JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Perspective

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Natural Product and Material Chemistries—Separated Forever?

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ABSTRACT: Chemistry research is an eloquent, yet extremely complex discipline consisting of a diverse range of topics. The complexity of every sub-discipline requires extensive focus, which can limit cross-talk between fields, thus leading to their isolation. In particular, natural product and material chemistries have experienced this trend, and it has led to an ever growing separation between them. Yet by looking at the fundamental aspect of the relationship between molecular design and the resulting properties, it is possible to remind chemists of their ability to bridge these research areas. It is intradisciplinary collaborations that can provide a path toward collectively addressing the many challenges of chemistry.

Unfortunately, research in the fields of natural product and material chemistries has continued to drift apart. This is evidenced by the fact that most significant chemistry conferences tend to categorize and separate meetings on the basis of highly specific areas of interest, whether they be based on natural product or material chemistries, with limited desire to promote stimulation between them. To address this alarming rate of segregation among chemistry sub-divisions, one must first understand its driving force. The constant influx of new knowledge in each area of science forces individuals to maintain a high level of involvement within their specialized field in an effort to develop an expertise. This significant time commitment to truly become an expert in a discipline tends to limit interactions with neighboring fields, and is the cause behind the separation between natural product and material chemistries.

Furthermore, the climate in modern, industrialized societies to provide research that leads to economically viable products, compared to that which is of interest for fundamental scientific understanding, has significantly encouraged the isolation of scientific sub-divisions. In regard to fundamental scientific research, one can argue that chemistry was in a more favorable position a century ago, when scientists could follow their thirst for knowledge without the pressure to thrive within an individual specialty. This opened the door to a wide range of natural processes and materials that were not yet understood on the molecular level. For instance, look at the laboratories of Emil Fischer in Berlin at the close of the 19th century that employed scientists in fields that ranged from detailed organic syntheses to biochemistry, and nuclear chemistry to microanalysis. These chemistry disciplines formed a synergetic atmosphere that promoted interdisciplinary education, and also happened to produce seven Nobel Prize-winning scientists between 1923 and 1951 (Otto Hahn, Fritz Pregl, Hans Fischer, Otto Diels, Adolf Windaus, Otto Warburg, and Karl Landsteiner).[1−3] If Fischer's lab was the model of diversified research interests at the time, the contrast to today's research groups is profound. Again, this can be attributed to recent expectations that scientific research should lead to commercial products, as well as the financial influence from funding agencies to focus on specific areas. It further complicates the process when members of these funding agencies are given predetermined grading criteria for applications, which can lead to decisions that are not based on the scientific merit of the proposal, but on a singular goal. The pressure to maintain funding forces scientists to focus on a narrow spectrum of approaches, limiting their freedom to explore innovative alternatives. In essence, the pressure to reach the final target restricts the paths that are investigated, and naturally leads to the further separation of chemistry sub-disciplines.

This Perspective provides a number of examples that highlight the fundamentals of chemistry research, involving the relationship between chemical structures and their properties. In any field, whether it is natural product or material chemistry, questions are based on how changing a defined chemical structure can manipulate its function (i.e., biological, photophysical, catalytic, etc.). This is a beautiful concept because it is not topic specific, and thus qualifies all chemists as capable of collaborating within multiple chemistry disciplines. Hence, it can be argued that by looking at chemistry research through the concept of how chemical structures determine their properties, it is possible to encourage collaborations between sub-divisions, such as natural product and material chemistries.

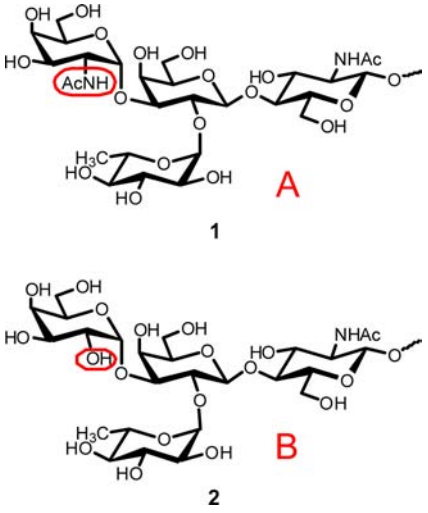
When addressing scientific problems, it is natural for chemists to take part in interdisciplinary projects, which can be described as collaborating with scientists outside of their area of expertise. Many of these interdisciplinary collaborations involve natural product chemists working with life scientists, and material chemists engaged with physicists and engineers. Yet it would be a mistake to assume that in these projects the physicists/engineers or life scientists define a problem for which the chemists are expected to blindly provide a series of model compounds to be investigated. This disregards the strong scientific reasoning that researchers have developed for investigating these compounds on the basis of the relationship between the chemical structures and their properties. An eloquent example of the decisive role of the molecular structure is observed in the blood group substances and their biological effects.[4,5] The tetrasaccharide determinants of the two opposing blood groups A (**1**) and B (**2**) are almost identical, except for a

Received: September 16, 2012
Published: May 29, 2013

dx.doi.org/10.1021/ja309186q | J. Am. Chem. Soc. 2013, 135, 8764−8769

single functional group at the 2′-position of the terminal α-galactoside unit: it is an acetamide substituent in blood group A (**1**), but a hydroxyl group in blood group B (**2**) (Scheme 1).

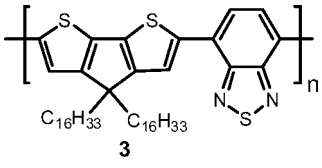
Scheme 1. Blood Group Determinants A (1) and B (2)



The small structural difference between blood group A (**1**) and blood group B (**2**) results in a significant change in the ability of the glycoproteins to differentiate between "self" and "not self", stemming from differing abilities to hydrogen bond to recognized proteins, specifically antibodies. Keeping in mind that the functionality at the 2′-position of these molecules can be a question of life or death when blood is being transferred from one person to another, we should appreciate the precise selectivity of these blood groups, and the necessity to understand the structure–function relationship of natural products, in this case carbohydrates.

The relationship between the chemical structure and property of materials can also be exemplified in organic electronics, where there has been significant efforts toward optimizing light harvesting in bulk heterojunction organic photovoltaic devices (OPVs) and rapid charge carrier transport in field-effect transistors (FETs).[6−9] This optimization heavily depends on the chemical structure and processability of the materials (typically based on conjugated polymers), where collaborations among chemistry disciplines have led to the development of an efficient array of polymers with alternating donor and acceptor units.[10] However, it can be easy to underappreciate the complex syntheses of these conjugated polymers, such as polymer **3** (Scheme 2), and studies on their performances. Yet by developing an understanding of the relationship between polymers and their performance, it becomes possible to target donor/acceptor materials through educated hypotheses of their photophysical and electronic properties, accelerating research in the field of organic electronics.

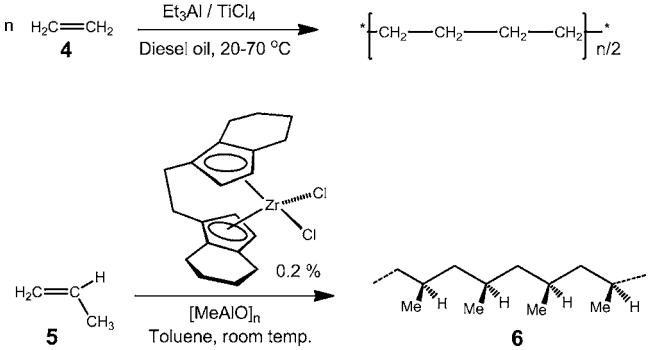
Scheme 2. Light-Harvesting and Semiconducting Conjugated Polymer 3 Based on Alternating Donor and Acceptor Components



A great number of donor and acceptor combinations have been screened and used as active components in devices. This has only become possible since the discovery of Suzuki coupling, which leads to a strictly alternating sequence of the different building blocks.[11] The development of such transition-metal-catalyzed C−C bond formation has proven of utmost importance in recent syntheses of conjugated polymers. Optimization of experimental conditions, for example of the catalyst−ligand complex, and mechanistic studies of model reactions are instrumental for achieving precise polymers of high molecular weight. However, there is still significant room to improve the syntheses of these polymers on the basis of advances made by organic chemists. The Suzuki-type aryl−aryl coupling toward polyarylenes has long been regarded as a polycondensation following a step-growth protocol. Recent mechanistic studies have revealed that a chain-growth mechanism can also be followed, which holds enormous promise toward the possibility of "living" end groups that can be used for the clean synthesis of block copolymers.[12]

Another example of understanding the chemical structure−property relationship is illustrated by the work of Karl Ziegler and Giulio Natta,[13,14] who investigated alkene complexes of alkylaluminum compounds and titanium halides, and discovered their function in the polymerization of alkenes (**4**, **5**).[15,16] This process was developed into an efficient polymerization technique (Ziegler−Natta, Scheme 3) that played a crucial role

Scheme 3. Metallocene Catalysts Provide Microstructural Control over Polyolefins

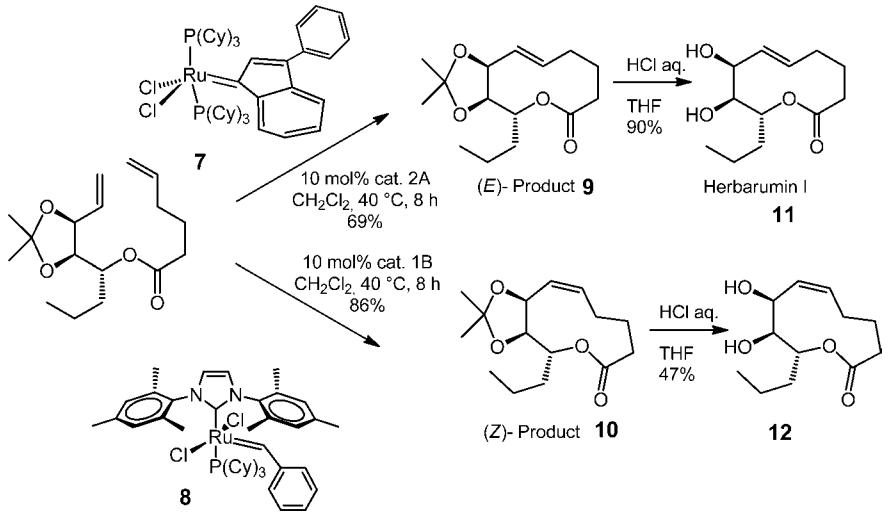


in the development of material science and its economic output. Additionally, polyolefin synthesis was further improved in the 1980s when chiral titanocenes and zirconocenes were introduced as catalysts, which were shown to be efficiently activated by methylaluminoxane (MAO, $(MeAlO)_n$) at room temperature and used to produce highly stereoselective isotactic polypropylene in good yield.[17] The ability to synthesize large quantities of these polymers with such control over their molecular configuration (tacticity) was a direct result of understanding the monomer−catalyst system at a molecular level in relation to the polymers synthesized.[18]

In turn, the efforts of polymer chemists to modify and optimize metallocene catalysts led to experiments with olefins in the presence of tungsten hexachloride and ethylaluminum dichloride, resulting in the metathesis of olefins[19] and ring-opening metathesis polymerization.[20,21] Understanding the functionality of these catalysts on the structural level provided breakthroughs in organic syntheses that opened the door for

dx.doi.org/10.1021/ja309186q | J. Am. Chem. Soc. 2013, 135, 8764−8769

Scheme 4. Ring-Closing Metathesis Reactions Using Grubbs Catalysts Towards the Synthesis of Phytotoxic Herbarumin I

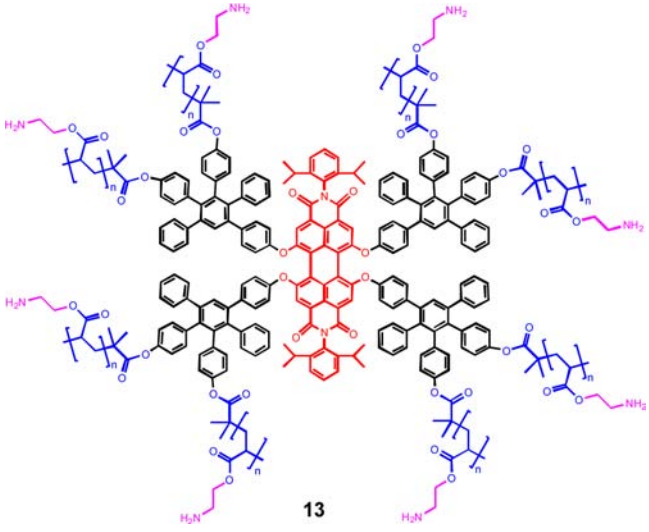


current research to optimize metathesis catalysts by groups around the world (Grubbs, Schrock, Hoveyda, etc.).[22−24] Catalytic systems for olefin metathesis continue to evolve and play a major role in natural product chemistry. For example, Scheme 4 highlights the ability to efficiently transform *E*-diastereomer **9** to yield phytotoxic fungal macrolactone herbarumin **11**, while *Z*-diastereomer **10** was shown to produce diastereomer **12** of the natural product after deprotection.[25] Though the formation of diastereomer mixtures cannot be completely prevented in ring-closing metathesis reactions, particularly if large rings are targeted,[26] current research aims at novel catalysts to optimize the selectivity.

An area where natural product and material chemistries have strongly overlapped is in researching dendrimers, which are described as tailor-made polymers of a well-defined size and shape. Dendrimers are hyperbranched, three-dimensional macromolecules that can be prepared by either divergent or convergent methods of synthesis.[27−29] Based on their structure, it is possible to visualize dendrimers as "molecularly defined nanoparticles", and due to the combination of their aesthetic appeal and unique functionalities, chemists strive to synthesize increasingly complex, yet still defect-free macromolecular structures for a variety of applications. There are three levels of a dendrimer—the core, scaffold, and surface—any of which can be modified for a specific purpose. For example, a polyphenylene-based dendrimer was synthesized with a perylene diimide core, and its surface was functionalized with atom-transfer radical polymerization initiators.[30,31] 2-Aminoethylacrylate was polymerized from the dendrimer surface by a grafting-from approach (dendrimer **13**, Scheme 5). This dendrimer showed reasonable cell-uptake, where the perylene diimide core acted as a fluorescent tag, and the poly(2-aminoethylacrylate) provided necessary solubility and interactions with the cell membrane. A very unique aspect of such polyphenylene dendrimers is that they are composed of twisted, tightly packed benzene rings that promote extremely high chemical stability, and more importantly, they are shape-persistent. This feature leads to a perfect nanosite definition of functional groups placed in their interior without the possibility of their spatial realignment.[32]

Polyphenylene dendrimers can also serve as carbon-rich precursors to graphene derivatives via oxidative planarization in the presence of iron trichloride.[33,34] This provides a controlled

Scheme 5. Dendrimer with Core−Shell Structure for Cell Uptake



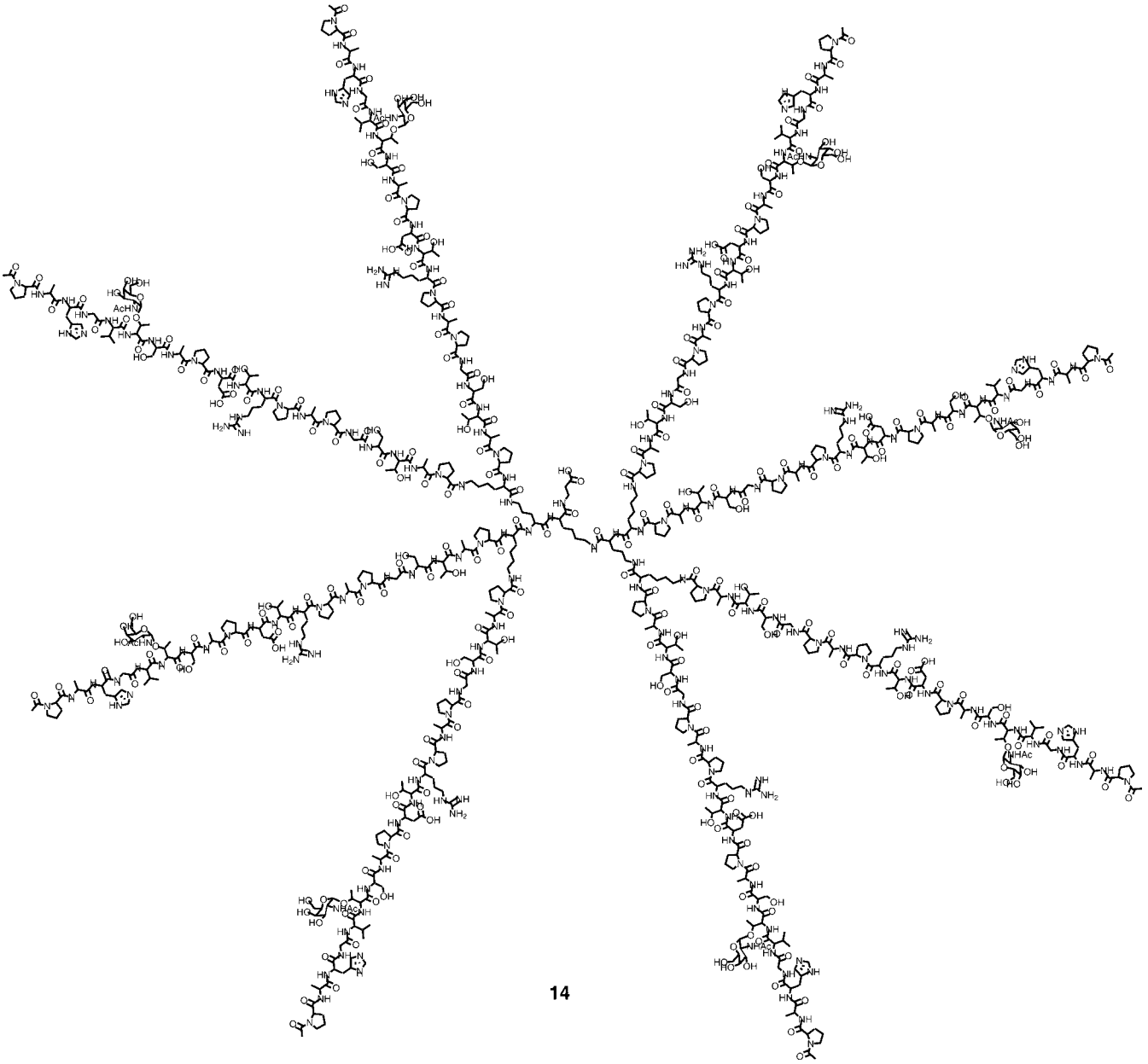
(bottom-up) synthesis of structurally perfect graphenes through a reproducible procedure, as opposed to physical techniques (top-down), such as the exfoliation of graphite, that are not as controllable.[35,36] Thus, research in the formation of graphenes represents an area that is strongly governed by physical methods of materials fabrication, but can take advantage of creative chemical input to improve such processes.

Dendrimers also offer a unique opportunity to create precise ligand structures for biological recognition processes. This is highly desirable if a partial structure of an endogenous protein or glycoprotein of insufficient immunogenicity is to be converted into a vaccine which elicits an immune reaction. The dendrimer **14**, for example, exposes eight copies of a glycopeptide antigen from the tumor-associated membrane glycoprotein MUC1 (Scheme 6).[37,38] The ^{1}H NMR spectrum of **14** in d_6-dimethylsulfoxide displays a single set of the glycopeptide signals, indicating the formation of a chemically well-defined dendrimer. Vaccination of mice with dendrimer **14** induced not only IgM but also protective IgG antibodies.

These dendrimer examples emphasize the importance of understanding the structure- and chemistry-driven nature of the

dx.doi.org/10.1021/ja309186q | J. Am. Chem. Soc. 2013, 135, 8764−8769

Scheme 6. Dendrimer Vaccine 14



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research, and could eliminate the stereotype that chemists simply provide photolabeled derivatives for biological experiments. This is meant to highlight the synthesis of useful model compounds, which increase the understanding of why such molecules work in various environments. Thus, research can promote interest in the molecular modification of compounds to enhance their effect and selectivity (i.e., drug delivery, vaccination, and electronic properties), a concept that overlaps both natural product and material chemistries.

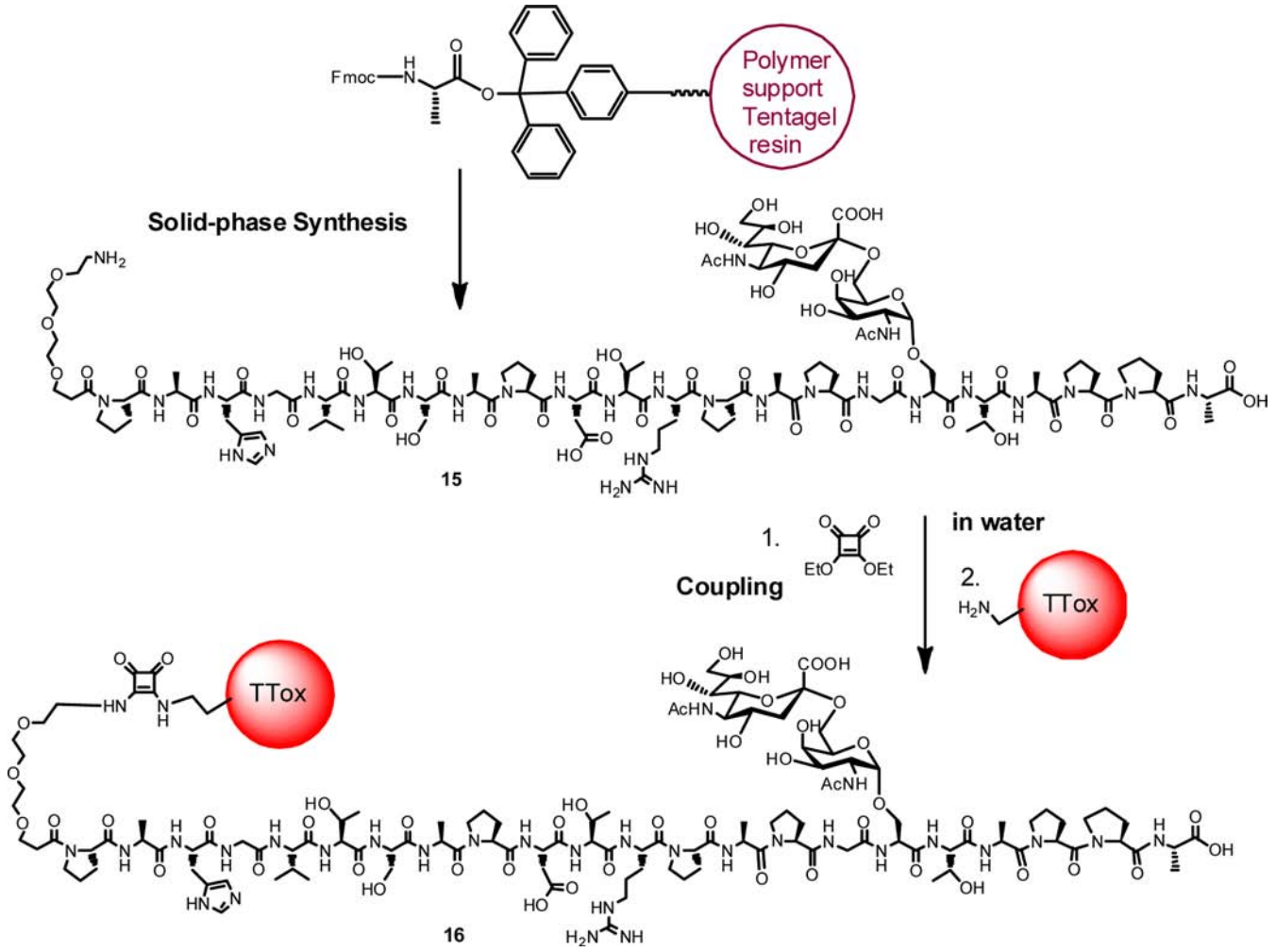
An area where natural product chemistry has been strongly influenced by polymer science is in the field of solid-phase syntheses of polypeptides[39] and polynucleotides.[40−42] These innovations opened unprecedented avenues toward the synthetic access to DNA and RNA structures, as well as to peptide factors involved in biological regulatory processes. Merrifield and co-workers[39] developed a method to synthesize oligo- and polypeptides from a polymer-linked amino acid ester that revolutionized not only peptide chemistry but also the overall field of medicinal chemistry. Solid-phase syntheses have become very efficient at providing many highly sensitive structures, such as the sialic acid-containing tumor-associated glycopeptide antigen **15**, shown in Scheme 7.[43,44] Coupling of these glycopeptide antigens to tetanus toxoid afforded synthetic vaccines, in this case **16**, which have been shown to induce very strong immune responses (titers up to 10^6), and IgG antibodies that bind to tumor cells and tissues.

Polymer-supported syntheses[39−41] have favorably been supplemented by recent developments of polymer-linked reagents, trapping components, and immobilized catalysts.[45]

The intention of these examples is to stimulate the reader to look across the fence into neighboring fields, and ask himself how her/his own competence might help to open new avenues, just by knowing of another's problems. At least some of the examples outlined herein show that interdisciplinary collaborations between physical and life sciences do not necessarily hinder the intense contact between both schools of chemistry.

dx.doi.org/10.1021/ja309186q | J. Am. Chem. Soc. 2013, 135, 8764−8769

Scheme 7. Synthetic Antitumor Vaccines Obtained by Solid-Phase Syntheses from a Polymer Support (TTox = Tetanus Toxoid)



On the contrary, solid-phase synthesis and its further development into microchip technology provides a perspective that would not exist without interactions between chemistry disciplines. However, it is necessary that the scientific problems investigated in theses collaborations are not reduced to the questions raised by the physicists and biologists. After analyzing the role of the synthetic factor, ligand, or material in a process, it is necessary to question why the structure functioned in a particular manner and how that function can be varied by structural modification. This urges chemists to aim at novel structures and innovations in the preparations of these molecules, and to search for stimulating ideas from other areas of chemistry.

In this regard, aspects of supramolecular chemistry, formation of films or membranes, and processes at interfaces are also important for material chemistry, as well as for biological chemistry. It is thus clear that the relationship between chemical structures and their properties must be generalized to also include supramolecular and morphological characteristics. For example, in many organic electronics (OPVs, FETs, etc.) the active layer consists of a thin film of a polymer composite whose morphology heavily influences the performance of the device. Therefore, it is necessary to understand factors that influence supramolecular ordering, and tune these features through molecular design and processing techniques.

Additionally, intensifying mutual interests in the work of other chemical sub-disciplines needs support and acknowledgment by funding agencies. It is crucial to highlight the benefits of such research ventures to panels of referees responsible for grant approvals, research projects, or awards. Courageous concepts crossing borders between the sub-domains should not be disqualified on the basis of trivial mistakes in formal terminology of a proposal or similar "I know better" attitudes. An atmosphere is needed which ranks general scholarliness in chemistry higher than perfection in narrow, specialized corners. With some resignation, one may argue that problems brought forward to chemistry by life and material sciences have become too demanding to still cultivate the generalist's approach. This is well reflected in chemical education, since curricula that are centered around material chemistry, nanoscience, or biomedical chemistry have become more and more common. Also, it might be worthwhile to mention that professors of chemistry, when dealing with the enormous growth of knowledge, have often been more imaginative in adding rather than removing information from the "classical" canon. So, how to define the weight of generalization and specialization?

The given examples have provided convincing evidence that synthetic competence is at the heart of all achievements. Complexity in target structure, mechanistic understanding of reactions, and improved catalysis, both homogeneous and heterogeneous, as well as the transition to automated syntheses,

dx.doi.org/10.1021/ja309186q | J. Am. Chem. Soc. 2013, 135, 8764−8769

up-scaling, and arranging supramolecular structures, are issues of undiminished importance, which also serve to link material and natural product syntheses and create mutual stimuli.

Finally, a scientific atmosphere which favors general knowledge combined with an open-minded, yet focused research interest is best generated by an education in which students are not just forced to learn, but are inspired to study, reflect, and collect their own experiences. Therefore, experimental knowledge cannot be substituted by seminars and lectures. In particular, independently performed experiments are valuable, even if they fail in the first attempt. It is satisfying to determine the reasons for an unsuccessful experiment and to finally succeed. These experiences shape a personality, and ultimately a professional self-assurance, which enables young researchers to cross borders of scientific sub-divisions, and to develop, in a modest however creative way, their own original ideas. Keeping these pathways wide open during chemistry studies would certainly ensure productivity of science, in general, and fruitful collaborations between natural product and material chemistries, in particular, in the future.

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Notes

The authors declare no competing financial interest.

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