Looking forward: a glance into the future of organic chemistry†

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What will organic chemistry do in the next forty years? This *Perspective* lists six tasks that have emerged during the first edition of ESYOP, a symposium devoted to the future of organic chemistry. The collective answer presented has been elaborated following a 4-step process: stimulating plenary lectures given by outstanding chemists and philosophers, short presentations given by each participant (average age: 34 years old), think-tank sessions and writing of the final report after the symposium.

Introduction

Organic chemistry, where now?[1] Where will the next scientific revolutions come from? What is the "holy grail" of organic chemistry? What is the future for this science?

These questions challenge and stimulate the mind of every organic chemist. We cannot avoid making assumptions about the future even if we know that our endeavours are doomed from the start, the future being not discernible by definition. However, attempting to define one's future is strategically vital, since predicting is acting and defining oneself. The way we act today depends on how we envision our future. As scientists, we constantly try to anticipate the day after tomorrow, whatever the difficulty of this task. In the context of organic chemistry, attempts at providing answers to these questions are crucial since this discipline interfaces with many areas of the chemical sciences, but also with other fields of research such as physics, biology and medicine. Identification of dreams or grand challenges is essential if we want to define the identity of organic chemistry, a science that is simultaneously an art and an industry. Beyond pure scientific interest, this quest would also be helpful to communicate the excitement and promise of organic chemistry to the public. The objective of the first edition of the ESYOP workshop[2] was to bring together young organic chemists[3] willing to envisage collectively the possible futures of organic chemistry. The answers presented in this article have been elaborated following a 4-step process: stimulating plenary lectures given by outstanding chemists and philosophers,[4] short presentations given by each participant telling their personal view, think-tank sessions[5] and the writing of the final report after the symposium. The impossible question of the future of organic chemistry raised six more focused questions. These challenges, although often interrelated, present specific characteristics in terms of innovation ranging from the clearly unattainable to the achievable, from the fundamental to the applied science and are as follows:

– Can we do "simple"?
– Physics, a promising tool to reach total selectivity?
– Artificial cell, a chemist's creation?
– CO_2: a versatile organic building block?
– Can we design the "magic bullet"?
– Chemists: inventors and creators of their own tools? Towards an intelligent NMR?

Each challenge is briefly explained and the initiative was taken to propose paths or a few starting points from existing research. The tasks presented here constitute a snapshot of a collective work that has emerged during a 3-day workshop gathering young chemists with diverse opinions and expertise. An exhaustive review of prior work is of course well beyond the scope of this paper. The authors are also aware that the list of challenges underrepresents some important areas of organic chemistry. While easily challenged, these tasks were intended to initiate discussion. As the historian G. Minois said: *it is not the completion of the prediction which matters but the action it will initiate*.[6]

1. Can we do "simple"?

The search for simplicity is an emerging and fundamental theme in organic chemistry. The aim of this challenge is to seek maximum, sustainable results from minimal means. In organic

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† *The only limit to our realization of tomorrow will be our doubt of today. Let us move forward with strong and active faith.* **Franklin D. Roosevelt**, an undelivered address prepared for Jefferson Day, 1945.
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chemistry, turning complexity into simplicity involves mastering selectivity, reactivity and the organization of molecular systems. Conquering complexity while minimising the costs (atoms, chemical steps, energy, *etc*...) is a major issue in both fundamental and applied research, which includes the development of renewable resources. This challenge arises directly from societal needs and demands. Simplifying is about doing chemistry better, with fewer steps, reagents, solvents and waste products.[7] It means controlling a complex phenomenon through the use of a limited number of well defined parameters.[8] Once simplicity has been mastered, the challenges, such as those encountered in scaling-up processes, can be addressed and optimized. The question thus remains; how does one achieve such simplicity? At first, one must think anew about organic chemistry and bypass acquired thinking processes and place as first priority simplicity, *i.e.* "simplicity-oriented synthesis".[9] For instance, to combine selectivity with simplicity, it is possible to imagine voluntary research programs where protecting groups in synthesis are strictly banned[10] or only tolerated if they are participating in some other way in the building up of the molecules.[11] New methods to foresee the reactivity of a molecule might improve synthetic efficiency. Systematic and controlled functionalization of non-activated C–H bonds would be a strategy of choice to remove synthetic steps usually required for activation *via* leaving groups for example.[12] As such, each C–H group of a molecule would be considered as a potentially reactive and therefore functionalizable entity whatever its position in the molecule is. This approach requires and favours a better comprehension of reactivity. The first step towards this objective requires the development of novel intramolecular activation strategies.[13] Keeping in mind that for synthetic efficiency, it is necessary to impose constraints related to the number of synthetic steps.[14] To the question: "Is it possible to perform *de novo* synthesis of a natural sugar in two steps?", the answer[15] is not necessarily a resonating "No"! The challenge of efficiency and selectivity could also be overcome using new tools developed from physics (Section 2). Simplicity could also result from an efficient domestication of molecular or biological systems capable of carrying out synthetic steps. For instance, we already have enzymes synthesising their own inhibitors.[16] The long term objective would also be to conceive other molecular systems that could adapt and be interactive thus producing a specific response to external stimuli (Sections 3 and 5).[17] The never-ending quest for simplicity is a powerful drive for progress which combines fundamental research and societal needs.

2. Physics, a promising tool to reach total selectivity?

The total control over selectivity is one of the main challenges of organic chemistry. Up until now, chemists have partly solved this problem by utilising their own chemical tools and strategies (protecting groups, chiral ligands, catalysts, *etc*...). However, a conceptually simpler solution might come from physics. Physicists have developed amazing analytical tools such as NMR spectroscopy and X-ray crystallography which have allowed chemists to cope with the ever increasing complexity of the molecular structures that they have created. It is possible that one day, the chemist will be able to apply physical principles to manipulate selectively a specific sub-molecular moiety or a given functionality and thus favour one reaction manifold over another (Fig. 1).

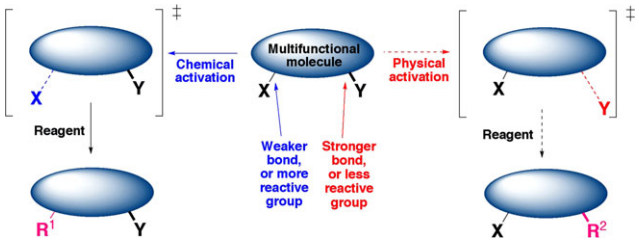

Fig. 1 Schematic representation of the complementarity between chemical activation of the "more reactive" group and physical activation of a "stronger bond", in a multifunctional molecule.

Can one imagine the possibility of synthesising a product from a one-pot mixture of substrates and reagents by developing a step-by-step, totally selective synthetic process involving a clever game-play of physical activations of specific bonds? How can the reactivity of one functionality be emphasized over the others in a multifunctional molecule using physics? The fact that matter behaves differently when placed in physical fields could be translated into controllable chemoselectivity in organic chemistry. NMR spectroscopy demonstrates that each functional group placed under a given magnetic field provides a distinct and characteristic signal. A few examples in the literature have shown that the yields and the rates of some radical reactions in solution can be influenced by a magnetic field.[18] It is also possible to influence the intramolecular motion of rotaxanes in dioxane solution with an alternative electrical field.[19] A theoretically promising approach is the control of complex quantum systems using the electric field induced by tailored femtosecond laser pulses, to sample the potential energy surface and find the trajectories leading to the desired product.[20] This technique allows selective bond dissociation. It is, for instance, possible to dissociate lactic acid to produce ethanol[20a] and to control the dissociation mode of non-symmetrical ketones using strong field pulses.[20b] The chemist can hope that these techniques will become efficient synthetic tools by continuing to push their limits including yield, selectivity, applicability in the solution phase,[20c] and equipment accessibility.

Directing the stereoselectivity of a reaction while utilising an external physical influence as the sole source of chirality constitutes the ultimate challenge in asymmetric synthesis (absolute asymmetric synthesis).[21a,b] Taking into account current knowledge, it is possible to imagine that this challenge could be met. One can for example envisage achieving absolute asymmetric synthesis by following two key steps.[21b,c] In the first instance, an external physical chiral influence,[22] such as circularly polarized light (CPL),[23] tailored polarized femtosecond laser pulses[20a,24] or a laser beam in a magnetic field,[25] could provide means to generate a small initial enantiomeric excess of a reagent, which in a second step would be amplified by a positive non-linear effect.[26] Studying the influence of chiral physical forces on stereoselectivity should provide the

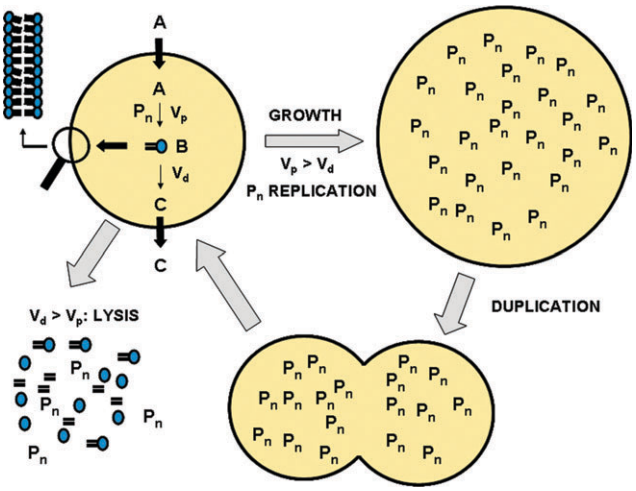

Fig. 2 Schematic representation of a protocell.

organic chemist with general methods for asymmetric synthesis with no need for molecular devices such as organic chirality inducers. Thus, one could imagine that one day, the control of the stereoselectivity of a given reaction would be totally automated and driven solely by an external chiral influence. Meeting the above challenge calls for a need to go much further in the systematic exploration of the action of diverse physical fields to attain total stereocontrol. Freed from chiral auxiliaries, protecting groups and other chemical prostheses, the chemist would succeed in coupling simplicity to efficiency.

3. Artificial cell, a chemist's creation?

The overarching philosophy guiding this challenge relates to the statement made by the Nobel Prize winner in Physics, Professor Richard Feynman: *what I cannot create, I do not understand*.§ Why not attempt to synthesize simplified cellular models[27] to better understand how living cells function? The long-term ambitious goal of this challenge is to construct molecular artificial models featuring two fundamental characteristics: the capacity to respond to external stimuli while adapting itself in an evolutionary manner to an external medium and the ability to self-replicate.

A first approach towards the development of an artificial protocell can be the creation of a simple working unit, based on the structure of liposomes and on the notion of chemical autopoiesis illustrated in Fig. 2.[28]

This model is a liposome with a semipermeable boundary formed by a single component B. The chemical composition of this cell membrane-like layer favours the permeation of compound A, a precursor of B, and compound P, a precursor of P_n. Owing to the particular conditions inside the liposome, A is converted by a single chemical reaction into the surfactant B with velocity V_p. A self-replicating molecule[29] (P_n) is present inside the liposome and is able to catalyze this reaction. P_n could be an RNA molecule, a peptide or, more generally, a self-replicating synthetic molecule composed by monomers (P) such as Rebek's replicators that are able to catalyze their own replication through the formation of an amide bond between activated ester and amine functionalities.[29d,f] P_n molecules could be rationally designed using computational methods such as virtual screening or virtual genetic evolution.[30] Another chemical entity should ensure the transformation (degradation) of B into C with a velocity V_d. It is clear that this system permits various kinetic conditions which may simulate, although at the most primitive level, the overall behaviour of a minimal cell. If both velocities are numerically equal, the autopoietic unit is in homeostasis. If V_d is greater than V_p, the autopoietic unit will be destroyed (simulating apoptosis). Finally, if the velocity of formation is larger than the velocity of decay, the system will tend to grow due to the accumulation of the membrane's constituent B.

A key feature will be the direct coupling between the growth and replication of the membrane and the duplication of polymer P_n. The fact that P_n is able to catalyze the formation of the membrane constituent B is of fundamental importance to achieve this task. Moreover, compound P_n should have an evolutionary advantage to be compartmented into a vesicle. This advantage is given by the increased concentration inside the protocell that would speed-up the replication. The self-replication process would also be subjected to some mistakes (mutations) that would ensure a basis for Darwinian evolution. From a chemical point of view, all reactions that would take place in this system (formation of B, degradation of B, duplication of P_n) must be compatible with an aqueous environment, and could be click chemistry-type reactions.[7c,16b,31] The next step would be the introduction of a second chemical system capable of responding to stimuli by the release of a chemical. This approach may involve cell-membrane transporter-like molecules that would allow the reactants and reagents to enter the liposome and products to be released from the liposome.[32a] Although this step towards a cell-like system can be seen as science fiction or may require years of investigation, liposomes have already been used as microreactors. In practice, one liposome containing chemical D and one liposome containing chemical E can merge into a larger liposome containing a mixture of D and E.[32b]

If the tools available to, or attainable by, the organic synthetic chemist allow him or her to create an advanced version of such a protocell, we could finally be in a position to answer the fundamental questions: does this molecular system react "cleverly" to external condition variations and can it multiply itself using molecular building blocks available in its environment?

4. CO_2: a versatile organic building block?

Every two hundred years, every atom of carbon [...] enters and reenters the cycle of life, through the narrow door of photosynthesis [...] knowingly or not, man has not tried until now to compete with nature on this terrain, that is, he has not striven to draw from the carbon dioxide in the air the carbon that is necessary to nourish him, clothe him, warm him and for the hundred other more sophisticated needs of modern life. He has not done it because he has not needed to: he has found, and is still

§ This phrase was found on the top of the blackboard of Feynman's office on the day of his death. See, for example, ref. 57.

finding (but for how many more decades?) gigantic reserves of carbon already organicized, or at least reduced. This citation of Primo Levi[33] taken from the chapter "Carbon" found in his book *The Periodic Table* clearly summarizes one of the biggest technological and scientific challenges of the twenty first century. For the past one hundred years, we have exploited every easily accessible source of carbon such as coal, petrol or natural gas necessary to our development. However, the shortage of these reserves will soon change the chemical industry and our society in general. As a result, organic chemistry will be hurt at the heart of its practice. The nature of the synthetic starting materials currently available, many of which are obtained from crude oil, will be unarguably changed. In this context, where should we seek new sources of carbon, that are renewable to replace the fossil source? Using atmospheric carbon dioxide as the carbon source offers numerous advantages but also raises a challenge. CO_2 is indeed a cheap, non-toxic source of carbon and one of the most abundant. Additionally, as a greenhouse gas, the reduction of its production from human activities would reduce its impact on the environment.[34] How society can reasonably envisage the use of carbon dioxide as a carbon source? This question will probably find an answer in the close future since more and more researches are devoted to this subject. Some works are already on the way and among them one can already cite the carboxylation reaction, the use of CO_2 as solvent, as oxidant, as additive to CO for the production of methanol or as additive to natural gas for the production of hydrocarbons.[35c] Unfortunately, in most cases, these reported processes are not yet economically viable since the energy required for the transformation of carbon dioxide is too important. Indeed, carbon dioxide, the final stage in the degradation of all organic molecules, is a highly stable molecule and its use as carbon source requires overcoming high energetic barriers. In the next decade, scientists will have to find efficient ways to transform CO_2 with lower energetic cost.

Major advances have been made towards capturing atmospheric CO_2, to photochemically reduce it and to use it in chemical reactions.[35,36] The present challenge would be to combine these three approaches in order to convert atmospheric CO_2 into novel carbon-containing building blocks using a renewable non-polluting form of energy, ideally sunlight. Means of CO_2 capture at the outlets of large manufacturing and energy producing factories, often big offenders at releasing greenhouse gases, are "easily" conceivable.[36] The organic chemists' objectives would therefore be to develop synthetic processes that would use CO_2 directly from its source, thus avoiding issues related to storage and transport.

In addition, how to transform CO_2 selectively into useful building blocks (methanol, formaldehyde…) without producing side products? As in petrochemistry, catalysis will be probably the main key. The principal aspect of this challenge is therefore to explore systematically the reactivity of CO_2 in order to develop novel synthetic methodologies. Numerous routes can be considered, such as replacing phosgene with CO_2 or using CO_2 in the making of novel C–C bonds[34] or C–O bonds.[35d] High throughput screening could be applied to the discovery of novel catalysts that would additionally help in the identification of novel reactivities.[37] It is also important to go further in the use of CO_2 in order to achieve an efficient synthesis of polymers. Would it be possible, for example, to use CO_2 to prepare polyester-based materials for which most carbon atoms would come from this simple monomer? The ultimate objective would be to carry out the necessary chemical reactions in the presence of photoactivated catalysts, therefore using mainly sunlight as an energy source and water as a proton source.[38]

Clean and economically viable processes, that could transform CO_2 into stable materials or useful organic building blocks, would provide the much needed new means necessary to maintain industrial development while respecting the environment.[39]

5. Can we design the "magic bullet"?

The dream of one medicine able to cure all diseases and ailments is as old as Panacea, Asclepius' daughter, the Greek god of medicine. Diverse middle age alchemists' texts already suggested the conception of one unique and universal miracle remedy from gold. In 1900, Paul Ehrlich presented the "magic bullet" concept, a compound that would have a particular attraction for a microorganism responsible for the onset of a specific disease.[40] These myths which have been with us throughout the ages are challenges that need to be tackled. The active drug component of such a universal medicine could be capable of molecular intelligence based on the following criteria: adaptability, autonomy and multi-competency.

Building blocks perfectly tolerated by the body could be activated or self-assembled at the target site to create the active molecule, thus extending the principle of dynamic combinatorial chemistry.[16] Such a medicine would "self-switch on" by using the target's biological tools,[41] thus limiting side effects. In this context, it is the targeted biological system which would synthesize the active molecule. A "magic bullet" should also be capable of possessing simultaneously diagnostic, preventive and curative properties. Ideally, these "molecular soldiers" would second our own immune system. They could possess distinct units, each responsible for a particular function (seek, detect, signal and destroy), all articulated around a core responsible for coordinating the sequence of actions necessary for the treatment of a given pathology (Fig. 3).

In the case of cancer treatment, the development of non-toxic prodrugs or antedrugs,[42] that can be selectively activated at the tumor site, have already shown some promise as being "intelligent medicines".[41] Constituted of three parts (trigger, linker, effector)[43] programmed to perform a predetermined function, these molecules are potentially innocuous to healthy tissue and only unleash their antitumor activity upon recognition of the cancerous tumor. Recent publications have reported that it is now possible to activate in a consecutive manner a series of molecules under the action of a single stimulus.[44] As such, after the initial activation, the central core could regenerate itself to be able to release one or a few other molecules of the anticancer agent again. Similarly, a recent study has been initiated to enable the recruitment of an army of prodrug molecules in the vicinity of the tumor, by adding a recognition marker to the three units previously mentioned.[45]

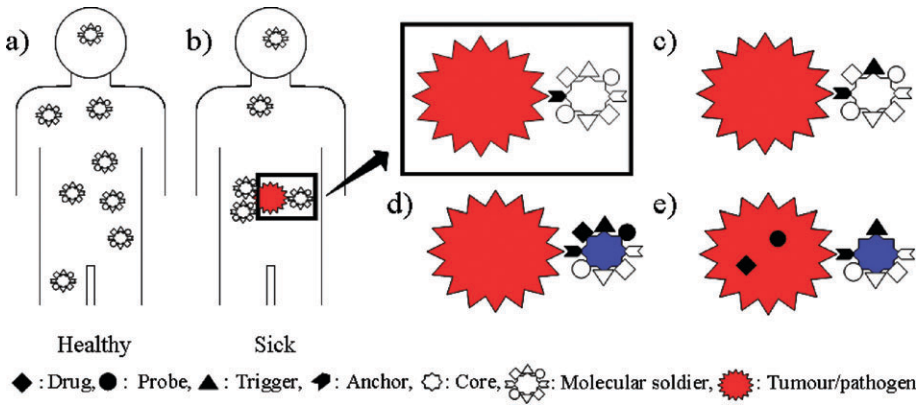

Fig. 3 Schematic representation of the "molecular soldiers" concept. In this scheme, "molecular soldiers" are designed in order to seek, detect, signal and destroy two types of tumors or pathogens according to the following key steps. (a) Stochastic distribution of non-toxic "molecular soldiers". (b) Gathering of the "army" around a pathogenic area by means of specific "molecular soldier" black anchors (only treatment of a red labelled "enemy" is presented here). (c) Activation of the corresponding trigger. (d) Transmission of the information to each unit through the core. (e) Release of the suitable drug and probe able to penetrate through the tumor or pathogen cell membrane and then signal and cure the disease.

"Never sick again": this could be the grail for the chemists in charge of elaborating the medicine of tomorrow. This medicine may possibly be similar to a hive,[46] consisting of independent elements with specific properties, thus creating an autonomous assembly, capable of defending itself against any foreign or pathogenic entities.

6. Chemists: inventors and creators of their own tools? Towards an intelligent NMR?

Due to its central position in chemistry, organic chemistry has the power to answer fundamental questions or to solve specific problems met by other disciplines such as physics or biology. Synthesis and savvy use of molecular probes has, for example, uncovered complex biological mechanisms. In an even more applied manner, medicine and pharmacology employ the chemist's expertise to meet challenges related to the health services. The risks are often great for the chemist to become absorbed in external aims and problems and to overlook the core of his/her discipline. Quick synthesis, whatever the yields or the methods, of molecules that are to be rapidly tested should not become the sole preoccupation of the chemist. The following challenges reverse this process by placing the chemist at the heart of the design of strategic tools necessary to empower his/her research. Many exciting questions have to be asked concerning for example the visualization of reaction processes in real time or the exploitation of the power of computer science in organic chemistry. What if, at a glance, the chemist could see what is going on in the reaction flask?[47] Do we employ the computing tool to its full capacity in total synthesis? To answer such questions, the chemist will have to be the moving force in multi-disciplinary research teams including, amongst others, computer scientists, mathematicians and physicists. We will focus on the following question: what about designing an intelligent NMR?

The Chemical Abstracts Service is registering an exponential increase in the publication of novel organic compounds.[48] This acceleration in the progress observed in organic chemistry is related to the efficiency with which these new molecules are being characterized. The objective of this challenge is to conceive an intelligent NMR, which would provide the chemist directly with the structure of the compound being analyzed (within a minimum error range), using a single sample (Fig. 4).

Most of the technologies necessary to build such a tool are already available. However, they have not yet been combined in a concerted and autonomous manner. A NMR machine can, once programmed, automatically acquire 1D and 2D NMR spectra on multiple elements. Software packages, such as LSD[49] (logic for structure determination), have been developed to structurally analyze samples. These software packages can reconstruct molecular fragments as a function of the analytical data obtained from 1D and 2D spectra. Another approach to facilitate the identification of compounds consists of simulating spectra from analytical data of known chemicals. Structure prediction algorithms using small data bases are already being used in high throughput screening.[50] Theoretical chemistry and DFT (density functional theory) have recently made possible the simulation of the NMR spectrum of a compound, taking into account the different conformations such a compound could adopt.[51]

An intelligent NMR could be constituted around a central computer, which would activate the NMR spectrometer to acquire the data necessary to determine the structure, combined with a worldwide network (NMR-NET) in which all NMR data would be recorded in an FID format and

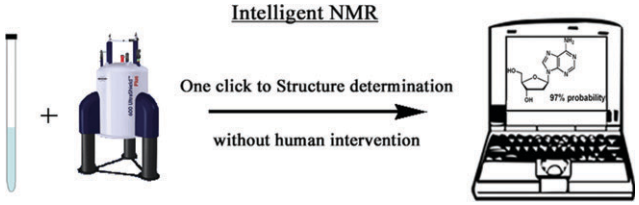

Fig. 4 Intelligent NMR: from NMR tube to structure determination without human intervention.

correlated to their structures, in other words a worldwide interactive NMR data bank. This would permit, firstly, one to establish whether a compound has been previously identified, by simple comparison of the FIDs. Secondly, by importing into its memory the structures corresponding to spectra possessing similar FIDs, the computer would be capable to compare molecular fragments to those already deduced from prior structural analyses. The spectrum corresponding to the structure would then be simulated and compared to the original. This iterative process (data acquisition, comparison with data bank, structure analysis, simulation) would be repeated until a final structure can be proposed with an accuracy level satisfactory to the user. To this end, the computing algorithms should be conceived so that the computer decides autonomously whether supplementary data acquisitions are required. Compound mixtures could also be identified in a similar manner by conducting NMR experiments such as DOSY 2D,[52] thus allowing the separation of the components' signals.[53]

An intelligent NMR could shorten the time necessary for analyses, thus freeing synthetic chemists' time and providing the chemical industry with an extremely useful analytical tool in combinatorial chemistry. Furthermore, this method coupled with an effective automated separation method could facilitate the identification of millions of natural compounds which still remain unknown.

Conclusion and perspectives

The process and the results of this first edition of the ESYOP workshop have revealed many surprises. The first was certainly the enthusiasm shown by all the participants who have put aside their expertise to propose a collective answer and explore unfamiliar paths. The starting point for the different discussions has rarely been the definition of a purely scientific task but has often been related to societal views. The myth of the researcher behind closed doors in his/her ivory tower seems to have been eclipsed by that of a researcher influenced by society's needs and demands. A balanced position is certainly to be found between these two opposite states. Another surprise came from the technological aspects of a part of the proposed challenges and the will to initiate the creation of complex tools, indispensable to the future development of organic chemistry. This approach was found in parallel to utopian challenges that provide promising directions. Three central but interdependent themes emerge from the proposed challenges. The first concerns the search for simplicity to "make" or to understand. Through this theme, fundamental research, industry and renewable development converge. The second highlights the influence of Nature as a guide and an inspiration to the chemist.[54] The third theme is linked to the design and use of autonomous, adaptable systems in organic chemistry.[55] The face of tomorrow's organic chemistry might be that of a science looking to construct, using the simplest means, intelligent molecular systems inspired by Nature. The future directions will also heavily depend upon innovations in other disciplines and more or less foreseeable external constraints, such as a shortage of hydrocarbon resources. The conclusions of ESYOP thus established, it would be interesting to compare them to conclusions obtained from similar meetings of chemists of different age groups or of chemists from across the world.[1,56] To further expand communication between the various research areas encompassed by chemistry, why not extend this idea to other scientific areas, such as analytical or materials chemistry? We are also determined to capitalize on the knowledge gained during this very first edition of ESYOP and to improve the overall heuristic process. The experience will be renewed every four years and centred on the 30–39 age group to compare answers and measure their evolution. Beyond its result, the interest of such an experiment is also to find out how a group of chemists of a given age, at a given time, with various backgrounds reacts to the challenging question of the future of their discipline.

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1 This first question is a tribute to Prof. D. Seebach's outstanding review: D. Seebach, Organic synthesis: where now?, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1320.

2 The first edition of ESYOP (Entretiens de Synthèse Organique et de Prospective) workshop was held on March 20–23, 2005, near Orléans, France (http://esyop.site.voila.fr/Index.html). For a more detailed account of the ESYOP experience see: P. Compain, V. Desvergnes, C. Ollivier, F. Robert, F. Suzenet, M. Barboiu, P. Belmont, Y. Blériot, F. Bolze, S. Bouquillon, E. Bourguet, B. Braida, T. Constantieux, L. Désaubry, D. Dupont, S. Gastaldi, F. Jérome, S. Legoupy, X. Marat, M. Migaud, N. Moitessier, S. Papot, F. Peri, M. Petit, S. Py, E. Schulz, I. Tranoy-Opalinski, B. Vauzeilles, P. Vayron, L. Vergnes, S. Vidal and S. Wilmouth, Alchimies futures: compte rendu de l'expérience ESYOP, *C. R. Chim.*, 2006, **9**, 127 (in French).

3 The number of participants has been chosen to cover a wide range of expertise, themes and scientific backgrounds while facilitating small group workshops. Thirty two scientists were present at the meeting. The average age of the participants was 34, providing an interesting combination of youth and expertise. Amongst these scientists were fifteen CNRS researchers "chargés de recherche", twelve lecturers and five industrial researchers, coming from seventeen French research centres and three non-French based universities. The most represented research areas were the synthesis of biologically active molecules and the development of synthetic methodologies. The following themes were represented by at least one participant: catalysis, supramolecular chemistry, green chemistry, renewable resources and synthesis of molecules used in theoretical chemistry and physics research.

4 The five lecturers were: Professors J. M. Lehn (ISIS, Strasbourg and Collège de France, Paris), D. Seebach (ETH, Zürich), B. Bensaude-Vincent (University of Paris X, Paris), a specialist in philosophical sciences, Mr T. Gaudin (Prospective 2100, Paris), a specialist in futurology, and Mr G. Ricci (Sanofi-Aventis) who presented an industrialist's view of what defines chemistry.

5 Think-tank sessions and debates were orchestrated by two professional facilitators (Sud Performance company). The brainstorming sessions were achieved through two phases. The first stage was conducted in groups of 10–11 and called upon discussing freely diverging and contentious ideas while the second stage, conducted in smaller groups (3–4) was to promote convergent thinking. The first step's objective was to identify as many ideas as possible in a non-judgemental manner. Four main categories of thoughts were thus identified: utopia, knowledge, creation *de novo* and society's needs. Each participant was then asked to choose amongst one of these themes before the second step was initiated. This second stage, carried out in small group, aimed to focus the thoughts of each group on a specific and group-identified challenge. The workshop was then concluded by each group presenting their challenge to the remainder of the participants. This presentation followed a specific pro-forma where answers to the following questions were given: why, how, pros and cons. Following the conclusion of the conference, these challenges were organized in a written format by each group and restructured by the organizers to provide the core of the present manuscript.

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