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DESIGN VERSUS SELECTION IN CHEMISTRY AND BEYOND

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Design is "a thing planned for, or an outcome aimed at" (Webster's dictionary). What is central to its nature is that it has the intentionality of a conscious being as its origin. Such can – but does not have to – be the case for *Selection*.

Examples of design range from the use of tools by primates in order to collect food, to the cultural interference of early humans with the natural growth of plants ("agriculture"), and on to the Hubble telescope and the world of modern technology that surrounds us.

Focusing in this paper on science and technology, the term "design" refers more to the realm of technology than to that of science. Normally, a design is a product of science, it has comprehensive and approved scientific knowledge as its prerequisite. Needless to say, more often than not an inextricable entanglement of a technology and the science it is derived from blurs the border between the two, and the history of science abounds with examples which show how progress in science can depend on the emergence of technologies. There are, of course, quasi-unlimited opportunities for human creativity in design, and there can be great art in it.

The "designedness" of the modern high-tech world mostly sprung from physics. What we call chemistry today was originally a field of experimental inquiry which the physicists of the eighteenth and nineteenth centuries "delegated", so to say, to specialists, because the phenomena observed in the metamorphoses of matter were so alien and so complex that they were not amenable to mathematical compression according to the state of the art in physics of that time. Today we know, mostly as a consequence of the workings of those specialists – the chemists – that this complexity is largely the reflection of an immense structural and behavioral diversity of mol-

ecules. “The molecule”, a central concept in the hierarchical description of matter, was unknown to the physics of that time.

Whenever the excessive complexity of phenomena surpasses the capacities of an established science that is dedicated to pursuing its traditional goals and successes, it is time for the birth of a daughter science. As with physics in the eighteenth century, the same happened to chemistry in the twentieth century. This time it was the complexity of the structure and functions of the macromolecular biomolecules inside and outside living cells that surpassed the capacities of chemists and, therefore, escaped their interest. Traditional chemists, busy with harvesting the fat crops of their field, had to leave the “chemistry of life” to the molecular biologists.

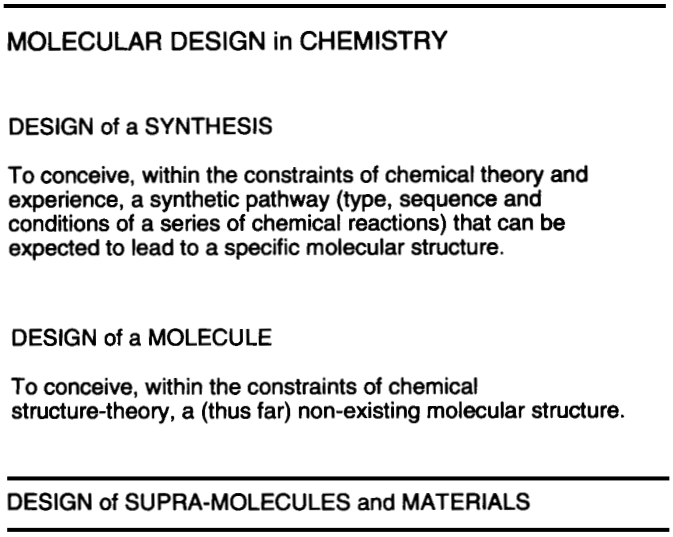

Fig. 1. Design in chemistry.

Chemistry, particularly organic chemistry, has long been an *eldorado for design*. First, there is the *design of the synthesis of a molecule*: to conceive – within the constraints of chemical theory and experience – a synthetic pathway (type, sequence and conditions of a series of chemical reactions) that can be expected to produce a specific molecular structure from simpler molecular precursors.

Hardly anywhere else is the aforementioned entanglement of science and technology more pronounced than when a chemist synthesizes a mol-

ecule for the first time. The complexity in the behavior of organic molecules is such that the first execution of a complex synthesis based on design is almost always also a venture into the uncertain, an experiment run for finding out whether and under what conditions the elements of the design do correspond to reality. Science in chemical synthesis is a harsh battle for new knowledge fought out in those steps of the synthesis where the design turns out to be incomplete, misleading, or wrong. Misleading or wrong not as a consequence of weaknesses in the design as such, but misleading or wrong because of gaps in existing knowledge.

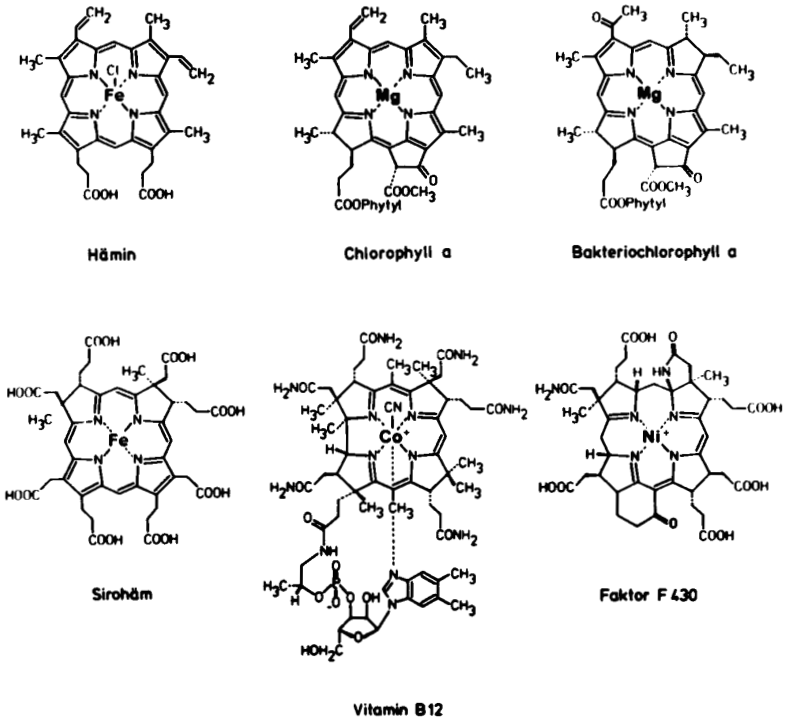

Fig. 2 Structure of Vitamin B12 (center below) and of important porphinoid biomolecules.

It is in the very nature of a design that it is done for a *purpose*. A traditional scientific objective of executing a synthesis is to extend the frontier of molecular complexity that separates what can and what cannot be done. This is chemical synthesis as a means by which to acquire new chemical

knowledge. A perhaps special, yet nevertheless representative, example, is the chemical synthesis of Vitamin B12. There was never a need for producing this most complex of all vitamins by chemical synthesis – microorganisms produce it plentifully and cheaply – for its medical use, yet the questions were: could chemists do it? What is the sort of chemistry that would allow such a synthesis to be achieved? Is new chemistry needed?

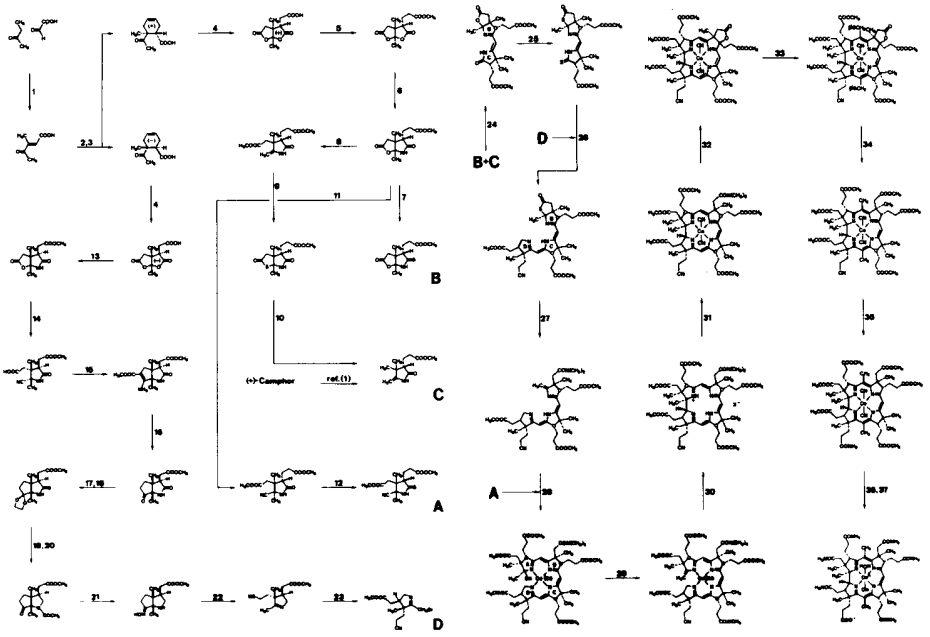

Fig. 3. Vitamin B12: An example of a chemical synthesis by design.

It was in fact in an complex interplay of synthetic design and chemical discovery that such new chemistry was uncovered. One of these discoveries even changed the way chemists think about chemical reactions. The chemical synthesis of vitamin B12 can also be said to have laid the final capstone on the grave of “chemical vitalism”, the ancient belief that chemical substances occurring in the living world can only be produced by living organisms. Vitamin B12 was a contribution of chemistry to the ongoing process of demystifying living matter by science, a process that started in 1828 with the first chemical synthesis of a natural substance produced by animals – Wöhler’s discovery of artificial urea.

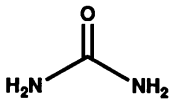

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Fig. 4. Friedrich Wöhler (1828) discovered the first chemical synthesis of a natural product occurring in animals.

A century later, the process found its most dramatic expression in the landslide insights of molecular biology. And it is proceeding further, harshly enough, by what we are told is going to be possible in genetic engineering. The path from synthetic urea to partially synthetic organisms is a drama that, perhaps more than any of the other dramas in science and technology, reminds us how science is the force of our time that drives the expansion of mankind's consciousness.

There is another type of design in chemistry: *to design the structure of a molecule*, to imagine, to think of a new type of molecular structure, a molecule that may never have existed before. If such a design of structure is followed up by a design of its synthesis, then the execution of that synthesis amounts to the creation of a new piece of chemical matter (Fig. 5, see p. II).

For more than a hundred years chemists have known the program according to which molecules are built, the rules by which the laws of physics translate into the existence and behavior of molecules. The program is expressed in their global language of chemical formulas, a language that in its astonishing simplicity, as well as consistency, allows the prediction of the central property of virtually any aggregate of atoms such as carbon, oxygen, nitrogen, hydrogen etc., namely, whether such an aggregate has a chance of existing or not. Due to the practically unlimited compositional and structural diversity of molecules and the immense variety in the detail of their chemical properties, chemistry stands, in a way, continually at its beginning. Molecular diversity on our planet is breathtaking and fundamental at the same time, it is the foundation on which life is thriving. It is the immense diversity of structures as well as the diversity of the finest details in the behavior of complex macromolecules on the constitutional, conformational and constellational level which has made the evolution of chemical life on earth a contingency or, as some scientists dare to affirm, a necessity.

Organic chemistry has grown up with a long history of studying molecules discovered to occur in living nature. However there has always been,

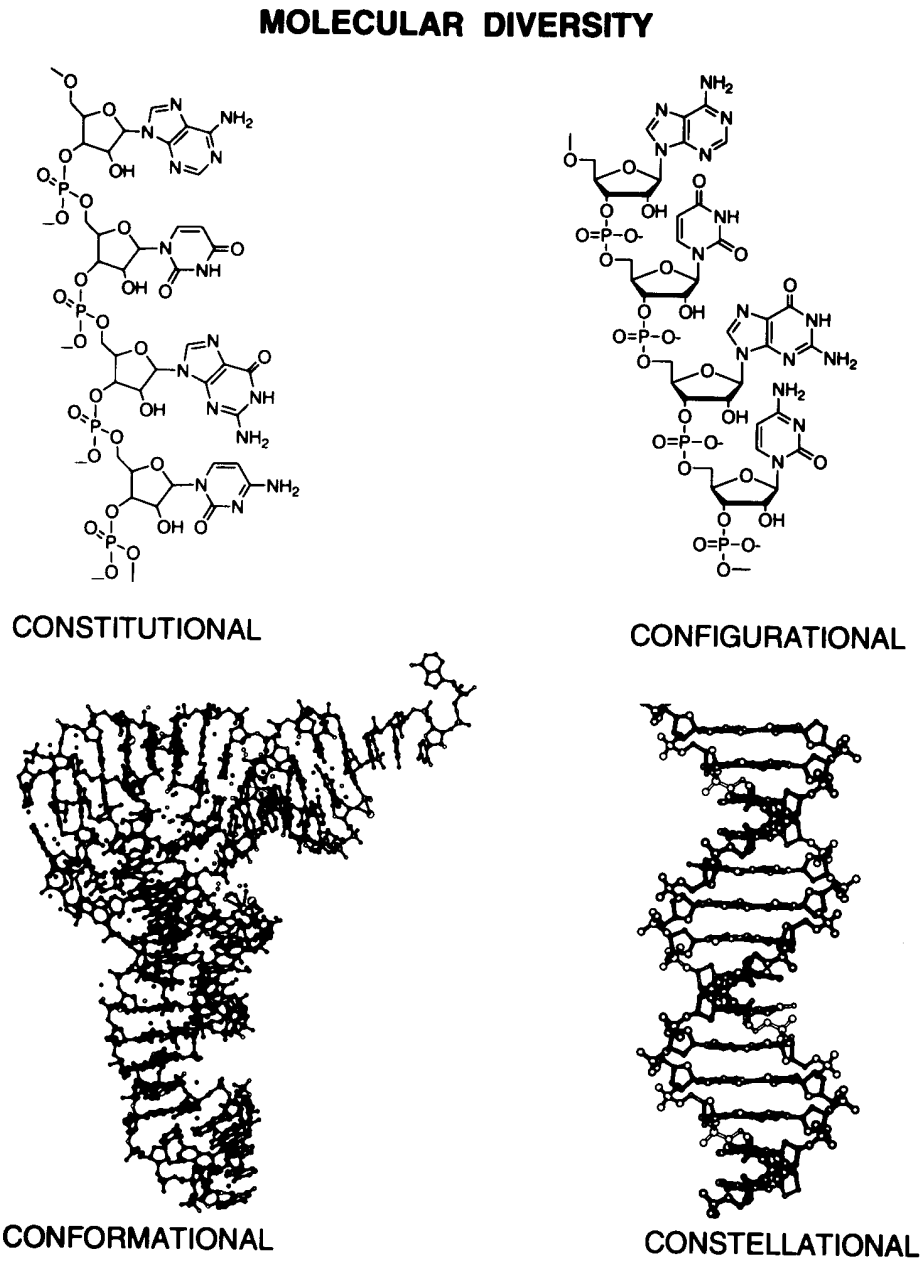


Fig. 6. Four levels of describing the structure of biomolecules: Nucleic acids.

and still is, room for discovering molecules of the non-living world: C60, *Buckminster-fullerene*, is one of the most recent and most interesting examples (Fig. 7, see p. II).

The marvelous symmetrical structure of the football-shaped C60 structure had in fact been conceived and designed by chemists before its existence was discovered in interstellar space. But those designers had to abandon their quest of following up their design of a structure with a design of its synthesis. This brings us to a challenge chemists are confronted with today: the quest to make use of the intrinsic potential of molecules to self-assemble. Self-assembly is the coming into existence of a molecular (or supra-molecular) structure by a multi-step reaction path in a given environment without instruction from outside. C60 obviously has to self-assemble in interstellar space, otherwise it would not be there. Chemists grasped that lesson and learnt how to make the molecule on earth by setting up conditions under which in fact it assembles itself (condensation of vaporized carbon) (Fig. 8, see p. III).

Chemists distinguish two types of self-assembly, molecular and supramolecular, or constitutional and constellational. Either *molecules* assemble themselves from molecular or atomic components by reacting together and becoming joined through covalent bonds, or *supramolecular aggregates* assemble themselves from partner molecules by being held together through essentially non-covalent bonds, most often by so-called hydrogen bonds. The formation of C60 both in interstellar space and in the chemist's laboratory is an example of the first kind, the formation of the DNA double helix from DNA single strands both in living cells and in the chemist's laboratory is a – if not the – prototypical example of the second kind.

When we look at matters more closely, each multi-step chemical synthesis is actually to be seen as a succession of steps in which the chemist, at each step, sets the stage for a specific act of constitutional self-assembly to occur. Setting the stage means: creating the boundary conditions, the specific physical and chemical environment necessary for "the reaction to proceed", providing the instruction the system requires in order to take over and to react in a specific direction. In a laboratory synthesis, it is the chemist who is the source of this instruction. In a multi-step biosynthesis proceeding in the living cell, the instruction is conveyed by the ambassadors of the genome, the enzymes that make a biosynthesis occur. The channel through which the instruction reaches the reaction partners is *catalysis* – positive catalysis that accelerates a specific reaction step or negative catalysis that slows it down. From a chemist's point of view, a multi-step biosynthesis amounts, in principle, to an overall constitutional self-assembly of the target molecule in a

genome-controlled environment. Fundamentally, what living nature has so irresistibly explored in Darwinian evolution is the immense potential of the molecular world for constitutional and constellational self-assembly.

Constellational self-assembly is in the focus of interest today in structural biology as well as in chemistry. It was only about a year ago that we could marvel at the x-ray structures of a ribosome, the heart of biology, as some of us would say.

The ribosome is a constellational aggregate of more than fifty different protein – and RNA – molecules held together by non-covalent bonds in a specific arrangement relative to each other, and orchestrated for acting as a machine capable of decoding the information contained in genes by converting base-sequences of nucleic acids into amino-acid-sequences of proteins. Chemists are perhaps the most propitious people for judging how miraculously biological supramolecular systems such as the ribosome are actually built. This is because chemists, particularly synthetic chemists, in being confronted with such a structure react in a sort of reflex action by asking: "how would I make it?" The ribosome structure immediately gives them a lesson in modesty, by pointing to the breathtaking distance between the state of the art in what chemists might be able to achieve by design, and what biological evolution has accomplished (Fig. 9, see p. IV; Fig. 10, see p. III).

In basic chemical research, constellational self-assembly is today a central topic. On the other hand, besides the design of new molecular structures and the design of syntheses, the study of supramolecular aggregates is also the concern of chemists in more utilitarian areas of chemistry, namely in the factories of drug design. Traditionally, drug research was mostly concerned with the isolation of biologically active natural products with medical potential. In this way important drugs were discovered and developed: from the drug-veteran aspirin a hundred years ago, to penicillin about fifty years ago, and on to Taxol more recently. The latter was first isolated from the bark of the Pacific yew tree; it showed dramatic effects in cancer therapy and, therefore, induced a burst of designs for its chemical synthesis.

Modern drug design is based on the strategy of interfering with the natural function of specific proteins by small molecules of specific structure which, by virtue of their specific affinity to a protein, influence (usually inhibit) the function of that protein in vivo. In the focus of this strategy are specific supramolecular aggregates between the small molecule and the bioactive site of the corresponding protein, the occurrence and stability of such aggregates being mostly dictated by shape complementarity between the small molecule and the protein at its bioactive site.

In the second half of the last century, pharmaceutical companies invested a huge amount of money on what was then intended to become rational drug design through the use of computer assisted modeling of supramolecular aggregates between small molecules and the active sites of proteins. It was believed that with the advent of computer technology and the x-ray structure analysis of proteins the time was ripe for a major paradigm shift in pharmaceutical research: the shift from *discovering drugs by chance* to being able to *design drugs*, to design the structure of small molecules that would fit in shape and reactivity the relevant bioactive sites of proteins.

It was the dramatic, worldwide and very costly failure of this hope that eventually led to a realistic assessment of the problems of drug design. Small-molecule-protein interactions – leaving aside the question of the environment of a living cell – are for the time being still too complex a problem for the design of the chemical structure of a drug to be feasible.

It was in this period of disillusionment that a real paradigm shift in drug research emerged – combinatorial synthesis.

About a decade ago, the new strategies and technologies of combinatorial chemistry flooded the laboratories of pharmaceutical research worldwide. For centuries, the organic chemist's imperative was to work, whenever possible, with pure compounds. In drug research, the traditional empirical search for natural and synthetic drugs demanded the sequential preparation and biological testing of single molecular species. Too slow and too inefficient a strategy in a modern world of globally competing pharmaceutical companies! In the combinatorial search for drugs, whole libraries – that is to say thousands, hundreds of thousands, millions of constitutionally related but different substances, each species in necessarily minute amounts, are synthesized in one go – and the library of substances is then screened for a desired property by microanalytical methods. If a response is observed, the structure of the responding component is decoded, synthesized in bulk amounts and tested for its bioactivity. What this approach is aiming at is not to *design* a drug, but to *discover* a drug by artificially creating a huge diversity of new molecular species through the stochastic variation of reaction partners in a multistep combinatorial synthesis, followed by selection and amplification of compounds which happen to possess a desired property.

In combinatorial chemistry, the central message of evolutionary biology, *variation*, *selection* and *amplification*, finally reached the heart of chemistry. The inspiration for its development had originally come from biology, and it has changed the chemist's thinking about his own world. To be sure, in the chemist's shift from design to selection there remains a distinct ele-

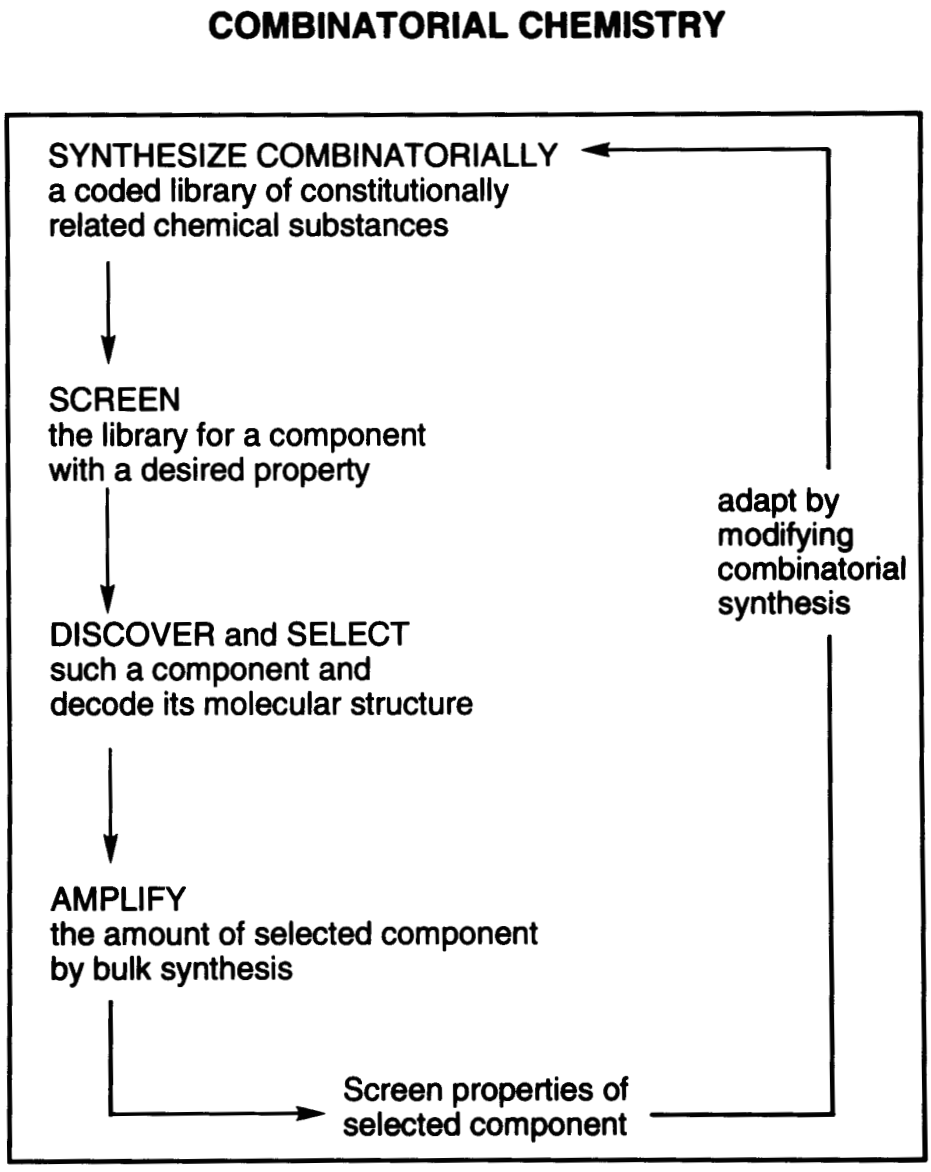
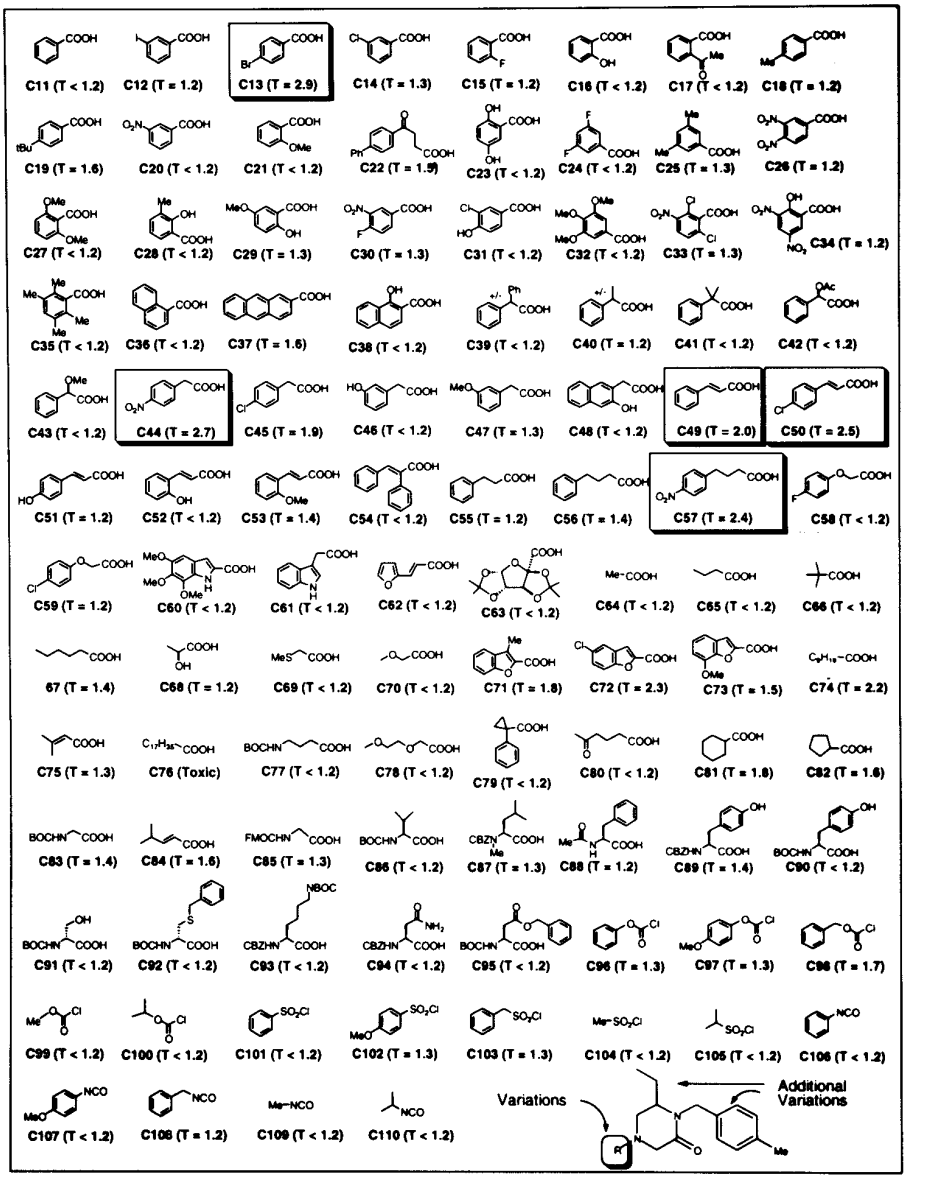


Fig. 11. Combinatorial chemistry (see also Fig. 12, p. V).



D. L. Boger, J. Goldberg, S. Satoh, S. B. Cohen, and P. K. Vogt
Helv. Chim. Acta **2000**, *83*, 1825–1845.

Fig. 13. Example of a library of reaction partners in a combinatorial synthesis (courtesy of Prof. D. Boger, TSRI).

ment of design – the Lamarckian element – so to say. The chemist can and does, of course, judiciously choose the structure type of the molecular diversity which he is creating for a given purpose, design libraries based on previously acquired knowledge, practicing thereby a most powerful mix of the basic strategies “design” and “selection”. This mix of strategies dominates research and development in academic and industrial laboratories today. It is the modern way of searching for new drugs, new catalysts, and new materials (Fig. 14, see p. VI; Fig. 15, see p. VII).

Let us have a look at the structure of a ribosome again. The most surprising and perhaps also most important aspect discovered in this structure is the fact that in the neighborhood of the molecular machinery, where the peptide bonds are actually made, there is only RNA and no protein. The catalyst that promotes the covalent-bond chemistry of protein synthesis is an RNA, not a protein, a ribozyme, not an enzyme. This constitutes the strongest argument we have today in favor of the conjecture that an RNA world may have preceded our present DNA-RNA-protein world. In this our present world, RNA connects the genotype with the phenotype, in an RNA-world, RNA would simultaneously have fulfilled the role of both: the genotype role as a replicating nucleic acid, the phenotype role by virtue of its great diversity in sequence-specific molecular shapes. Base-sequence determines RNA’s molecular shape, and the diversity of these shapes is the source of catalytic activity. “Constitution codes for conformation” is a basic tenet of chemistry.

That RNA molecules can act as catalysts is a fact, and not just a hypothesis, ever since Cech and Altmann discovered the first ribozymes about two decades ago. Great strides have been made since then in charting the landscape of the catalytic properties of RNA-molecules of varying base-sequences and of correspondingly varying molecular shapes. In vitro-evolution of catalytic RNAs, using enzymatic methods, is being pursued in a number of laboratories as one of the most powerful experimental strategies for discovering RNA’s potential for catalysis.

If RNA is the alleged master molecule of an early life form that eventually evolved into ours, how did RNA originate? Was the origin of RNA the origin of life itself, as many biologists tend to think?

Nowhere will biology and chemistry ever meet in a more fundamental and more intimate way than in relation to the problem of the origins of life. This has been referred to as one of the great unsolved problems of science. In its generalized form, it is perhaps the most challenging problem of chemistry as a natural science: Can inanimate chemical matter transform itself into adaptive, evolving, and eventually living matter? The pragmatic

scientist's attitude towards this question must be that it *can* and, furthermore, that it *did*. Otherwise he will not invest the effort of attempting to find out *how* it could and *how* it might have happened. Due to the pioneering theoretical studies of physical chemists such as Manfred Eigen, Ilya Prigogine and others, there are no longer any theoretical barriers against the concept of self-organization of matter towards life.

Experimental efforts will be launched in two directions: towards the creation, in the laboratory, of what may be referred to as *artificial chemical life* in order to produce a proof of principle, and towards reconstructing the natural pathways to the origins of our own life. The nature of the two approaches nicely reflects, interestingly enough, the two traditional faces of organic chemistry: the latter in the study of natural products – culminating in molecular biology – and the former in the creation of new chemical matter, culminating in the making of materials with new properties.

From a chemist's point of view, it seems quite improbable that RNA could have assembled itself prebiotically without external instruction, given the scale of the difficulties encountered in attempts to simulate experimen-

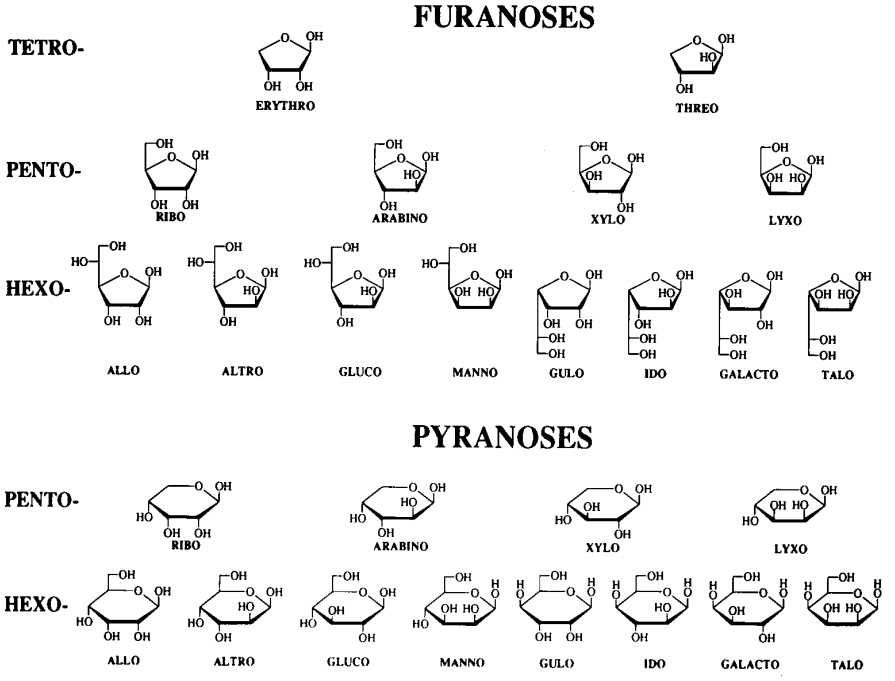


Fig. 16. The library natural of carbohydrate monomers.

tally the required steps of such a constitutional self-assembly under potentially natural conditions. One school of thought conjectures that chemical evolution started from simpler informational polymers – simpler not necessarily structurally, but with regard to accessibility – and that the evolution of such precursor systems had led to, and eventually was taken over by, RNA. The experimental search for such potential precursor systems has hardly started.

There is yet another experimental approach to the problem of the origins of RNA. It is one that focuses on function. It originates in the question: why it is that the ribofuranosyl nucleic acid system, rather than some other family of molecular structures, has been chosen by nature as the molecular basis of life's genetic system? The experimental strategy of the approach is to conceive – through chemical reasoning – potentially natural alternatives to the nucleic acid structure, to synthesize such alternatives in the laboratory by chemical methods, and to systematically compare them with the natural nucleic acids with respect to those chemical properties that are fundamental to the biological function of RNA and DNA, namely, base-pairing and replication (Figs. 17 and 18, see p. VIII).

Basic to this research is the supposition that the RNA structure originated through a process that was *combinatorial* in nature with respect to the assembly and functional selection of an informational system within the domain of sugar-based oligonucleotides; the investigation can be viewed as an attempt to mimic the selectional part of such a hypothetical process by chemical means. In principle, such studies have no bias with regard to the question of whether RNA first appeared in an abiotic or biotic environment.

Such studies have revealed that the fundamental chemical property of the natural nucleic acids, informational Watson-Crick base-pairing, is not a unique and specific property of the ribofuranosyl-oligonucleotide system. The capability is found in a surprising number of systems with an alternative backbone structure. Among them is the family of pentopyranosyl oligonucleotides, in which the pentose-sugar units have a six-membered ring, and in which each of its members show Watson-Crick pairing that is much stronger than that of RNA. Another alternative with remarkable properties is the threofuranosyl-system. Its backbone unit contains only four carbons and, therefore, it is structurally a far simpler system than RNA itself. The threofuranosyl-oligonucleotide system is at present under comprehensive study since its properties make it a candidate in the search for genetic systems that might have been ancestors of RNA.

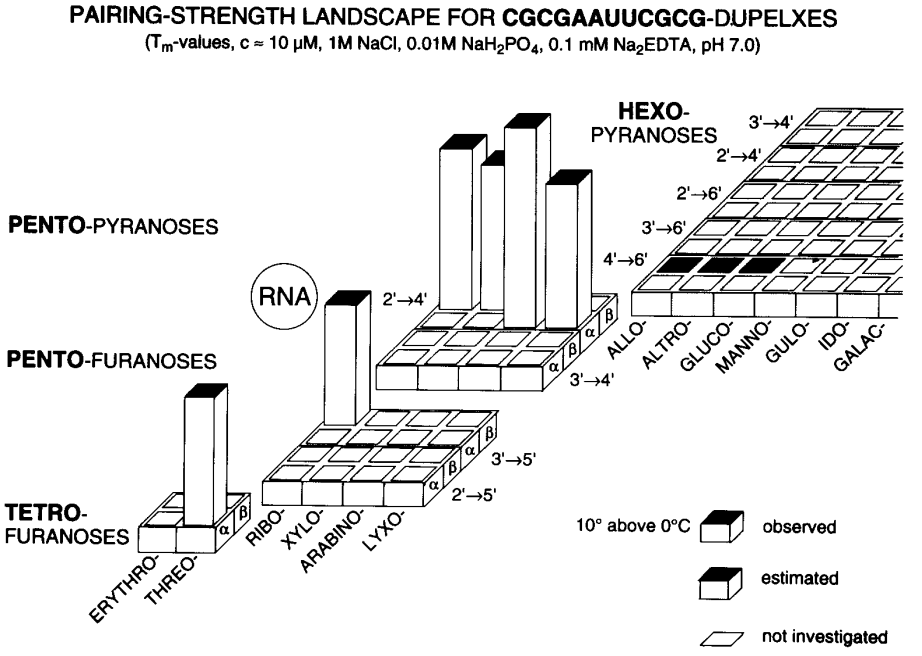


Fig. 19. Base-pairing strength landscape

Evolution – variation, selection and amplification – *can substitute for design*. This is a, if not the, central message of the Darwinian doctrine. Biologists have followed it for a long time; chemists recently adapted to it in their practical pursuits; and cosmologists are invoking evolutionary aspects in their thinking on a grand scale. The latter are confronted with the "design versus selection" dichotomy in their area in a very remarkable way. Gradually, they came to appreciate that the necessary conditions for evolution of complex life in the universe are dependent on a number of remarkable coincidences between the values of various fundamental physical constants. Our universe appears as if these constants had been tuned towards the evolution of conscious observers.

It is remarkable how the aspect of the apparent tuning of physical constants even extends into the detailistic world of chemistry; this becomes evident when one looks at the central chemical interaction in molecular biology – the Watson-Crick base-pairing.

The existence of Watson-Crick base-pairing is crucially dependent on the position of the chemical equilibrium between tautomeric forms of the nucleobases. If the average bond energy of the carbonyl double bond relative to the bond energies of the carbon-nitrogen and carbon-carbon double bond were less by only just about a few kcal per mole, the nucleobases would exist as the phenol-tautomers. Watson-Crick pairing and, therefore, the kind of life we know, would not exist.

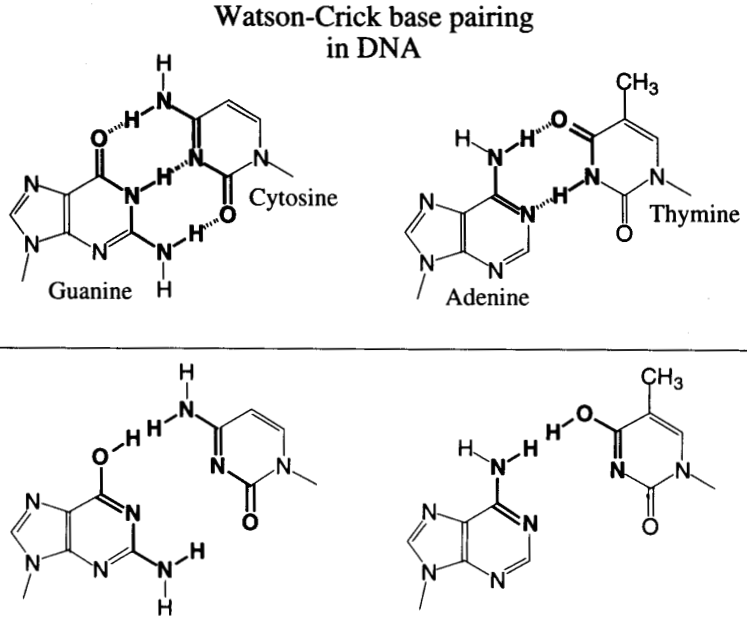


Fig. 20. “Fine-tuning of chemical bond energies” and the existence of the Watson-Crick base-pairing

The dichotomy *“design versus selection” penetrates the whole of natural science*, and, to many, refers to aspects that go far beyond. It is this dichotomy that is underlying the creationist's crusade against Darwinism in America and elsewhere. Today, experimental chemists can experience in their work the superiority of evolutionary strategies in their searching for

solutions, as compared to finding them by design. Whenever a situation such as this arises, it may be that it is the science that is not advanced enough, but more often it is the immense diversity of states, structures, patterns and relationships that overwhelms the designer and incapacitates his strategy. Basically, the experimentalist's credo is design, it is the ideal which he cannot help aiming at and striving for. . The physicist Richard Feynman is known to have written on his blackboard at Caltech: "What I cannot create, I do not understand". Humans are said to do natural science for the sake of understanding. But do we perhaps want to understand in order to be able to make, to create? It seems fortunate that among the sciences there are some truly pure ones, like, e.g., astronomy and cosmology. The technologies which people imagine springing from them exist only in science fiction. Remarkably enough, there are scientists who ask: for how long?

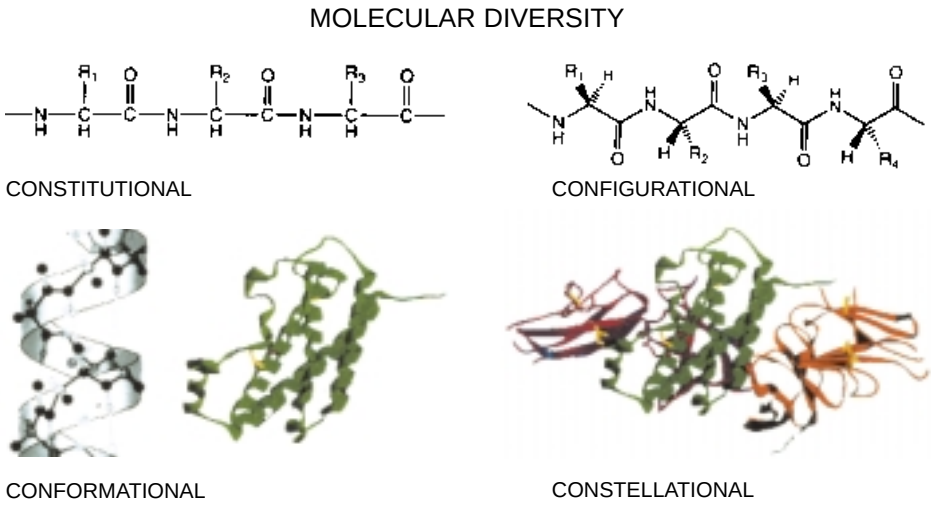


Fig. 5. Four levels of describing the structure of biomolecules: Proteins.

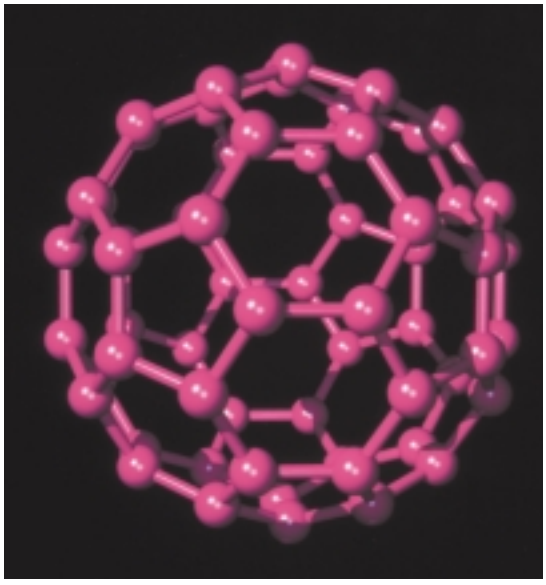
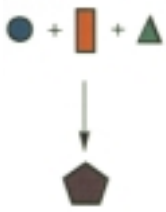
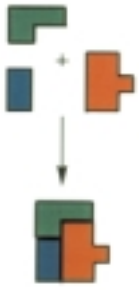


Fig. 7. Buckminsterfullerene. A complex molecule that can assemble itself (courtesy Prof. F. Diederich, ETH).



Constitutional self-assembly of complex molecules from simpler molecules (or elements) by transformation of covalent bonds.



Constellational self-assembly of supramolecular species by aggregation of molecules through non-covalent bonds

Fig. 8. Self-assembly of molecules and self-assembly of supramolecules.

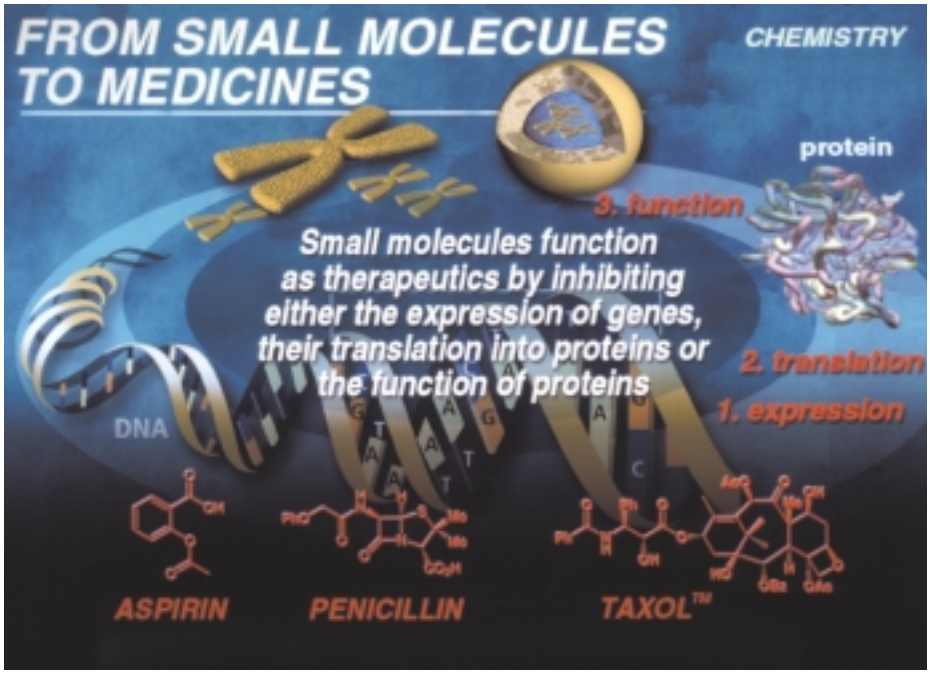


Fig. 10. Medicinal natural products chemistry (courtesy of Prof. K. C. Nicolaou, TSRI).

Fig. 9. The structure of the Ribosome: a landmark in biological chemistry.

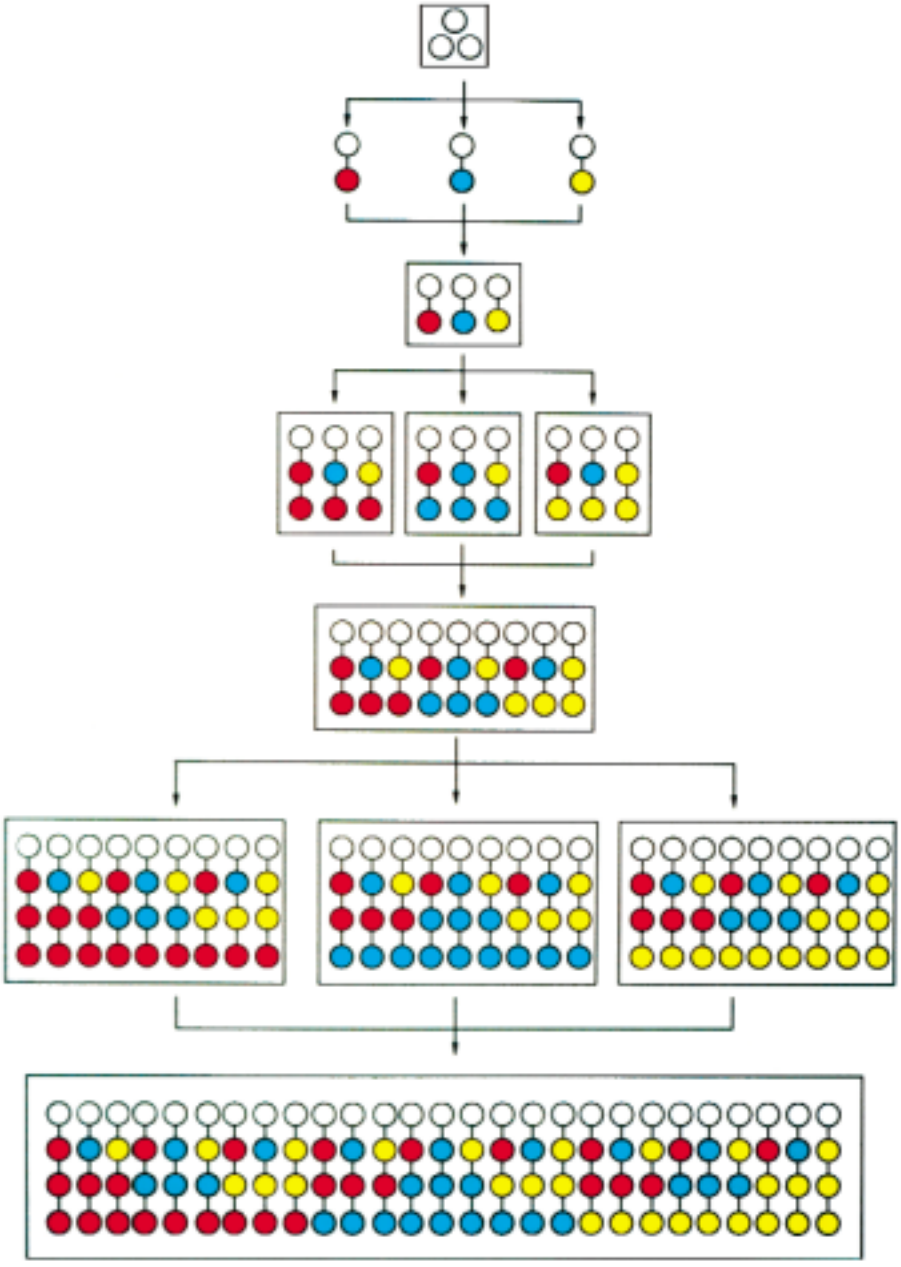


Fig. 12. The principle of combinatorial synthesis illustrated (courtesy of Prof. G. Quinkert, Frankfurt).

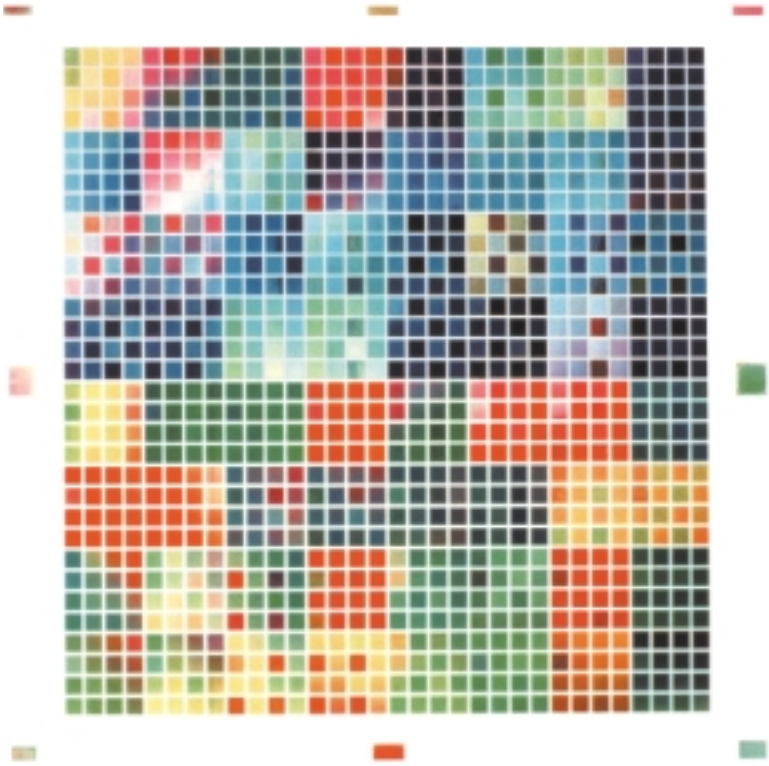


Fig. 14. Materials science: combinatorial search for catalysts (courtesy of Prof. P. Schultz, La Jolla).

Fig. 15. The ribosome again.

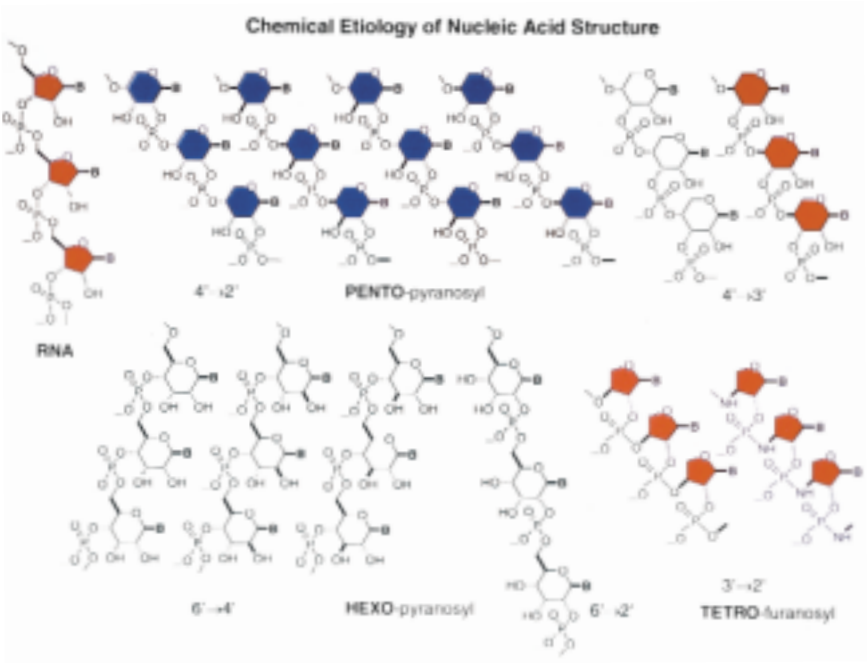


Fig. 17. Potentially natural nucleic acid alternatives studied experimentally so far.

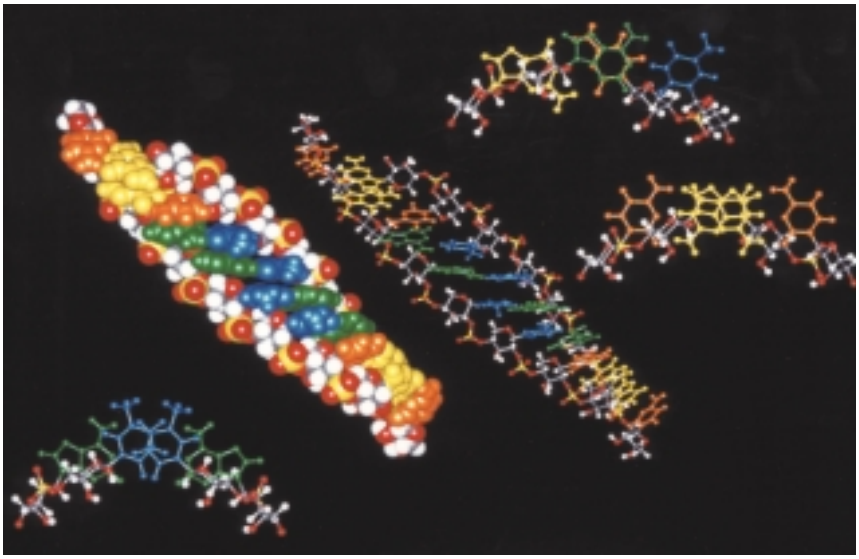


Fig. 18. Pyranosyl-RNA, an example of an alternative nucleic acid that shows stronger Watson-Crick pairing that RNA itself (NMR-structure).