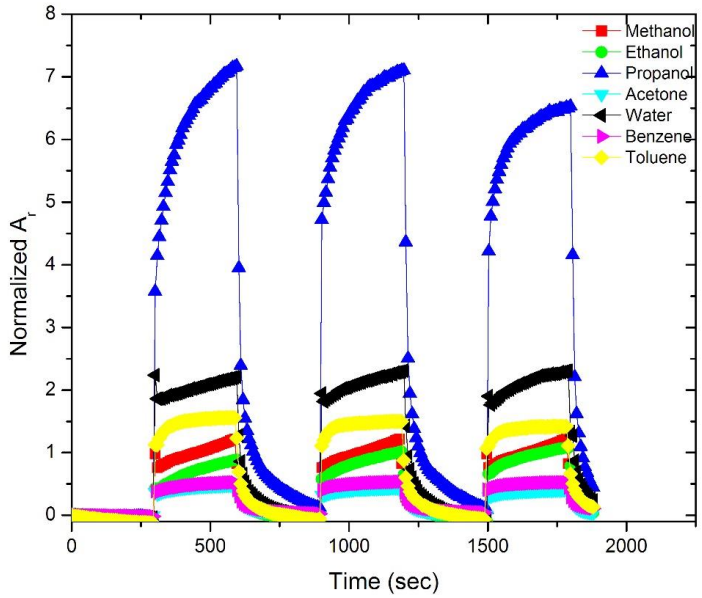
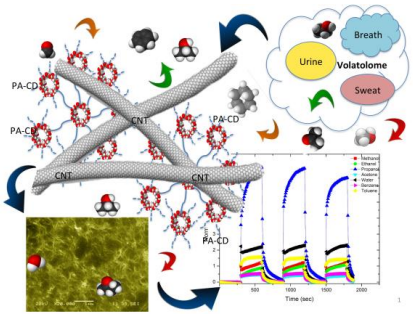


Figure 6. Effect of flow rate of different vapours on the amplitude *A*r of branched polyamide based on β-CD(OH)$_{14}$(NH$_2$)$_7$-CNT sensor.

The synthesis of new biobased polyamides from different β-cyclodextrin monomers and the (Z) octadec-9-enedioic acid is investigated. The aim of this study is to design different sensors having different sensibilities and selectivities to a set of various volatile organic compounds relevant in the early detection of lung cancer. The sensors are designed from the polyamides with multi walled carbon nanotubes.

Lisday Duarte, Sananda Nag, Mickaël Castro, Elena Zaborova, Mickaël Ménand, Matthieu Sollogoub, Véronique Bennevault, Jean-Francois Feller, Philippe Guégan

Chemical sensors based on new polyamides bio-based on (Z) octadec-9-enedioic acid and β-cyclodextrin