

Natural Products Chemistry: New Opportunities, Uncertain Future

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This manuscript is dedicated to *Dulio Arigoni* for his friendship and for everything he represents in the sciences

Natural products chemistry, a field greatly invigorated nowadays by its partnership with chemical ecology, is currently being de-emphasized. We argue that such curtailment will restrain an exploratory process of immense scientific promise.

The realization that ours is a chemical world has had a profound influence on human thought. It has led to the postulate that both the inanimate and biotic domains are explicable in atomic and molecular terms, providing the basis for the reductionism that drives so much of scientific inquiry today. Biologists and chemists, emboldened by common purpose, joined forces at the beginning of the 20th century to set in motion the gigantic investigative venture that was to culminate in the establishment of the present-day field of molecular biology. Also emergent during this period, and owing its advent to molecular biology, was a second venture, similarly interdisciplinary in character and focused specifically, not on the chemical makeup of organisms, but on their chemical interactions. That field, which by mid-century was to acquire the name *chemical ecology*, derived its strength from its extraordinary exploratory capacity.

Chemical ecology was the consequence of a realization that had long been part of the biological consciousness, a realization that, simply put, states that chemical interactions are ubiquitous in nature, that all organisms emit chemical signals and are responsive to the chemical emissions of other organisms. Chemical ecologists made it a point to focus on chemical interactions. Documentation of the existence of interactions, at all levels of biological organization, became commonplace, and terms were coined, such as *pheromone*, *allomone*, and *kairomone*, to designate different categories of communicative signals [1][2]. Chemical ecology, as a discipline, was clearly on its way, except for one thing. Chemical ecologists, coming mostly from the biological community, lacked the capacity to characterize molecules. To decipher chemical messages, they needed chemical collaborators. They solved the problem by joining forces with natural-products chemists, and together the two partners created the contemporary field of chemical ecology.

¹⁾ The authorship sequence was determined by the flip of a coin.

For natural-products chemists, the expanded mission created new opportunities. Their focus had hitherto been largely on molecules of use, on substances of medicinal, agricultural, and industrial interest. Their outlook was now to be broadened, as would the implication of their findings. Discovery in the realm of chemical ecology meant expansion of basic knowledge, and it was through such expansion that the new combined efforts of the chemical ecologist and the natural-products chemist made their mark (*Figure*). The future seemed golden. The natural-products chemist brought constantly improving technical capacities to the partnership. Isolation procedures by which individual components were separated from mixtures were greatly refined, as were the techniques for structure determination. Characterization of novel substances became vastly more efficient. The new chemical ecology was poised for expanded long-term exploratory effort. Journals were founded to accommodate the growing body of pertinent literature, and institutes were created specifically to provide focus for the research.

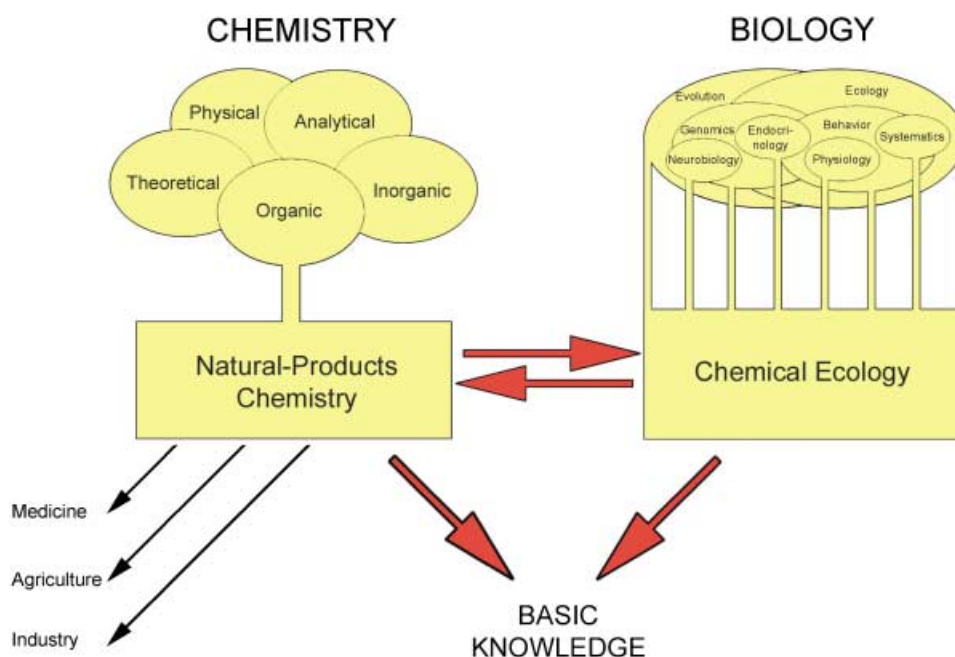


Figure. *Natural-Products Chemistry, shown in its contemporary relationship to Chemical Ecology.* The principal potential contribution of natural products chemistry, henceforth, is not only in the applied domain (medicine, agriculture, industry), but also in the exploratory domain aimed at clarifying the chemical interactions of organisms (basic knowledge). To curtail natural-products chemistry now is to put such exploratory effort on hold.

Almost incredibly, natural-products chemistry is now in danger of losing momentum. There is a widespread belief, entirely unfounded, that most species have already been studied chemically and that, consequently, most of the 'interesting' naturally occurring compounds have been characterized. Nothing could be further from the truth. Even higher plants, among the primary targets of past chemical scrutiny,

doubtless hold many secrets. There are some 250,000 species of flowering plants, but fewer than 10% of them have been studied chemically, and hardly any in depth.

With respect to microbiological metabolites, current investigations, motivated chiefly by the ever more pressing demand for novel antibiotics, have barely begun to reveal the chemical capacities of microbes. Taking into account that over 95% of all soil microorganisms are still unculturable, it is obvious that we are just at the beginning rather than at the culmination of our molecular scrutiny of the microbial world.

The seas constitute yet another frontier. Covering two thirds of the earth's surface, the oceans are the primary site for carbon fixation. Oceanic biodiversity, much of it still undescribed, promises to be an enormous source of chemical diversity. Marine invertebrates alone have yielded many unexpected types of chemical structures, largely of obscure function and origin. Marine microbes and algae are comparably interesting.

While there can be no doubt that undreamed-of compounds, holding the key to significant biotic interactions, await discovery, it is apparent that the most-important pharmaceutical companies, traditionally major players in the field of natural-products chemistry, have reduced their research in this area over the past decade. This reduction of effort can be viewed in part as an unintended consequence of the development of truly remarkable techniques for the rapid, automated screening of hundreds of thousands of compounds for selected biological activities (such as enzyme inhibition or receptor binding). The hope has been that the combinatorial synthesis of vast libraries of compounds will provide leads useful for future drug development. Since the isolation of pure constituents from organismal sources still tends to be both time-consuming and costly compared to combinatorial synthesis, industrial pharmaceutical scientists have leaned away from biological materials as their major source of new molecules to study.

There has been a simultaneous de-emphasis of natural-products chemistry within academia. Ironically, there is actually growing excitement within many chemistry departments about the opportunities for chemists to contribute to our understanding of some of the most-basic biological problems. Proteins can now be sequenced with startling rapidity, and even three-dimensional protein structures, both in the solid state and in solution, are often readily obtainable as a result of dramatic advances in single-crystal X-ray crystallography and multidimensional NMR spectroscopy, respectively. Consequently, it is now possible to model in great detail the interactions of low-molecular-weight, biologically active molecules with relevant proteins, as well as the interactions of protein molecules with one another, bringing much of biochemistry back into the hands and minds of chemists. These dramatic advances have even led some chemistry departments to change their name to '*Department of Chemistry and Chemical Biology*'. As important as these advances are, however, they complement rather than replace research on low-molecular-weight signaling molecules themselves.

To scale down natural-products chemistry now is to deprive chemical ecology of its future. Exploration for new chemical interactions is a fundamental component of the investigative process in basic science, and of the utmost significance if we are to understand how organisms interrelate and maintain their integrity as part of the fabric of nature.

There can be no question that the partnership of chemical ecologists and natural-products chemists will continue to pay off. As is patently clear from what we know already, reality surpasses fantasy in the realm of chemical interaction. Who, for

example, could have predicted the details of tritrophic interaction – of how parasitic wasps are attracted to their caterpillar hosts by the combined action of salivary factors from the caterpillar and emissions from the injuries inflicted by the caterpillar on its foodplant [3]? Who could have anticipated that bolas spiders lure the male moths that they eat by emitting replicas of the female moth's sex attractant pheromones [4][5]? And who would have imagined that there are plants capable of defending themselves against insects by producing chemical analogs of the insect's developmental hormones [6][7]? Or that the cellulose-digesting symbiotic protozoa in the gut of a wood-eating cockroach should have sexual cycles coupled to the oscillations of the cockroach's developmental hormones [8]? Or that the mites inhabiting the ears of certain moths lay a trail to one ear only, insuring that the other ear will remain uninhabited and functional, and therefore usable by the moth to detect approaching predatory bats [9][10]? Or that certain rotifers develop defensive spines when they sense, by way of a chemical emitted by predaceous rotifers that feed on them, that these predators are achieving dangerous levels of population density [11]? Or that certain insects should engage in 'pillow talk', whereby the females put their prospective mates to the test, to see if they are in possession of chemical gifts that the female can invest in egg protection [12]? Or that humans possess pheromones, including factors by which the male regulates the sexual cycle of the female [13]?

Humans are bound to be intriguing in other ways as well. Just this year, an 'olfactory' receptor protein has been discovered in the tails of human spermatozoa. Trace concentrations (10^{-7} M) of a synthetic aromatic aldehyde induces directed swimming to the signal source. Although the presumption is that the human egg is the source of an endogenous pheromone that binds to this olfactory receptor and serves to increase the likelihood of fertilization, the nature of the actual chemical signal remains to be elucidated [14].

And there are mysteries that are downright global in scope. It has become apparent recently that isoprene, the simple five-carbon parent structure of the 'isoprenoids' (comprising *ca.* 30,000 natural products, including menthol, vitamin A, progesterone, cholesterol, and rubber) is released into the air by oaks, poplars, *etc.* at the astounding rate of 500 million tons per year. Some of this isoprene is taken up by soil bacteria, but most of it is oxidized in the atmosphere, contributing to photochemical smog. It is already known that plants produce isoprene *via* the recently discovered 'non-mevalonate' pathway, but the adaptive value(s) of isoprene emission to the producing organisms remains a mystery. In this case, the chemistry is ahead of the biology [15–17].

Exploration of the unknown in the field of chemical ecology is bound to continue to uncover the unimaginable. The venture has every chance of succeeding, but only if the chemist remains linked to the effort. At stake is the understanding of the workings of nature. Nature *is* chemistry. If it is to be understood, if it is to be portrayed in full 'color', it will need to be revealed in chemical detail.

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