Convocatorias 2014
Proyectos de I+D "EXCELENCIA" y Proyectos de I+D+I "RETOS INVESTIGACIÓN"
Dirección General de Investigación Científica y Técnica
Subdirección General de Proyectos de Investigación

AVISO IMPORTANTE

En virtud del artículo 11 de la convocatoria **NO SE ACEPTARÁN NI SERÁN SUBSANABLES MEMORIAS CIENTÍFICO-TÉCNICAS** que no se presenten en este formato.

Lea detenidamente las instrucciones que figuran al final de este documento para rellenar correctamente la memoria científico-técnica.

Parte A: RESUMEN DE LA PROPUESTA/SUMMARY OF THE PROPOSAL

INVESTIGADOR PRINCIPAL 1 (Nombre y apellidos)**:**

Joré Lorenzo Alonso Gómez

INVESTIGADOR PRINCIPAL 2 (Nombre y apellidos)**:**

María Magdalena Cid Fernández

TÍTULO DEL PROYECTO: Sistemas Moleculares y Supramoleculares para Transducción Sensórica

ACRÓNIMO: SMol-Supra-Sens

RESUMEN Máximo 3500 caracteres (incluyendo espacios en blanco):

El envejecimiento de la población es uno de los grandes problemas que afronta Europa en los próximos años (según la ONU en 2050 en España más del 38% de la población será mayor de 60 años), esto conlleva inevitablemente un aumento de enfermedades crónicas y de personas que necesitan un seguimiento médico personalizado. Para afrontar este nuevo escenario demográfico de forma sostenible, es esencial un cuidado integrado controlado por la propia persona. El avance de la telemedicina abre el camino para el diagnóstico a distancia evitando desplazamientos innecesarios y reduciendo tiempos de espera. Por ello, es de gran interés explorar nuevas vías para detectar biomarcadores, de tal forma que ayuden tanto a minituarización como a reducir el coste de los BioSensores.

Los sistemas quirales presentan respuestas especiales frente a la luz. Estas respuestas llamadas quirópticas son fuertemente sensibles a cambios conformaciones así como a interacciones supramoleculares. Es por ello que espectroscopías como el dicroismo circular (CD) o la rotación óptica de dispersión (ORD) se emplean a menudo para la caracterización de estos compuestos y sus complejos. Por otro lado, el acceso a estructuras con respuestas quirópticas muy potentes abre la posibilidad de su uso como transductores.

Este proyecto pretende construir Estructuras Quirales Inteligentes (EQI) moleculares y supramoleculares con respuestas chiróticas intensas, sensibles a la interaccionen con biomarcadores, y así explorar su uso para la construcción de sensores (Figure 1). La adecuada combinación de espaciadores, para impartir funcionalización, y ejes quirales, para impartir quiralidad, permite el diseño y la síntesis de moléculas Abiertas, Cíclicas y con Forma de Caja (Figure 2). El Reconocimiento Molecular de estos sistemas asociado a sus Respuestas Quiróticas abrirá las puertas a su uso en BioSensores. El estudio de Complejos

de Inclusión de biomarcadores con los macrociclos y cajas moleculares construidas, perimitirá el uso de estas estructuras como transductores en Disolución. El auto-ensamblaje de EQIs en superficies permite la construcción de arquitecturas quirales erguidas (AQEs) que por el momento son poco estables. Este proyecto pretende mejorar la estabilidad de las AQEs y funcionalizar superficies para su implementación como transductores. Por otro lado, se pretende explorar la construcción de Netanos, auto-ensamblaje de complejos de inclusión de cajas moleculares en superficies por interacción entre las moléculas invitadas de cajas moleculares vecinas. Este objetivo ambicioso, permitiría el uso de EQIs en optoelectrónica. Por último, se espera que el auto-ensamblaje de EQIs abiertas induzca una amplificación significativa de las respuestas quiropticas, permitiendo así el uso de estos sistemas quirales como transductores.

El objetivo global de este proyecto es obtener estructuras quirales inteligentes y poner las herramientas necesarias para su implementación en Biosensores.

PALABRAS CLAVE: Sensor – Chiralidad – Reconocimiento Molecular – Chiroptica – Sintesis – Superficies quirales

TITLE OF THE PROJECT: Molecular and Supramolecular Systems for Chiroptical Sensing

ACRONYM: Mol-Supra-Sens

SUMMARY Maximum 3500 characters (including spaces):

Population aging is one of the major problems facing Europe in the coming years (according to the UN in 2050 in Spain more than 38% of the population will be over 60 years old), this inevitably leads to an increase in chronic diseases and people who needs personalized medical monitoring. Medical care controlled by the individual patients is, therefore, essential to sustainably face this new demographic scenario. The advancement of telemedicine paves way for remote diagnosis avoiding unnecessary travel and reducing waiting times. To reduce costs and sizes, it is of great interest the exploration of new sensing methodologyes for biomarkers.

Chiral systems have special responses to light. The, so called, chiroptical responses are strongly sensitive to conformational changes as well as to supramolecular interactions. That is the reason why circular dichroism (CD) or optical rotation dispersion (ORD) are often used for the characterization of these compounds and their complexes. Furthermore, access to structures with very potent chiroptical responses will open the possibility for using them as transducers.

The aim of this project is to build molecular and supramolecular Smart Chiral Frameworks (SCF) with stron chiroptical responses, sensitive to interactions with biomarkers, to explore their use for the construction of sensors (Figure 1). Apropriet combination of funtionalized spacers and chiral axes, allows the design and synthesis of Open, Cyclic, and Cage-shaped frameworks (Figure 2). Molecular Recognition of these systems alonge with their strong chiroptical responsesres will enable their use in biosensing. Host–Guest inclusion complexes of cycles and cages with will allow their use as biosensors in solution. Self-assembly of open SCFs can be used for the construction of Up-standing Chiral Architectures (UCAs) that for the moment have low stability. This project aims at improving the stability of these UCAs to funtionalized surfaces for their use as transductors. Furthermore, Host–Guest inclusion complexes of helical cages will be teilored for their further self-assembly directed by the invited guests in order to generate regular chiral networks, we call them Netanes. This very ambitious goal would open the use of SCFs in optoelectronics. Finally, it is expected that the self-assembly of open SCFs into chiral gles will induce significant chiroptical amplification, thus permitting the use of these chiral systems as transducers.

Overall, this project aims to obtain Smart Chiral Frameworks and provide the neccesary methodology for implementating them in Biosensing.

KEY WORDS: Sensing – Chirality – Molecular Recognition – Chiroptics – Synthesis – Chiral Surfaces

Parte B: INFORMACIÓN ESPECÍFICA DEL EQUIPO

B.1. RELACIÓN DE LAS PERSONAS NO DOCTORES QUE COMPONEN EL EQUIPO DE TRABAJO (se recuerda que los doctores del equipo de trabajo y los componentes del equipo de investigación no se solicitan aquí porque deberán incluirse en la aplicación informática de solicitud). Repita la siguiente secuencia tantas veces como precise.

1. Nombre y apellidos: Sandra Míguez Lago
   Titulación: Máster en Química
   Tipo de contrato: Beca pre-doctoral Xunta de Galicia
   Duración del contrato: temporal

2. Nombre y apellidos: Silvia Castro Fernández
   Titulación: Máster en Química
   Tipo de contrato: con cargo a proyecto
   Duración del contrato: temporal

3. Nombre y apellidos: Eduardo Troche Pesqueira
   Titulación: Máster en Química
   Tipo de contrato: con cargo a proyecto
   Duración del contrato: temporal

4. Nombre y apellidos: FPI solicitado
   Titulación: Máster en Química
   Tipo de contrato: FPI
   Duración del contrato: temporal

5. Nombre y apellidos: Stefan Stefanov
   Titulación: Máster en Ingeniería Física
   Tipo de contrato: con cargo a proyecto
   Duración del contrato: temporal

6. Nombre y apellidos: David Fernández Abet
   Titulación: 3er año graduado en Ingeniería.
   Tipo de contrato: en formación
   Duración del contrato: sin contrato

7. Nombre y apellidos: Marcelo Rodríguez Teijeiro
   Titulación: 3er año graduado en Ingeniería.
   Tipo de contrato: en formación
   Duración del contrato: sin contrato

B.2. FINANCIACIÓN PÚBLICA Y PRIVADA (PROYECTOS Y/O CONTRATOS DE I+D+I) DEL EQUIPO DE INVESTIGACIÓN (repita la secuencia tantas veces como se precise hasta un máximo de 10 proyectos y/o contratos).

1. Investigador del equipo de investigación que participa en el proyecto: José Lorenzo Alonso Gómez
   Referencia del proyecto: CTQ2013-50575-EXP
   Título: **Smart Chiral Frameworks to Control and Inhibit Corrosion**
   Investigador principal: **José Lorenzo Alonso Gómez**
   Entidad financiadora: **MINECO**
   Duración: 2 años.
   Financiación recibida: **70.000 €** más costes indirectos (hasta un 21%)
   Relación con el proyecto que se presenta: está algo relacionado con uno de los objetivos de este proyecto (UCAs)
   Estado del proyecto o contrato: concedido pendiente de resolución definitiva

2. Investigador del equipo de investigación que participa en el proyecto: José Lorenzo Alonso Gómez
Referencia del proyecto: CTQ2011-28831
Título: **Chiral [14_2] Allenophanes: Synthesis, Chiroptical Properties and Applications**
Investigador principal (nombre y apellidos): **José Lorenzo Alonso Gómez (2014) Armando Navarro Vázquez (2012 - 2013)**
Entidad financiadora: **MINECO**
Duración: 01/01/2012 – 31/12/2014
Financiación recibida (en euros): **99.220 €**
Relación con el proyecto que se presenta: está algo relacionado con uno de los objetivos de este proyecto (propiedades quirópticas de macrociclos alenicos y aplicaciónes)
Estado del proyecto o contrato: concedido

3. Investigador del equipo de investigación que participa en el proyecto: José Lorenzo Alonso Gómez
Referencia del proyecto: EM2013/017
Título: **Design and Synthesis of Chiral Spiro Macromolecules for Molecular Recognition**
Investigador principal: **José Lorenzo Alonso Gómez**
Entidad financiadora: **Xunta de Galicia**
Duración: 08/08/2013 – 30/11/2014
Financiación recibida (en euros): **30.200 €**
Relación con el proyecto que se presenta: está algo relacionado con uno de los objetivos de este proyecto (macrociclos espiránicos para reconocimiento molecular)
Estado del proyecto o contrato: concedido

4. Investigador del equipo de investigación que participa en el proyecto: José Lorenzo Alonso Gómez
Referencia del proyecto: CTQ2010-18576
Título: **[14_2] Alenofanos quirales: síntesis y propiedades quirópticas**
Investigador principal (nombre y apellidos): **José Lorenzo Alonso Gómez**
Entidad financiadora: **MINECO**
Duración: 01/01/2011 – 31/12/2011
Financiación recibida (en euros): **9.122 €**
Relación con el proyecto que se presenta: está algo relacionado con uno de los objetivos de este proyecto (propiedades quirópticas de macrociclos alenicos)
Estado del proyecto o contrato: concedido

5. Investigador del equipo de investigación que participa en el proyecto: José Lorenzo Alonso Gómez
Referencia del proyecto: 212111120
Título: **Cavitand Capped Chiral Capsules**
Investigador principal (nombre y apellidos): **José Lorenzo Alonso Gómez**
Entidad financiadora: **National Natural Science of China**
Duración: 01/01/2013 -31/12/2013
Financiación recibida (en euros): **24.000 €**
Relación con el proyecto que se presenta: está algo relacionado con uno de los objetivos de este proyecto (uso de espiranos como alternativa a los alenos)
Estado del proyecto o contrato: concedido

6. Investigador del equipo de investigación que participa en el proyecto: María Magdalena Cid Fernández
Referencia del proyecto: INCITE08PXIB383129PR
Título: **Diseño y Síntesis de oligómeros de beta-hidroxiaminoacidos y oligómeros alenofánicos con potencial actividad antibacteriana.**
Investigador principal (nombre y apellidos): **María Magdalena Cid Fernández**
Entidad financiadora: **Xunta de Galicia**
Duración: 01/08/2008 – 30/07/2011

Financiación recibida (en euros): **64.561 €**
Relación con el proyecto que se presenta: está algo relacionado con uno de los objetivos de este proyecto (diseño de alenofanos)
Estado del proyecto o contrato: concedido

7. Investigador del equipo de investigación que participa en el proyecto: María Magdalena Cid Fernández
Referencia del proyecto: PIRSES-GA-2012-318930
Título: International network on integrated techniques in structural elucidation (InTechSE)
Investigador principal: **María Magdalena Cid Fernández**
Entidad financiadora: **Uinión Europea**
Duración: 01/09/2012 – 31/08/2015
Financiación recibida (en euros): **76.000 €**
Relación con el proyecto que se presenta: está algo relacionado con uno de los objetivos de este proyecto
Estado del proyecto o contrato: concedido

8. Investigador del equipo de investigación que participa en el proyecto: María Magdalena Cid Fernández
Referencia del proyecto: CTQ08237-E
Título: **Técnicas espectroscópicas avanzadas en investigación biomolecular**
Investigador principal: **María Magdalena Cid Fernández**
Entidad financiadora: **MICININ**
Duración: 01/11/2009 – 31/10/2010
Financiación recibida (en euros): **5.000 €**
Relación con el proyecto que se presenta: está algo relacionado con uno de los objetivos de este proyecto
Estado del proyecto o contrato: concedido

9. Investigador del equipo de investigación que participa en el proyecto: Stefano Chiussi
Referencia del proyecto: (MAT2011-24077)
Título: **Ingeniería de materiales para nuevos dispositivos microelectrónicos y fotónicos: Procesamiento Láser para activar boro en aleaciones de germanio con estaño (LaserActiv)**
Investigador principal: **Stefano Chiussi**
Entidad financiadora: **Ministerio de Ciencia e Innovación**
Duración: 2012 - 2014
Financiación recibida: **74.380 €**
Relación con el proyecto que se presenta: está algo relacionado
Estado del proyecto o contrato: concedido

10. Investigador del equipo de investigación que participa en el proyecto: Stefano Chiussi
Referencia del proyecto: PSE-300100-2006-1
Título: **Funcionalización de polímeros para la fabricación de productos biomédicos** avanzados (BIOAVAN)
Investigador principal: **José María Múgica Iraola** (INASMET) y **Juan Pou Saracho** (U Vigo)
Entidad financiadora: **Ministerio de Educación y Ciencia**
Duración:2006 - 2009
Financiación recibida: **372.200 €**
Relación con el proyecto que se presenta: está algo relacionado
Estado del proyecto o contrato: concedido

Parte C: DOCUMENTO CIENTÍFICO

C.1. RESEARCH PROPOSAL

C.1.1. Precedents and State of the Art

- **Chiroptical properties**

Systems non-superimposable with their mirror images are set to be chiral and exist in two enantiomeric forms. When chiral molecules interact with an achiral entity, the two opposite enantiomers are indistinguishable, as far as most physicochemical properties are concerned. However, as in the famous case of thalidomide, they may respond differently when interacting with another chiral entity. Light can be also chiral, as circularly polarized light (CPL) is, and the different response of a chiral system when interacting with opposite CPLs give rise to chiroptical spectroscopies[1] e.i. circular dichroism (CD) and optical rotatory dispersion (ORD) (Figure 1a).[2],

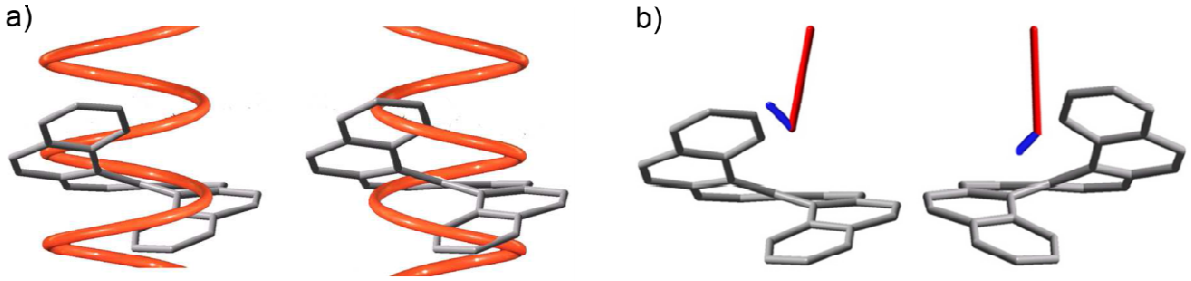

Figure 1. a) Superimposition of left (L-CPL) and right circularly polarized light (R-CPL) with (*P*)-[7]helicene; b) TEDM (blue) and TMDM (red) representation for the lowest electronic transition of (*P*)-[7]helicene, left and (*M*)-[7]helicene, right. Simulated with ZINDO.

Electromagnetic fields interact with molecules when coinciding with the energy difference between ground and excited states. The intensity if the absorption in a UV/Vis spectrum depends only on the electron density displacement during the electronic transition, the transition electric dipole moment (TEDM). However, the sign and intensity of the CD and ORD bands depend also on the strength of the magnetic moment generated in such electron density displacement, the magnetic transition dipole moment (TMDM) as well as in the angle between TEDM and TMDM (Figure 1b). Therefore, chiroptical spectroscopies are extremely sensitive to the geometry of the studied system and have been used for absolute configuration determination[3] as well as for conformational assignments.[4] On the other hand, molecular recognition processes have also been monitored by chiroptical spectroscopies due to their high sensitivity to supramolecular interactions. More recently, the sensitivity of chiroptical responses to intermolecular interaction is been explored for their used in sensing applications.[5] In this respect, access to systems with very strong chiroptical responses is desired in order to use chiroptical sensing in real devices.

- **Open and cyclic allenic systems with outstanding chirotical properties.**

Incorporation of bulky groups, to preclude any side reaction over the cumulenic moiety, as well as the incorporation of acetyls, rendered over a decade ago diethynylallenes (DEAs)[6] as stable building blocks for the construction of well define morphologies.[7] It was only few years later when DEAs could be enantioselectively synthetized[8] and obtain in enantiopure form.[9] This gave access to the first enantiomerically pure alleno-acetylenic macrocycle. The total conformational stability and electronic properties rendered chirotical responses record for organic compounds (Figure 2a).[9] The use of quantum mechanical (QM) simulations enabled uncovering the origin of such remarkable chiroptical properties.[10] Furthermore, the postulated amplification of chirality for open allenic systems was confirmed experimentally on a set of mono- to hexa-DEA derivatives. The combination of experimental chiroptical responses and QM predictions deciphered the helical conformation of these open DEA oligomers in solution (Figure 2b).[11]

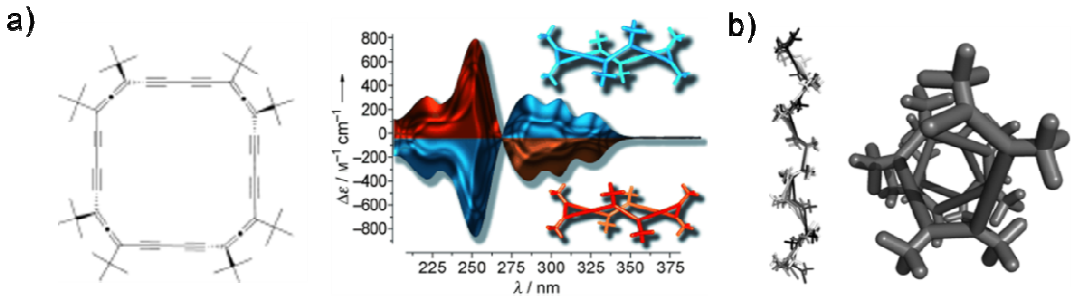

Figure 2. a) Structure of enantiopure macrocycles bearing four (P)-DEA units (left) and CD response for the two enantiomers (right);[9] b) predicted helical conformation of open DEA oligomers.[11]

Recently, Diederich and coworkers had being modifying the periphery of the DEAs in order to improve the conformational stability of these systems to further improve their chiroptical responses. This access to systems with powerful chiroptical responses is the starting point in order to explore them for real applications. However, the lack of functionality able to interact with different relevant species hampers their exploration as sensing probes.

- **Incorporation of functionality in allenic macrocycles.**

In order to functionalize allenic macrocycles, we have designed and synthetized allenophanes by the appropriate combination of **DEA**s and different aromatic spacers (**S**) (Figure 3, CTQ2010-18576 and CTQ2011-28831). The long synthesis of allenophanes bearing four allenes and four *para*-substituted anthracene[7] or pyridine[12] spaces (**DEA$_4$*p*S$_4$**) made difficult the access to functionalized macrocycles (Figure 3).

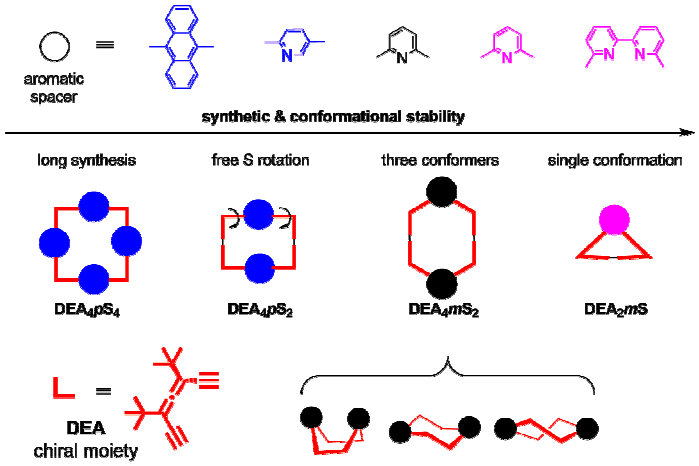

Figure 3. Schematic representation of the different synthetized allenophanes.

In order to significantly simplify the synthesis, we have developed a straightforward methodology for the synthesis of analog macrocycles bearing only two spacers.[13] **DEA$_4$*p*S$_2$** macrocycles bearing *para*-substituted pyridine and anthracene spacers were successfully prepared, however the free rotation of the aromatic unis rendered on a low conformational stability. For better understanding the structure-chiroptical responses relationship, conformational stable systems are desired. As a fact, while the *para*-substitution allows free rotation of the spaces, incorporation of *meta*-substituted pyridine rings instead in **DEA$_4$*m*S$_2$** completely block this rotation and largely enhanced the conformational stability to only three possible conformers (Figures 3 and 4a).[14] As an example for the efficiently of our synthetic methodology, enantipure **(*P*)-DEA$_4$*m*Py$_2$** could be synthesized in only three steps from the enantiopure **(*P*)-DEA** and in an overall yield of ca 40% (Figure 4b).[15] Despite the different possible conformations of this system its chiroptical responses are remarkable (Figure 4c).

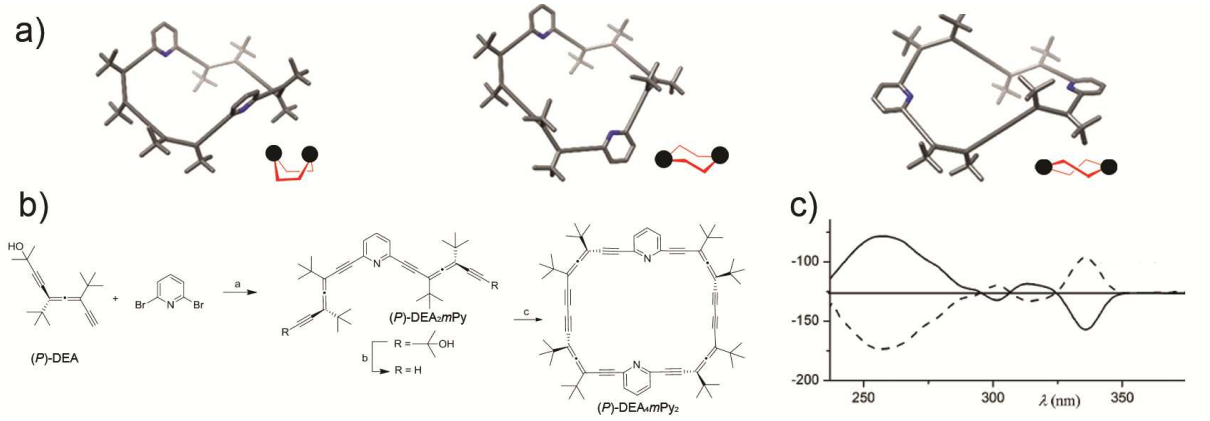

Figure 4. a) Three possible conformations of **(*P*)-DEA$_4$*m*Py$_2$** and its correspondence with scheme from figure 3; b) synthesis of **(*P*)-DEA$_4$*m*Py$_2$** (a) [$PdCl_2(PPh_3)_2$], CuI, TMEDA, toluene, 110 °C, 20 h, 79%; (b) NaOH, toluene, 110 °C, 2 h, 80%; (c) $CuCl_2$, CuCl, pyridine, 25 °C, 72 h, 57%; c) Experimental CD spectra of **(*P*)-DEA$_4$*m*Py$_2$** (solid line) and **(*M*)-DEA$_4$*m*Py$_2$** (dished line) in chloroform.

Finally, we wanted to go one step further in the conformational stability. To do so, we designed macrocycles bearing only two DEA chiral unis and one spacer, **DEA$_2$*m*S** (Figure 3),[16] to present one single conformation. Enantiopure **DEA$_2$*m*Py** and **DEA$_2$*m*bPy** were recently successfully synthesized and characterized (unpublished results). Particularly, **DEA$_2$*m*Py** showed strong chiroptical properties, however this allenophane rapidly photoisomerized under day light. We have previously observed the loss of chiral information in allenic structures for compounds bearing donating groups.[7,8] This phenomenon is certainly limiting the exploration of functionalized chiral species. Therefore, the search for more stable chiral building blocks is a critical issue if one aims at obtaining materials that could be used for real applications.

- **From allenes to spiranes, opening access to new chiral macrocycles.**

Spiranes, as allenes, can present axial chirality if appropriately substituted. Particularly, synthesis of photostable enantiopure 2,2'-diethynyl-9,9'-Spirobifluorenes (DES) in gram scale has been reported.[17] We considered this chiral building block as a candidate to further explore the construction of functional chiral frameworks. With the aim of evaluating the strength of the chiroptical responses of frameworks bearing DES moieties (Figure 5), in collaboration with C. Silva we performed a theoretical study comparing the CD and UV/Vis spectra of those with the DEA analogs (projects EM2013/017 and 212111120).

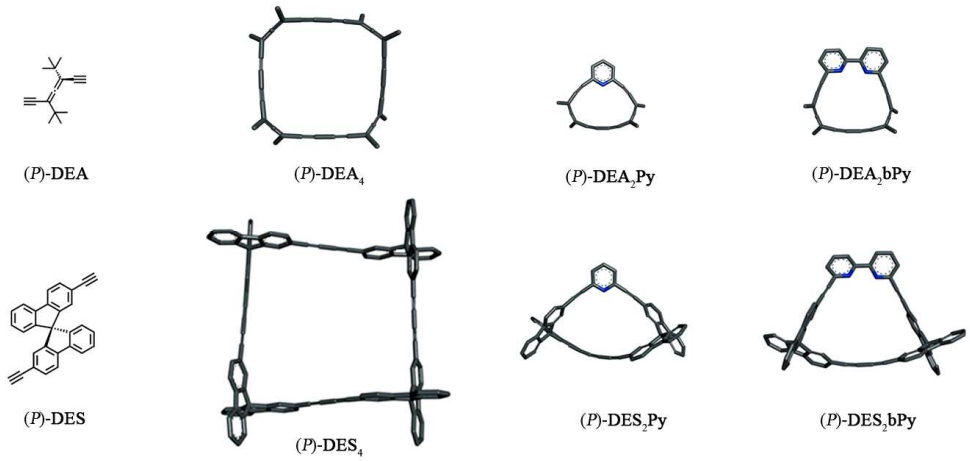

Figure 5. Schematic representation of (*P*)-DEA and (*P*)-DES chiral axes along with geometries of different macrocycles obtained at the cam-B3LYP/6-31G(d) level of theory. For the DEA derivatives *tert*-butyl groups were replaced by methyl groups to reduce computational cost.

Our predictions suggest that the chiroptical responses of DES macrocycles bearing pyridine or bipyridine as spacers should present as strong CD intensities as their DEA analogs. The same conclusion comes by comparing the DEA_4 and DES_4 (*submitted*) and therefore, exploration of DES will open access to new systems with strong chiroptical responses. More importantly, the quaternary carbon in DES should disrupt electronic conjugation. This phenomenon and its consequences in the chiroptical responses are now being studied by S. Castro-Fernández and J.L. Alonso-Gómez at Columbia University in collaboration with A. Petrovic and N. Berova (InTechSE). Development of a general simple model for the prediction of chiroptical responses of DES frameworks would certainly speed the design of new chiral frameworks with desired properties.

We are currently working on the synthesis of DES analogs to certify the theoretical predictions. Once the strong chiroptical responses are experimentally confirmed, the use of DES combined with spacers of different electronic character will open the exploration of new chiral frameworks for their use in real applications.

- **Helical Cages through Axial Chirality.**

From collagen to DNA, helical morphologies are ubiquitous in nature. Their fascinating chiral structures lead researchers to mimic them with helicates and helicenes. Molecular cages are also of great interest since they can act as artificial receptors and resemble propeller-like systems. However, the typically negligible or absent chiroptical responses limits their exploration for real devices. Axially chiral building blocks have been used to create new molecular topologies; yet, they have not been used in chiral cages.

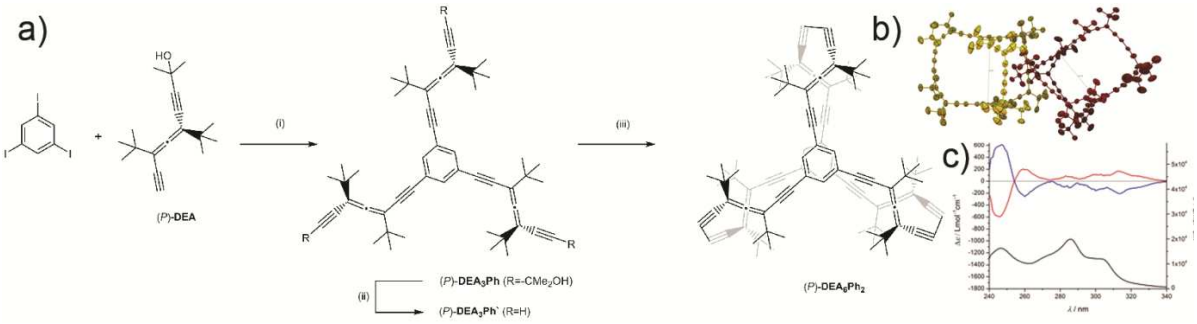

Figure 6. Synthesis of **(*P*)-DEA_6Ph_2**. (i) Triiodobenzene, (*P*)-DEA $[Pd_2(dba)_3•CHCl_3]$/CuI/ (ii), NaOH/toluene (iii) Cu(I)/Cu(II); b) ellipsoidal representation of the unit cell of the crystalline structure of **(*P*)-DEA_6Ph_2**. The unit cell contains two molecules, the red one being more twisted, which generate different intercentroid distances; c) CD and UV-Vis spectra of **(*P*)-DEA_6Ph_2 (blue) and (*M*)-DEA_6Ph_2** (red) in $CHCl_3$. In black UV-Vis spectrum of both enantiomers.

Recently, we have developed a general and simple methodology for the construction of helical cages through axial chirality. Moreover, we have synthesized **(*P*)-DEA_6Ph_2** (Figure 6a, project CTQ2011-28831) and unambiguously characterize its D_3-symmetric by X-ray diffraction (Figure 6b). The chiroptical properties of these shape persistent cages present, to the best of our knowledge, the largest *g*-factor reported to date for molecular cages (Figure 6c, *g*-factor is the ratio between CD and UV/Vis, and it typically measures the chiroptical efficiency of a particular system, *manuscript in preparation*).

This general methodology, supported by the first example of a helical cage, opens access to the construction of novel shape-persistent chiral cages with strong chiroptical responses, which, we believe will be very useful in the development of sensors.

- **Chiral Amplification through Self-assembly**

In Nature, homochirality is very present. This phenomenon has attracted the curiosity of many scientists. In this respect, understanding the transfer of chirality from a single molecule to its self-assembly is of great importance. The so called chiral amplification can provide remarkably enhanced chiroptical responses of the resulting aggregate compared to

the individual moieties. In this respect we were able to obtain a nanocomposite formed of a chiral gel and gold nanorods.[18] A theoretical model supports that the outstanding chiroptical responses are originated by the interaction between aquiral nanorods ordered chiraly in the bulk. We expect also a great chiroptical enhancement in systems bearing chiral allenes when self-assembled. On the oder hand, the study of chiral supramolecular systems at surfaces has attracted much attention in the last years due to their possible applications as sensors and catalysts. For the construction of such architectures, intrinsically chiral surfaces obtained by choosing particular planes of a metal crystal can serve as an initial platform. However, the use of organic molecules self-assembled on achiral substrates is a more versatile approach for the construction of chiral layers and nanosystems.

Scanning tunneling microscopy (STM) is a useful tool to investigate self-assembly of molecular architectures. The balance between substrate–molecule and molecule–molecule interactions along with the conformational freedom of the molecules determine the pertaining ordering scenarios. It has been demonstrated that homochiral domains may arise from interfacial resolution of racemic mixtures, or even from achiral molecules. Moreover, enantiopure substances can be employed in the construction of globally chiral architectures.[19] Chirality sensing is an emerging field with great potential for applications.[20] However, the very weak or absent chiroptical properties of the molecules commonly used for the construction of such sensors hamper their exploitation for real devices.

As mentioned above, cyclic and open allene oligomers feature outstanding chiroptical properties, which can be tuned by incorporation of aromatic units. On the other hand, J. Barth and coworkers explored the construction of 2D functional nanoarchitectures on surfaces, and programmed supramolecular chirality into 2D networks by adequate functionalization.[21] Conformationally flexible constituents proved to be advantageous to afford well-defined complex chiral architectures and networks. However, these self-assemblies can be classified as flat-lying architectures, in which nearly 50% of the van der Waals surface of each building block is in contact with the substrate, lowering versatility and molecular control. To overcome this shortcoming, up-standing chiral architectures (UCAs) are required in which only a small fraction of each tecton has contact with the substrate. However, to date, only in a few examples a partial decoupling of the functional chiral molecular unit from the metal substrate was achieved. In order to introduce the use of chiral allenes for the construction of UCAs, J.L. Alonso-Gómez stablished a collaboration with the Barth group (J.L. A-G stayed a total of 6 months over the last three years working closely with F. Klappenberger) at RUM in Munich, Germany.

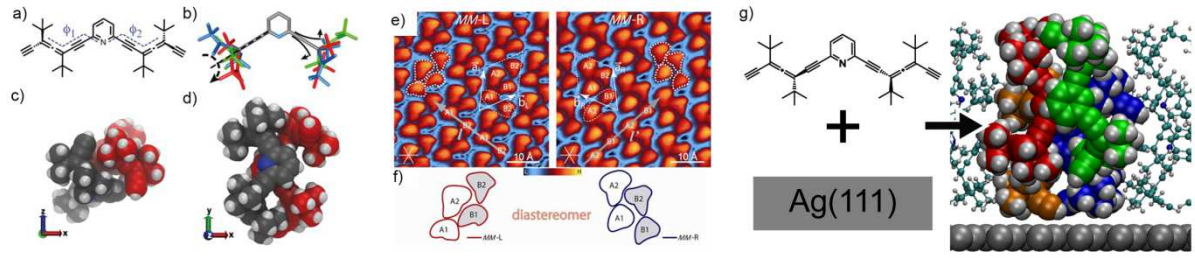

Figure 7. a) Chemical structure of **DEA_2Py** with definition of dihedral angles; b) scheme of the conformational freedom (black arrows); c) Top and d) side view of the intertwined dimer obtained from MD simulations; e) High-resolution STM images of MM-L and MM-R domains. Contours of single-molecule features depicted with dashed white curves; f) Schematic representation of A1, A2, B1, and B2 contours of MM-L and MM-R domains forming diastereomers.; g) MD model of the UCA over Silver (111).

We achieved the construction of a complex, up-standing chiral architecture from enantiopure allenes (CTQ2011-28831). Topological self-assembly was found to play a crucial role in the formation of these novel chiral surfaces as ascertained by a combination of computational modeling, mass spectrometry, and molecular manipulation studies. Careful analysis of high-resolution STM images confirms the transfer of chirality from single molecules to 2D networks (Chem. Comm., *accepted*). The use of enantiopure allenes with strong chiroptical responses along with their up-standing organization, in which the functional allene moieties are decoupled from the metal surface, opens great possibilities for the

construction of new smart materials that could be implemented into devices such as sensors or logic gates.

- **Chirality Sensing in Molecular Recognition.**

Chirality has inspired major advances in many research areas among which chemistry and life sciences are found, and it is the property by which a system gives different responses to right- and left-circularly polarized light. Most biomolecules are intrinsically chiral and such chirality implemented in the biopolymers enables stereoselective recognition of chiral external molecular stimuli by means of weak intermolecular forces. Thus, unraveling chiral recognition phenomena is of pivotal importance.[22] Here, we use the term Molecular Recognition as it includes host–guest, supramolecular and self-assembly processes. The interaction between two molecules is generally governed by either a single or a combination of non-covalent forces such as hydrogen bonding, metal coordination, hydrophobic, π-stacking, Van der Waals, and electrostatic interactions. In this context, there are several fields that use biosensing technology not only in life sciences such as general healthcare monitoring, screening for disease, clinical analysis and diagnosis of disease, but also in veterinary and agricultural applications, industrial processing and monitoring or even in environmental pollution controls. Biosensors can provide cost-effective, easy-to-use, sensitive and highly accurate detection devices in a variety of research and commercial applications.

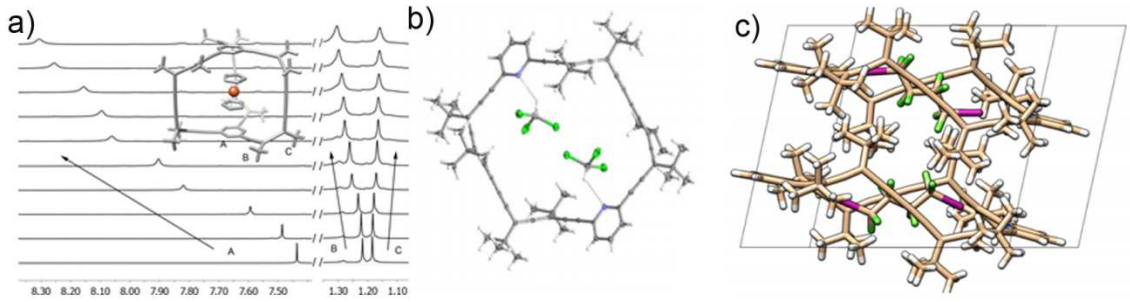

Figure 8. Inclusion complexes of a) ferrcenium, b) chloroform, and c) diiodo-perfluorobutane.

Shape-persistent macrocycles (SPM) are currently being the target of intense scientific research for their potential applications in sensing and guest recognition. A number of cyclophanes have been designed and developed over the years for the selective recognition of various guest biomolecules, such as nucleosides and nucleotides, amino acids, proteins and various nucleic acid structures.[23] Kawase and coworkers has reported the preparation of a chiral cyclophane with sensory abilities. However, the active form is in fast equilibrium with an achiral conformer which limits the usage of such systems.

Inspired by these findings, we have inserted DEAs into the molecular structure of achiral macrocyclic frameworks in order to create helical-chiral acetylenic cyclophanes because the availability of a chiral cavity provides the SPM with enhanced utilities in sensing processes (see the examples in figure 3). In order to delimit this cavity a bit further, we have embarked in the construction of chiral cages using DEA building blocks (figure 6). Whereas, supramolecular cages have been broadly studied, due to their ability in the recognition of biomolecules,[24] purely covalent organic cages are scarce.

We have studied the host-guest recognition of the **DEA_4pAnthracene** derivative with fullerenes and saccharides with no success. However, preliminary results have shown that the SPM bearing anthracene rings binds picric acid by π-π interactions (*manuscript in preparation*). The same type of interactions are most likely participating in the encapsulation of ferrocenium ion within the cavity of **(*P*)-DEA_6Ph_2** (Figure 8a) that showed an affinity constant in the range of 10 M^{-1} while ferrocene did not fit inside the cavity; the shorter size of the ferrocenium along with the presence of the charge, made the formation of the inclusion complex possible (manuscript in preparation).

A diasteromer of **DEA_4mPy_2** crystallized with two molecules of $CHCl_3$ per macrocycle (Figure 8b). The chloroform molecules and the macrocycle are involved in hydrogen bonding

interactions with a distance N•••H–CCl_3 of 3.244 Å, which indicates the presence of a weak interaction.[14] The formation of these hydrogen-bonded complexes led us to explore another important noncovalent interaction: the halogen bond, which are formed by donation from a lone pair containing donor such as amines to the σ-hole of an X–C bond (X = I, Br, Cl). Thus, the interaction of **(*P*)-DEA$_4$mPy$_2$** with diiodo-perfluorobutane rendered a bidentate iodine-bonded complex of C_2 symmetry in the AM1 potential surface. The K_a = 4.2 M^{-1} was determined by ^{1}H and ^{15}N NMR experiments (Figure 8c).[15] We have characterized this host–guest complexes by ^{1}H NMR and X-ray crystallography assisted by molecular modeling. However, up to now we were not able to use more sensitive optical techniques such as UV/Vis, steady-state and time-resolved fluorescence and CD due to the low affinity the complexes have shown. On the other hand, we used CD to characterize the inclusion complex between β-cyclodextrin and achiral resveratrol. The synergistic combination of CD, NMR and theoretical computations allowed describing the origin of a Cotton effect induced by β-cyclodextrin on resveratrol as electronic due to orbital mixing between resveratrol and β-cyclodextrin (Figure 9a).[25]

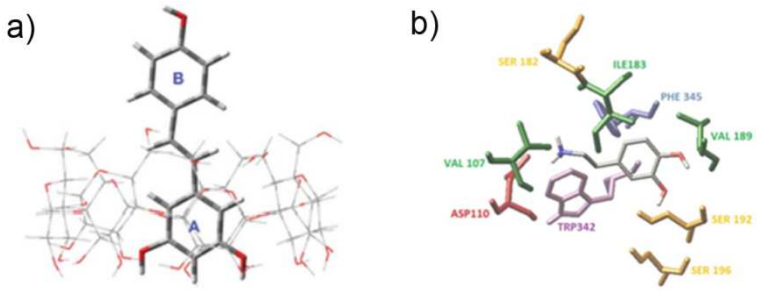

Figure 9. Inclusion complex of a) resveratrol and b) dopamine.

Aiming to design chiroptical devices with tailored functionalities, in collaboration with Prof. Fabrizio Santoro (CNR, Pisa, Italy, InTechSE) we are investigating the sources of the chiroptical responses by computational modeling since simple empirical correlations are in many cases insufficient for rationalizing the experimental observations.
In collaboration with C. Silva at UVigo and M. Loza at USC, we were set to design hosts for biologically relevant amines using the information of the crystallized natural receptor complexes, keeping in mind that the crystallized form is not often the active conformation. In this sense, the crystallization of the dopamine D3 receptor (D3R) forming a complex with the specific antagonist Eticlopride has stimulated *in silico* studies of the ligand-receptor interactions in the binding pocket because dopamine is an important neurotransmisor involved in the modulation of motor activity, cognition, emotion (Figure 9b). For the purpose of gaining atomistic detail of the binding pocket, we have carried out docking simulations of several antagonists and agonists along with the natural ligand, dopamine to determine the critical amino acids in the interaction of agonists vs antagonists and the existence of a second binding pocket, in which the selectivity could reside. We have also proven the importance of TM3 helix in the biding interaction (*submitted*).

- **OraganoGels as Sensors**

Organogels, consisting of low molecular weight organogelators (LMWOG) and organic solvents, have the unique structural feature of a fine distribution of nano-sized fibers, formed by self-assembly of the organogelator molecules, among solvent molecules. Gels have solid-like rheology and do not flow, despite being predominantly liquid in composition.[26]

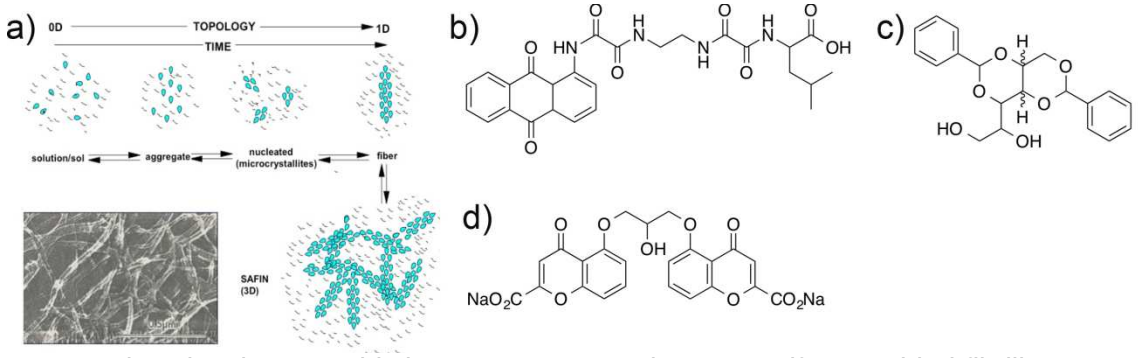

Figure 10. a) Molecule assembly into 3D structures (SAFIN, self-assembled fibrillar network); b) naphthoquinone oxalamide; c) dibenzylidene sorbitol; d) disodium cromoglicate.

In the early nineties stimuli-sensitive gels were developed inspired in previous work done by T. Tanaka[27] and, after some search of technical applications, nowadays they have been incorporated into commercialized devices, e.g. Hydrogel Valves.
In particular, remarkable efforts have been addressed to design pH sensors by adding either weak acidic or basic groups to the gelator, in which the phase transition occurs in a small range close to the apparent acid dissociation constant (pKa) of the gel which is mostly identical to the pKa of the ionisable group.[28]
Molecular gelation systems are characterized by a strong tendency of the small organic molecules to aggregate in solution into one-dimensional fibrillar architectures. Formation of these elongated structures is mainly governed by solvophilic–solvophobic effects stabilized by unidirectional non-covalent interactions such as hydrogen bonding and π–π stacking. One has to keep in mind that gelation depends on key structural features of the gelator but not on specific gelator-liquid interactions other than those related to solubility. Thus, the crucial point resides in the design of the gelator. A potential model is based on the concept of AL gelators. These compounds consist of a π-conjugated aromatic group (A) connected to an alkyl chain, modified alkyl chain, or aromatic group (L). However, the phenomenon of gelation is difficult to fully predict.
The past decade has witnessed an explosion of interest in and applications of low molecular weight compounds that form hydro- and organo-gels (almost 500 papers appeared in the literature using the search term ‘molecular gelator in Scopus from 1999-2012). As the techniques available to chemists and materials scientists for characterizing these fascinating, disordered materials, such as electron microscopy and neutron and X-ray diffraction techniques, continue to develop, in tandem with our growing understanding of the chemical basis for their self-assembly, it is likely that the field will continue to experience exponential growth at the frontiers of chemistry and soft materials science.

A particularly interesting area for future study is the design of functional gelators capable of providing an active medium as part of hybrid materials. In this field, our research group has reported the organization of nanoparticles into three-dimensional chiral arrangements, with a record level of optical activity, by adsorbing the nanoparticles onto a scaffold of supramolecular anthraquinone-based oxalamide fibers with chiral morphology, through specific non-covalent interactions. The fabrication process involves the self-assembly of gold nanorods on a fiber backbone with chiral morphology.[18]

One aspect that generates great interest among researchers is to control and better understand helicity of supramolecular structures because chiral supramolecular structures play an important role in Nature. We are currently focusing our efforts on the non-trivial task of preparing new organic precursors to obtain chiral fibers in which the helix morphology is well defined, and in which parameters such as diameter and pitch are controlled, with the aim of obtaining metal nanoparticle composites with intense optical activity. On the other hand, chromonic phases, phases formed by molecules that spontaneously form anisotropic assemblies in solution, due to their potential application in functional materials, nanotemplating, and biosensing have attracted interest. Cromolyn nematic liquid crystal phase has been demonstrated to be a good weakly aligning medium for small water- soluble organic molecules. We have demonstrated that the medium is compatible with a variety of samples regarding their polarity such as saccharides, a water-soluble non-ionic polycyclic alcohol and a water-soluble quaternary ammonium iodide alkaloid derivative, and that degree of alignment can be tuned by varying the mesogen concentration, the temperature and by

addition of brine. [29] In this field, M. Cid spent five months, under the mobility program of MEC, in the group of R. Weiss at Georgetown University, to study the gelating ability of cromolyn and naphthoquinones esters. Currently, E. Troche is deciphering the gelating abilities of another derivatives of both cromolyn and naphthoquinone also at Georgetown University under the support of the network InTechSE. Additionally, in collaboration with R. Weiss we are studying the structure of dibenzyledene sorbitol (DBS) regarding the unknown configuration of the hydrogens at the bridge carbons. DBS is a low molar mass organic gelator (LMOG) that self-organizes into nanofibrils inducing network formation in a variety of organic solvents and polymers to produce stable organogels widely used in several technological aplications.
As a general behavior for nematic liquid crystal phases, this phase becomes cholesteric upon addition of chiral guest molecules, such as amino acids. Because of their backbone rigidity (cf. low conformational fexibility) and relative ease of acetylene functionalization, axially chiral DEAs are also appealing candidates for the chiral doping of nematic liquid crystals.[30]

- **Stable Functionalized Surfaces**

Access to sensitive surfaces featuring selective molecular recognition is of great interes towards the development of new sensing devices. The prospect to use self-assembled monolayers (SAMs) of chiral molecules for modifying polarization of visible (Vis) to near infrared (NIR) radiation as a function of type and quantity of target molecules is particularly challenging, because it would open new routes to the design of miniaturized photonic biosensors, that can be integrated in microelectronic devices and ultimately in Photonic Integrated Circuits (PICs) for advanced LabOnChips. The integration of these chiral molecules in flexible electronics and mainstream Complementary Metal Oxide Semiconductor (CMOS) technology, would boost processing speed and detection accuracy, thus be of enormous benefit for telemedicine and the reliability of a variety of sensing devices for different health, environmental and home land security issues.

Main challenge is the efficient and stable anchoring of the chiral molecules on different surfaces, such as polymers, metals and group IV semiconductors or their stable oxides. To solve this challenge and achieve the requires SAMs, on PICs compatible materials, several strategies are well known (*Biosensors and Bioelectronics* 24, **2009**, 2528–2533), and can be also applied to chiral molecules:

i) Activating the chiral molecule through a functional group like –N_3 or –SH to promote its reaction with the surface of interest, and the formation of a stable bond between surface and chiral molecule, maintaining its capability to serve as chiral transducer.
ii) Achieve the same effect through activating the surface itself instead of the chiral molecule.
iii) Use an intermediate molecule that will react with both, the surface and the chiral molecule.

While the 3rd approach implies the synthesis of an additional component, thus additional costs, the first 2 approaches consist in straightforward processing routes that need to be studied for the proposed chiral molecules.

Main drawback of both approaches is that the anchoring has mostly been studied using wet chemistry processes, which are of low cost but sometimes not compatible with conventional processing lines of PICs and LabOnChips. This is specially the case if advanced photonic devices with efficient Group-IV materials, like Germanium or Silicon-Germanium-Tin alloys are aimed. To avoid cross contamination and oxidation of critical device components a “dry” approach in inert gas atmosphere or in high vacuum would be highly beneficial.

We have achieved enormous progress in the last years for both approaches (i) and (ii) as well as in developing new materials and structures for photonic devices and PICs, using laser assisted techniques or conventional heating processes in high vacuum, both for large area and local micro-processing. A complex molecule like BOC-Lysine-N_3 has been attached to polymer surfaces (approach (i)), polymer and metal surfaces have been locally funcionalized with with -NH_2 or -OH through approach (iii) and new materials for PICs been developed (*J. Applied Biomaterials and Biomechanics*, **2011**, 214-222, *Applid Physics Letters* **2013**, 192110S; *Microelectronic engineering*, **2014**, 18-21).

C.1.2. *Hypothesis and Objectives*

Hypothesis

- The new cyclic and cage-shaped frameworks aim of this proposal will recognize biologically relevant species and present chiroptical responses upon complexation. This hypothesis is based on two facts: chiroptical responses are very sensitive to supramolecular interactions and the frameworks under study present outstanding chiroptical responses.
- Chiral spiro frameworks will present strong chiroptical responses. This hypothesis is based on our theoretical simulations.
- Incorporation of anchoring groups to open chiral frameworks will render stable UCAs under ultra-high vacuum conditions. This hypothesis is based on examples in the literature of self-assembled monolayers.
- The chiroptical responses will be enhanced by self-assembly. This hypothesis is based on our experience on the collective chirality of nanorods and several examples in the literature of chiral amplification in gels and surfaces.
- The self-assembly of chiral frameworks bearing chiral axis will form chiral gels. This hypothesis is based on our own experience on the formation as gels, as well as on several examples in the literature.
- Stable surfaces will be built with our UCAs under ambient conditions for the construction of devices based on our experience and literature examples.

General Objectives: **Development of Smart Chiral Frameworks for Chirality Sensing**

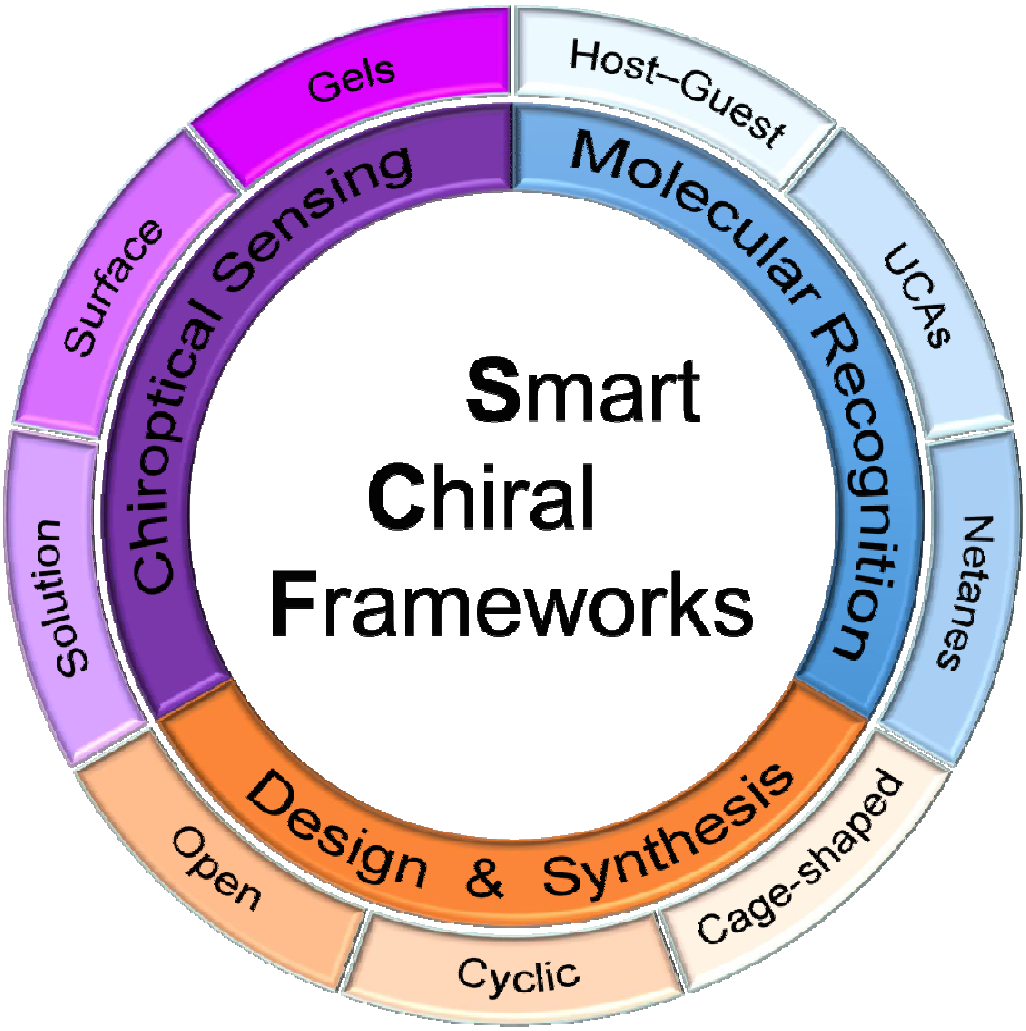

Figure 11. General Objectives

Work package 1: Design and Synthesis

- Design and synthesis of open, cyclic and cage-shaped chiral frameworks by an appropriate combination of allenic **DEA** and functionalized spacers.
- Design and synthesis of open, cyclic and cage-shaped chiral frameworks by an appropriate combination of spiranic **DES** and functionalized spacers.

Work package 2: Molecular Recognition

- Host–Guest molecular recognition of biologically relevant species by the cyclic and cage-shaped chiral frameworks.
- Self-assembly of open chiral frameworks for the construction of stable UCAs.
- Self-assembly of helical cages forming host–guest structures through the interaction of the invited guests for the formation of Netanes.

Work package 3: Chiroptical Sensing

- Chiroptical sensing of biologically relevant species.
- Preparation of chiral gels via the self-assembly of open chiral frameworks and study of their chiroptical responses.
- Preparation of stable surfaces functionalized with UCAs for the exploration of their chiroptical properties.

The ultimate objective of this proposal is to open the possibility of using smart chiral frameworks (SCF) for sensing. The achievement of the goals of this project would certainly be of great impact on the European challenge "**health, demographic change, and wellbeing**". Since 1980, the population of people 60 years of age and older has doubled and will reach 2 billion by 2050, according to the World Health Organization (WHO). Then, this age group will outnumber children up to 15 years of age – a shift that brings complex healthcare challenges. Access to smaller and cheaper sensors will contribute on the development of the telemedicine, of great importance for the sustainability of the European health system in the near future.
The goals of this project are expected to have an important impact in the scientific community, not only from the purely academic side, but also in medical diagnosis and technological applications.

C.1.3. *Specific Objectives*

Work package 1: Design and Synthesis

- Design and synthesis of macrocycles bearing two/four allenic DEAs and one/two spacer/s (**DEA_2S**/**DEA_4S_2**). (M. Cid)

- Design and synthesis of model DES systems to stablish a general simple model for the prediction of their chiroptical responses. (J. L. Alonso)

- Design and synthesis of macrocycles bearing four spiranic DES and two spacers (**DES_4S_2**). (J. L. Alonso)

- Design and synthesis of cages bearing six spiranes (**DES_6S_2**) or allenes (**DEA_6S_2**) and two spacers. (J. L. Alonso)

Work package 2: Molecular Recognition

- Host–Guest complexation studies of cyclic and cage-shaped chiral frameworks (M. Cid).

- Design and synthesis of open oligomers bearing two allenes and one spacer (**DEA_2S**) and their self-assembly for the construction of UCAs. (J. L. Alonso)

- Design and synthesis of open oligomers bearing two or three allenic DEAs and one spacer (**$DEA_{2/3}S$**) to form chiral gels. (M. Cid)

- Exploration of the self-assembly of host–guest complexes of helical cages with appropriate guests for the construction of Netanes. (J. L. Alonso)

Work package 3: Chiroptical Sensing

- Chiroptical sensing of host–guest complexes of cyclic and cage-shaped chiral frameworks. (J. L. Alonso)

- Study of chiroptical amplification of chiral gels. (M. Cid)

- Efficient anchoring of UCAs on different surfaces to allow their use as transducer in reusable chiroptical sensors. (S. Chiussi)

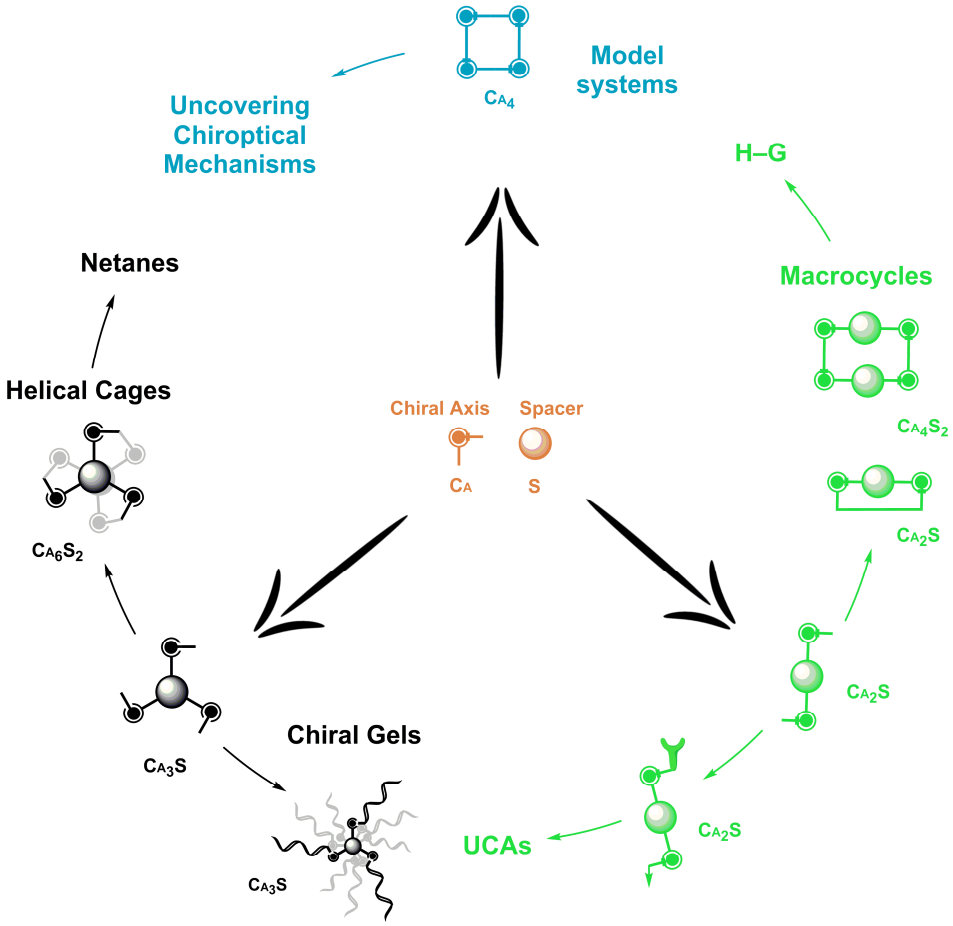

Figure 12. Specific objectives.

Methodology

Work package 1: Design and Synthesis

- **Design and synthesis of macrocycles bearing two/four allenic DEAs and one/two spacer/s (DEA$_2$S/DEA$_4$S$_2$). (M. Cid)**

The alteration in the photophysical properties of cyclic systems in the presence of guest molecules results not only in the chiroptical signalling of the recognition event, but also in the quantification of their supramolecular complex formation. A biosensor combines the selectivity of the molecular recognition of the biomolecules and the sensitivity of the signal

transducers. Besides, chiroptical sensors have advantages over potentiometric sensors in that they do not require a reference cell and are free from electrical interference.

Despite all of the work already done, we are still far from being able to exert intellectual control over most molecular-recognition phenomena. So, we will design new selective chiral-SPM to sense via hydrogen bonds neutral biomolecules such as creatinine (an indicator of renal function) or ions such as pyrophosphate (PPi).

The methodology developed in our group[13] will be applied for the construction of new chiral allenophanes bearing different functional groups to target the molecular recognition of biologically relevant species. As mentioned above, direct conjugation of DEAs with electron rich spacers results in loss of the chiral information due to isomerization of the chiral axis.[7] Consequently, the spacers chosen for the construction of allenophane will not have electron rich character (Figure 12 and electron poor spacers in Figure 13). While **DEA_2S** are expected to present a single conformation, we consider the exploration of the larger siblings **DEA_4S_2** since one of the three expected conformations maybe favorable upon molecular recognition with the target guest, inducing large alteration on the chiroptical responses.

- **Design and synthesis of macrocycles bearing four spiranic DES and two spacers (DES_4S_2). (J. L. Alonso)**

Spiranes will be used for the construction of **DES_4S_2**. The photostability of the DES chiral building block will permit the exploration of cyclic chiral frameworks with electron rich character. The synthesis of this moiety is known in the literature[17] and recently we were able of reproducing this gram scale synthesis in our laboratory. Based on our theoretical prediction we expect that tha spirophanes will present comparable chiroptical responses to the DEA analogs. Therefore, access to macrocyles with strong chiroptical responses and different electronic character will permit targeting the recognition of a large variety of biologically relevant species (Figure 12 and 13).

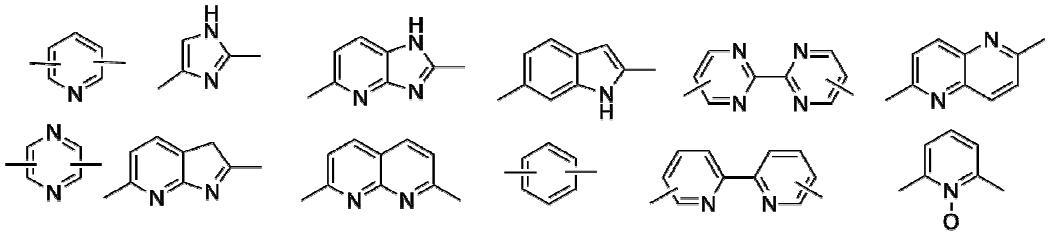

Figure 13. Proposed spacer for the construction of cyclic frameworks.

- **Design and synthesis of model DES systems to stablish a general simple model for the prediction of their chirotical responses. (J. L. Alonso)**

Comparison between already existing DEA derivatives, particularly with **DEA_4** and DES analogs would be perform in order to experimentally prove our theoretical predictions. S. Castro and J. L. Alonso are currently at Columbia University for two and one moth respectively, working with N. Berova and A. Petrovic. The aim of this stay is to develop a general method for the simple prediction of chiroptical responses of DES frameworks. Preliminary results show that the two parts of the DES connected by the quaternary carbon can be considered as independent chromofores. If this method can be obtain, it will be not only very valuable for cyclic and cage-shaped framworks but also for the study of chiroptical amplification of interacting self-assembled open frameworks in gels or UCAs (Figures 5 and 12).

- **Design and synthesis of cages bearing six spiranes (DES_6S_2) or allenes (DEA_6S_2) and two spacers. (J. L. Alonso)**

We will apply our developd methodology already tested in the synthesis of **DEA_6Ph_2** for the construction of the perfluorenated analog **$DEA_6Ph_2F_6$**. The corresponding DES analogs **DES_6Ph_2** and **$DES_6Ph_2F_6$** are also planned as model systems for the comparison of the chiroptical porperties of DEA and DES structures (Figures 12 and 14).

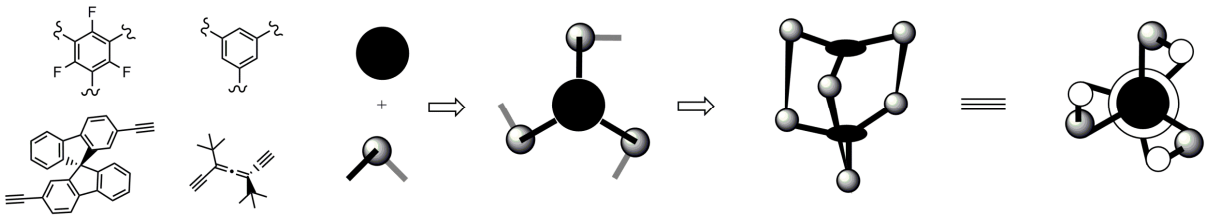

Figure 14. Formation of helical cages from axially chiral building blocks.

Use of larger spacers for a more appealing π–π interactions will be explored with triangulenes provided by M. Kivala.[32]

Work package 2: Molecular Recognition

- **Host–Guest complexation studies of cyclic and cage-shaped chiral frameworks (M. Cid).**

We have experience on the study of host–guest complexes[15,25,31] with NMR and X-ray. Exploration of the molecular recognition of the synthetized cyclic and cage-shaped chiral frameworks will be undertaken with different biologically relevant species mainly by means of hydrogen bonding and hydrophobic interactions (Figure 12).

Within the past decade, the ability to detect PPi has become important in cancer research. Various types of receptors with amide, pyrrole, urea, and imidazolium moieties have been used as anion chemosensors.

Sensing of saccharides is crucial for some therapeutic approaches and inspired by the X-ray structures of saccharide-protein complexes a number of artificial sugar host molecules have been developed, though not necessarily with a specific consideration of the chirality of the system that would help in detecting points to solve the problem. Hydroxyquinoline- and naphthiridine-based acyclic receptors have been reported to bind monoscharides via hydrogen bondings.

Another area of recent interest is the enantiomeric recognition of organic ammonium cations by chiral macrocyclic ligands. Chiral pyridine-containing macrocycle have indicated excellent enantiodiscrimination for the enantiomers of chiral organic ammonium guests. The pyridine subunit of these macrocycles were reported to be important for the complex formation due to its ability to form hydrogen bonds and also to stablish π-π interactions.

- **Design and synthesis of open oligomers bearing two allenes and one spacer (DEA_2S) and their self-assembly for the construction of UCAs. (J. L. Alonso)**

We have shown that up-standing chiral architectures (UCAs) can be formed by the self-assembly of open chiral frameworks **DEA_2*m*Py** (Chem. Comm. *accepted*). These novel chiral surfaces open a great opportunity for their exploration in chiroptical sensing. However, for the moment their stability is very low. In order to increase the stability of this promising surfaces, incorporation of anchoring groups to enhance molecule-surface binding stability will be carried out (Figures 12 and 15).

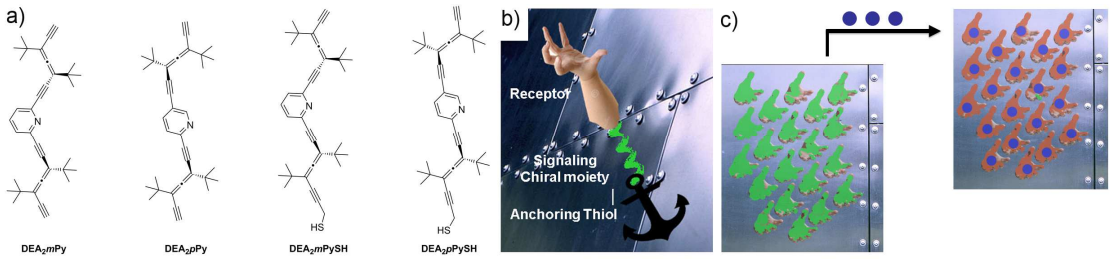

Figure 15. a) Structure of already used **DEA_2*m*Py** open chiral framework and the proposed structures in order to improve UCAs stability; b) General scheme with the different parts of a smart chiral framework (SCF) for the construction of functionalized surfaces for chiroptical sensing; c) Schematic representation of a surface functionalized with SCF sensing an analyte.

Enantiopure **DEA_2*m*Py** shows chiral transfer from the molecular level to the overall chiral surface. We expect that this morphological self-assembly could be improved by using

para substituted **DEA$_2$*p*Py**. Also the incorporation of thiol groups is expected to considerably enhance the UCA stability with **DEA$_2$*m*PySH** and **DEA$_2$*p*PySH**. The synthetized open chiral frameworks will be studied by STM at TUMunich thanks to a collaboration with F. Klappenberger. The results from the STM studies will help on the design or new SCFs for the construction of stable UCAs.

This objective is partially shared by the recently funded Explora Ciencia (CTQ2013-50575-EXP).

- **Design and synthesis of acyclic oligomers bearing two/three allenic DEAs and one spacer (DEA$_{2/3}$S) to form chiral gels. (M. Cid)**

Derivatives of mesogenic skeletons will be synthesized according to known very simple procedures, starting with commercially available naphthoquinone dihalides and diaminobenzenes, to prepare the naphthoquinone, the triazine and the phenazine derivatives, respectively (see figure 13 and 16). The chiral motifs will be appended directly via a C—C bond or via amides, urea or carbamate groups to take the advantage of the presence of additional hydrogen bonds to expedite gelation.

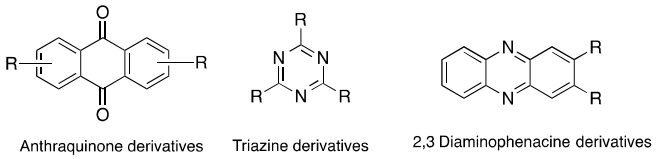

Figure 16. Proposed mesogenic cores.

Gelification conditions will be tested on standard solvents and, above all, in water. After gelification conditions are established, we will study the sensing capabilities of the structures by ECD and other chiroptical techniques. We will further characterize the structures of these phases using X-ray diffraction, if possible, as well as scanning electron microscopy. Modified derivatives with fluoroalkyl or ethylenglycol chains and carbamate or urea-capped derivatives will be properly synthesized and studied in the same way. Further studies, such as recording of ECD, UV-Vis, ^{1}H and ^{13}C chemical shift dependencies on solute concentration, combined with DFT computation of shifts in π-stacked dimers and trimers will provide further data about the structure of aggregates in solution.

Also, we will characterize the organogel at the molecular level by conventional techniques, such as NMR and semi-empirical calculations or assuming that the gelator shape is the same as that found by single crystal X-ray diffraction (where such data are available). In fact, it was reported that X-ray diffractograms of the organogels, aerogels and crystalline powders of either chiral or racemic 12-hydroxyoctadecanoic acid have almost the same structural features.

Those gels with an appropriate helical morphology, namely pitch size and width, will be used to construct nanocomposites to subsequently study the chirality of the resulting gel-nanoparticle nanocomposite either by individual chiral induction from the polymer to the nanoparticle or by a collective mechanism based on 3D assembling of nanoparticles on the surface of the polymers. This work will be done in a collaborative venture with Prof. L. Liz-Marzán group that has been established in past years.

- **Exploration of the self-assembly of host–guest complexes of helical cages with appropriate guests for the construction of Netanes. (J. L. Alonso)**

In addition to use helical cages as artificial receptors, our of our long term dreams is the construction of Netanes. This new concept aims at the regular ordering of helical cages in surfaces. The mechanism is proposed in two steps: the first is the formation of an inclusion complex, and the second is the self-assembly of the host–gest complexes by driven by the interaction between neighboring guests Figure 17).

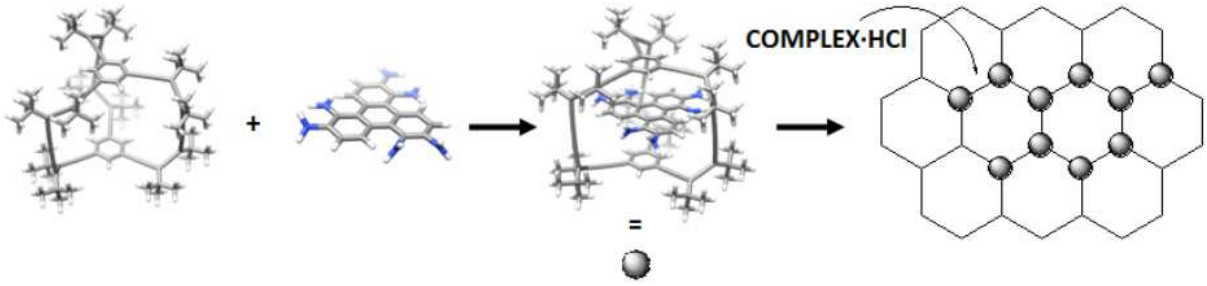

Figure 17. Schematic representation for the formation of Netanes.

In a stay of two months by S. Míguez at TUMunich, in collaboration with C.-A. Palma, molecular dynamic simulations MD were carried out. These simulations predicted the formation of a honey nest like structure by the partial protonation of hexaaminotripheniles (HATP) being guests of the helical cage **DEA_6Ph_2**. Unfortunately, the very different solubility of HATP compared with that of **DEA_6Ph_2** did not allow for inclusion complex formation. Several different aromatic compounds were tested for the host–gest formation without success. We considered that probably the ca 1 nm distance between the two opposite phenyl rings in the cage is too large for a favorable π–π interaction with both faces of the aromatic guest. Therefore we studied the complexation with organometallic sandwich compounds and found positively charger ferrocenium to form a complex (Figure 8a). This opens not only the use of helical cages for their use in chirotical coupled with electrochemistry sensing, but also the possibility of exploring the formation of Netanes by the interaction between the guest horganometalic sandwich species.

This objective is very ambitious and may not be in the scope of the present proposal. However, the exploration of these complexes will be of great importance for the development of chiroptical sensors.

Work package 3: Chiroptical Sensing

- **Chiroptical sensing of host–guest complexes of cyclic and cage-shaped chiral frameworks. (J. L. Alonso)**

The sensitivity of chiroptical spectroscopies like ORD and CD will be tested for the host–guest complexes found. Theoretical calculations will help to understand the induced responses and to enable the design of more efficient sensors. The experimental and theoretical studies of model systems will be very relevant also in this objective (Figure 11).

- **Study of chiroptical amplification of chiral gels. (J. L. Alonso)**

Amplification of the chiroptical responses of chiral gels compared to the constituting isolated monomers will be studied theoretically and experimentally. The development of the general model mentioned above and comparison with experimental results will help on the design of more chiroptically efficient gels. Sensitivity towards biologically relevant species will be tested (Figure 11).

- **Efficient anchoring of UCAs on different surfaces to allow their use as transducer reusable chiroptical sensors. (S. Chiussi)**

Once SCFs for efficient formation of stable UCAs are available, they will be used for the functionalization of surfaces that can be manipulated in ambient conditions. Aiming future application in biomedical devices can not only rely on wet chemistry processes, but implies the need to development and evaluation of anchoring processes that are compatible with photonic and microelectronic device technologies. We have experience in conventional thermal as well as in advanced UV laser assisted CMOS compatible deposition and functionalization processes that can provide SAM on large areas and as microstructures. Our experience in characterizating surfaces and ultrathin films as well as funtionalized structures through AFM-ESI, Raman, TERS; XPS, TEM and ellipsometry will guarantee the capability to obtain an exhaustive study on the anchoring processes and the stability of the resulting products. Additionally, ellypsometry will be carefully analyzed to explore the possibility of

measuring the chiroptical responses of the prepared chiral surfaces and AFM - Raman or TERS to study their morphology.

5. M**edios materiales, infraestructuras y equipamientos singulares**

This **research group** develops its work in laboratories assigned to the Department of Organic Chemistry as well as in the ISO-class 6 compatible clean room with ISO class-2 mini-environments of the New Materials group at the Industrial Engineering School.
The following infrastructure is available:
Department of Organic Chemistry laboratory: Lines to carry out reactions under an inert atmosphere. High vacuum line. Rotary evaporators for solvent removal. Small Equipment: storage of reagents, electronic scales, plate stirrer with heating, etc.
New Materials Clean room:
Several equipments for evaporation, sublimation and functionalization of materials through conventional thermal as well as UV laser assisted processes. UHV and HV processing systems Thermal Effusion system to determine thermal stability of functionalized surfaces
Several Raman spectrometers and characterization equipments (contact angle, reflectivity, ellipsometer, profiler, …) Equipments for microstructuring surfaces through UV laser radiationThe following means: Lines to carry out reactions under an inert atmosphere. High vacuum line. Rotary evaporators for solvent removal. Small Equipment: storage of reagents, electronic scales and plate stirrer with heating.

In addition, the **Chemistry Department** has equipment suitable for the development of several types of techniques: Ozonizer equipment. System for catalytic hydrogenation. Equipment to carry out high pressure reactions. Microwave equipment. Photochemical equipment. Gas chromatograph. Polarimeter.

The **Support Center for Scientific and Technological Research** (CACTI) of the University of Vigo has modern equipment: Nuclear magnetic resonance. Mass spectrometry and Infrared spectrophotometer Jasco FT / IR 4200. Elemental analysis. X-ray diffraction. Spectrophotometer from circular dichroism, linear dichroism and UV-vis. Jasco-815. UVISEL Spectroscopic Ellipsometer. AFM-Raman and Tip enhanced Raman spectroscopy (TERS) X-ray photoelectron spectroscopy (XPS). Time of Flight Secondary Ion Mass Spetroscopy (TOF-SIMS). Scanning Electron Microscopes (SEM) and Transmission Electron Microscopes (TEM) with Focussed Ion Beam (FIB) specimen preparation.

Researchers of the group have access to the resources of high performance computing center, **Supercomputing Center of Galicia**.

6. Un **cronograma**

Milestone	Work Package	Deliver month	Deliver
1	**1**	12th	First **DEA_2S** and **DEA_4S_2** derivatives
2	**1**	12th	First **DEA_6S_2** derivatives
3	**1**	6th	**DES_4** model compound
4	**1**	12th	First **DES_4S_2** and **DES_6S_2** derivatives
5	**2**	24th	**Host–Guest** complexes of cycles and cages
6	**2**	24th	Stable **UCAs** in Ultra-high Vacuum
7	**2**	18th	Preparation of gels of **DEA_3S**
8	**2**	30th	Stable **Host–Guest** cage complexes for Netanes
9	**3**	36th	**Chiroptical Sensing** with Host–Guest complexes
10	**3**	36th	**Chirotical Amplification** in gels
11	**3**	36th	Stable **Chiral Surfaces** in normal conditions

7. C**ontratación de personal.**

In an organic research laboratory there are some routine tasks that qualify to hire someone to assist in the advancement and development of the proposed project in its early stages. The researcher to hire will deal with the synthesis and separation of precursor compounds of the aim targets in the present proposal as well as with basic maintenance work of the organic

chemistry lab so that the scientific researchers could concentrate on and perform the more complex processes in the laboratory.
Tasks often involve: performing laboratory basic reactions in order to produce reliable and precise data to support scientific investigations; constructing, maintaining and operating standard laboratory equipment, ensuring the laboratory is well-stocked and resourced; keeping up to date with technical developments, especially those which can save time and improve reliability; conducting searches on identified topics relevant to the research.
This person should provide all the required technical support to enable the laboratory to function effectively whilst adhering to correct procedures and health and safety guidelines.

C.2. IMPACTO ESPERADO DE LOS RESULTADOS

Impact:

– Understanding of the origin of the chiroptical responses of allenophanes in particular and, in general, a better understanding of the mechanisms responsible for the optical activity. This knowledge can be used for the design of devices with tailored chiroptical properties.

– Understanding the origin of the optical activity together with the capability of conformational characterization will be very useful for studying host–guest chiral complexes via their chiroptical properties. In this context, allenophanes have great potential for chiral discrimination by complexation.

– This project is only the first part of a more ambitious and broader plan with the aim of designing systems with singular chiral properties which could further be combined with other properties to furnish new functional materials.

– The development of new sensing devices in solution, on surfaces of gel-like would improve the diagnostic abilitites of crucial ailments within the challenge of Horizon 2020 "**Health, demographic change and wellbeing".**

Diffusion plan:

And overview of the research group is located at the website: http://webs.uvigo.es/webqo3/
And more particularly concerning the present project at: www.smartchiralframeworks.com
The most important results from our research will be disseminated as:

- Publication of scientific papers in international journals.
- Doctoral theses and master projects of the graduate students
- Communications to national and international meetings.

The most important scientific journals related to our area, where we intend to publish our results are:

- Journal of the American Chemical Society
- Angewandte Chemie, International Edition
- Chemistry: An European Journal
- Organic Letters
- Journal of Organic Chemistry
- Nano Letters

The members of our research group have published several papers in scientific journals, such as Angewandte Chemie, Journal of the American Chemical Society or Accounts of Chemical Research, which is a proof of their capacity to generate high impact research.

Transfer:

We are already in contact with a biotechnology cluster in Galicia (Bioga) to pursue a company that could take advantage of our results.
Also, to make our results more visible to the scientific community and to the industrial world, we belong to the REGID (R+D galician network on drugs) led by M. Loza (USC) and participate in the organized meetings.

C.3. CAPACIDAD FORMATIVA DEL EQUIPO SOLICITANTE

The present project combines organic synthesis, chiroptical spectroscopies and applicability of the target systems. So, the students will have the opportunity to acquire solid basic and practical knowledge in organic synthesis and structural determination of organic compounds. The Postgraduate Program of the Department of Organic Chemistry of the University of Vigo is part of an interdisciplinary program in which University of Santiago de Compostela and Unviersity of A Coruña are also participating in which M. Cid teaches the course “Supramolecular Chemistry” and J. L. Alonso “New Materials”. Complementarily, we organize theoretical and literature seminars with other researchers from our area on a regular basis.

Our group has access to many technical resources to be used for our graduate students. We can emphasize the NMR facility of the Universidad of Vigo, with 600 and 400 MHz spectrometers, and the Centro de Supercomputación de Galicia (CESGA, Galician Centre for Supercomputation).

The research group has supervised the following PhD Thesis:

Title: Regioselectividad en acoplamientos cruzados catalizados por paladio de 2,4-dibromopiridina. Síntesis estereoselectiva del pigmento ocular A2EStudent: Cristina Sicre González Date: March, 17, 2006.

Title: Síntese de hetero-oligómeros cíclicos e non cíclicos de cromóforos aromáticos e 1,3-dietinilaleno. Estudio das súas propiedades electroquímicas, fotoquímicas e fotofísicas (European Doctorate and Doctorate Award) Student: José Lorenzo Alonso Gómez Date: July, 21, 2006

Title: Ciclofanos Quirais de 1,3-dietinilaleno: síntese, caracterización e estudo das súas propiedades quirópticas (European Doctorate)
Student: Mª Inmaculada Rodríguez Lahoz
Date: March, 23, 2012

Both member of the group are also supervising two other PhDs in the field of the present project and have supervised one master degree dealing with [14_1]-bipyridoallenophanes that was defended by Silvia Castro-Fernández in 2012. C. Sicre joined Galchimia, a chemical custom synthesis and medical chemistry company located in O Pino (Spain), after finishing her PhD. Recently she has moved to Lonza, a swiss multinational, chemicals and biotechnology company at her center in Porriño (Spain). J. L. Alonso has held two postdoc positions, one at ETH (Switzerland) and other at Colombia University (USA) before joining University of Vigo as a senior researcher under a Ramón y Cajal contract. I. R. Lahoz has been awarded with a Canon fellowship to spend one year at Nagoya Univesity (Japan) in the research group of Yashima. She will move soon to Gothenborg University (Sweden) to join M. Erdelyi group.

C.4. IMPLICACIONES ÉTICAS Y/O DE BIOSEGURIDAD

No aplicable.

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