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A Personal View of Chemistry (with Emphasis to Mathematical Chemistry) as Science and Art

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Abstract

After recalling that art and science belong to Snow's 'two cultures', a brief mention is made of the 'stimulus package' proposed by Vannevar Bush for basic science in USA. Common traits are shared by artists and scientists, especially when the latter ones also create their objects of study (invention versus discovery). A few personal contributions to mathematical chemistry are mentioned, such as encoding structures of cata–fused benzenoids by using dualists, inventing reaction graphs and several topological indices. Two trivalent cages with girths 10 and 11 have completed the series of cages up till girth 12. The extraordinary symmetry of cages with girths between 4 and 8 competes with the symmetry of polytopes; unfortunately, this type of beauty can be perceived only mentally, not visually.

Keywords. Graph theory; chemical graphs; reaction graphs; topological indices; chemical symmetry.

1 GENERALITIES

1.1 Learning from the Recent Past: Charles P. Snow and Vannevar Bush

Sir Charles Percy Snow in his book *The Two Cultures* deplored the fact that at present scientists and humanists no longer communicate among them, as they used to do till about a hundred years ago. A revised edition of this book was published in 1965 by the Cambridge University Press with a longer title: *The Two Cultures: and a Second Outlook. An Expanded Version of the Two Cultures and the Scientific Revolution* [1]. Yet, the pursuits of artists and scientists are in many ways similar, and the act of creation brings the same elation to both the artist and the scientist.

Dr. Vannevar Bush, who was the Director of the Office of Scientific Research and Development, presented in July 1945 to F. D. Roosevelt the landmark Report on a Program for Postwar Scientific Research entitled *Science – the Endless Frontier* [2]. This report, which synthesizes the conclusions of Dr. Bush's consultations with numerous personalities in his Advisory Committee, contains a

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treasure of valuable suggestions, valid even nowadays, more than fifty years later. Space and time limitations allow me to extract only a few of the most relevant ideas from this report. Its immediate effect was the creation of the National Science Foundation, a governmental organization that awards grants for basic research coupled with higher education. The five basic principles of this report that should characterize an effective program of this governmental support for scientific research and education are:

"(1) Whatever the extent of support may be, there must be stability of funds over a period of years so that long–range programs may be undertaken.

(2) The agency to administer such funds should be composed of citizens selected only on the basis of their interest in and capacity to promote the work of the agency...persons of broad interest in and understanding of the peculiarities of scientific research and education.

(3) The agency should promote research through contracts or grants to organizations outside the Federal Government; it should not operate any laboratories of its own.

(4) Support of basic research in the public and private colleges, universities, and research institutes must leave the internal control of policy, personnel, and the method and scope of research to the institutions themselves. This is of utmost importance.

(5) While assuring complete independence and freedom for the nature, scope, an methodology of research carried on in the institutions receiving public funds, and while retaining discretion in the allocation of funds among such institutions, the Foundation proposed therein must be responsible to the President and Congress."

The report then goes on with such headings as "Scientific progress is essential in the war against disease", mentioning that annual deaths from one or two diseases far exceed the total number of American lives lost in battle during World War 2. "Progress in the war against disease results from discoveries in remote and unexpected fields of medicine and the underlying sciences.... It is wholly probable that that progress in the treatment of cardiovascular disease, renal disease, cancer, and similar refractory diseases will be made as the results of fundamental discoveries in subjects unrelated to these diseases, and perhaps entirely unexpected by the investigator. Further progress requires that the entire front of medicine and the underlying sciences of chemistry, physics, anatomy, biochemistry, physiology, pharmacology, bacteriology, pathology, parasitology, etc. be broadly developed."

Another idea is that "basic research leads to new knowledge. It provides scientific capital. It creates the fund from which the practical applications of knowledge must be drawn.... A nation which depends upon others for its new basic scientific knowledge will be slow in its industrial progress and weak in its competitive position in world trade, regardless of its mechanical skill.... The distinction between applied and basic research is not a hard and fast one... but it is important to emphasize that there is a perverse law governing research: under the pressure for immediate results, and unless deliberate policies are set up to guard against this, *applied research always drives out pure*. The moral is clear: it is pure research which deserves and requires special protection and specially–assured support."

In the chapter entitled "Renewal of scientific talent", Dr. Bush and his advisory committee wrote that all boys and girls should be able to feel that, if they have what it takes, there is no limit to the opportunity. "Improvement in the teaching of science is imperative; for students of latent scientific ability are particularly vulnerable to high school teaching which fails to awaken interest or to provide adequate instruction."

The report declares that "if we were all–knowing and all–wise we might, but we think probably not, write you a plan whereby there might be selected for training, which they otherwise would not get, those who, 20 years hence, would be scientific leaders, and we might not bother about any lesser manifestation of scientific ability. But in the present state of knowledge a plan cannot be made which will select, and assist, only those young men and women who will give the top future leadership to science. To get such leadership there must be a relatively large base of high ability selected for development and then successive skimmings of the cream of ability at successive times at higher levels. No one can select from the bottom those who will be leaders at the top because unmeasured and unknown factors enter into scientific, or any leadership. There are brains and character, strength and health, happiness and spiritual vitality, interest and motivation, and no one knows what else, that must enter into this supra–mathematical calculus."

"We think we probably would not, even if we were all–wise and all–knowing, write you a plan whereby you would be assured of scientific leadership at one stroke. We think as we think because we are not interested in setting up an elect. We think it much the best plan, in this constitutional Republic, that opportunity be held out to all kinds and conditions of men whereby they can better themselves... We think it very important that circumstances be such that there be no ceilings, other than ability itself, to intellectual ambition. We think it very important that every boy and girl should know that, if he shows that he has what it takes, the sky is the limit. Even if it be shown subsequently that he has not what it takes to go to the top, he will go farther that he would otherwise go if there had been a ceiling beyond which he always knew he could not aspire."

"By proceeding from point to point and taking stock on the way, by giving further opportunity to those who show themselves worthy of further opportunity, by giving the most opportunity to those who show themselves continually developing – this is the way we propose. This is the American way: a man works for what he gets."

Very wise ideas, and when they were put into practice during the last 50 years, they indeed raised the USA to the level of first world power in all respects.

1.2 Historical Introduction

What are *art* and *science*, from the broadest definitions to their aims and motivations? From this starting point, we may find out where they overlap, where they only touch, and where they diverge.

To start with prehistorical times, for the first humans who were using wooden and stone tools, there was no difference between science and art. One had to discover which branches would be better suited for bows and which other ones yielded better arrows. For making arrowheads or cutting tools from a piece of flint or of obsidian, the *science* of cleavage planes was combined with the *art* of hitting the stone with the appropriate force and at the suitable angle. On looking at rupestric pictures or at cave paintings such as those in Altamira or Lascaux, one is filled with awe both by the artistic ability of the anonymous painters and by their scientific knowledge of the dyeing materials they were using.

We surmise that science started for certain useful purposes: geometry (as its name betrays) for measuring pieces of land, and astronomy for predicting when to plant, or when to expect the Nile to flood. We suspect that art depicting successful hunting, or erecting temples honoring the gods that were supposed to rule the oceans, the sky, the thunder, and the much needed rain also helped to build confidence, hence a useful objective.

It is only in historical times that science and art, as we now know them, started to diverge. Still the huge Egyptian pyramids and temples, the daring constructions of Babylon, and the gracious Greek temples and statues combine art with science to a high degree. Even during the Renaissance and a few centuries later, people such as Leonardo da Vinci were artists, scientists, and engineers. Looking at the San Pietro Cathedral’s dome in Rome, one feels awe at the thought that Bernini and Michelangelo could conceive and direct the construction of such an artistic and scientific wonderful monument.

It is probable that art started to diverge most from science during the few centuries of antiquity when Greek culture flourished. It drew its roots from Egypt and the Middle East. Then one had for the first time art for art’s sake (Phidias, Aeschylus, Euripides, Aristophanes) and science for satisfying the curious minds of Euclid, Thales, Anaximenes, and many others. The thirst for understanding the forces that govern the universe and shape the planet we live upon allowed the invention of philosophic systems, independent of religious beliefs. It is probably not a coincidence that the free minds of Sophocles, Plato and Aristotle could do what they did only in the short–lived and relatively democratic Greek society. It is interesting to recall the nine Muses of Greek mythology, whose mother was **Mnemosine** (Memory):

1. **Clio** (History)
2. **Eutherpe** (Music)
3. **Thalia** (Comedy)
4. **Melpomene** (Tragedy)

5. **Terpsichore** (Dance, choral song)
6. **Erato** (Love poetry)
7. **Calliope** (Heroic poetry)
8. **Polymnia** (Dance and *geometry*)
9. **Urania** (*Astronomy*)

It is noteworthy that the last two Muses dealt with sciences (as highlighted with italics) and not only with arts; also history is not an art (this leaves six arts: architecture, sculpture, painting, music, dance, and poetry, as proposed in lectures on aesthetics by Hegel, and that is why one speaks about the six arts, with cinematography being the 7th art). However, some sciences and arts were not cultivated by the Muses of Ancient Greece. Absent arts are Architecture, Sculpture, Writing, Painting (that were known by the ancient Greeks), and Opera or Cinema that were not. Absent sciences are Mathematics, Physics, Chemistry, Earth sciences, Life sciences.

1.3 Art and Science

An aspect that is common to art and science is the elation any creator feels when he or she has done something successfully for the first time in the world. However, the difference is that in science one adds new bricks to a continuously increasing edifice, whereas in art most often one starts from the beginning, and there is little obvious continuity. Almost to the contrary, most of the thorough innovations in art aimed at destroying rather than continuing what was done earlier.

Another trait that is common to both art and science is the total dedication of the best creators. The Latin aphorism *Ars longa, vita brevis* is applicable to both art and science. In this respect, I would like to recall what I. P. Pavlov told the audience in his lectures in USA (1923 and 1929): “if you had two lives, they would still not be enough, should you wish to devote your life to science”. Again, this applies equally well to art.

What I wish to convey is that science is not the cold, indifferent look for new facts but the ardent, passionate quest for understanding the truth, order, and beauty around us. Sometimes this quest is mixed with ambition for being the first to find and publish, as attested in J. D. Watson’s well–known book *The Double Helix* [3], but these human passions do not diminish the similarity between the flame animating both the creators in art and the true scientists.

If the aim of science is to find out the truth about the surrounding world around us, one should recall the words of John Keats (1795–1821) in his “Ode on a Grecian Urn”:

When old age shall this generation waste
Thou shalt remain, in midst of other woe
Than ours, a friend to man, to whom thou say’st,
‘Beauty is truth, truth beauty’ – that is all
You need to know on earth, and all you need to know.

Or, in the words of George Gordon, Lord Byron’s (1788–1824) poem entitled “On this day I complete my thirty–sixth year” that was composed a few days before his death at Missolonghi, and expressed Byron’s feelings about beauty:

“Tread those revived passions down,
Unworthy manhood! – unto thee
Indifferent should the smile or frown
Of beauty be.

If thou regrets thy youth, why live?
The land of honorable death
Is here. Up to the field and give
Away thy breath!

Seek out (less often sought than found)
A soldier’s grave, for thee the best.
Then, look around and choose thy ground
And take thy rest.

One of the main differences between art and science is the **repeatability** of scientific discoveries or inventions, whereas artistic creations are **unique**. **An art work lives forever** if conditions are favorable. When they are not, unfortunately, we know nothing of artistic creations that involved perishable materials. Similarly, nothing is known about antique music, although it was highly appreciated as revealed by the myth of Orpheus. Artistic creations may be imitated or it may initiate a trend, but they will always bear the signature of its creator. Only an original painting by Van Gogh or Vermeer will be valued in millions of dollars, but not a faithful copy.

To turn around my assertion about artistic aspects of science, one could recall Constable’s metaphor quoted by Gombrich [4] and Goodman [5]: ‘Painting is a science...of which pictures are but experiments’.

In science, reproducibility is the keystone for validating scientific discoveries or inventions. A scientific creation will always be **perfectible**, and it also will always lead to follow–ups. Thus scientific advances are always the result of collective work. Sometimes a scientific discovery is too much ahead of its time, as it happened with Gregor Mendel’s laws of genetic inheritance. Sooner or later, mankind is bound to arrive at that knowledge, so that scientists are conscious of their more modest role than the artistic creators.

1.4 Invention *versus* Discovery

All historical and contemporary art is invented, but science is part invention and part discovery. Dictionaries sometimes consider these two terms almost equivalent because there are no rigid borders between these two aspects of creative minds. Albert Szent–Györgyi (1893–1986) put these ideas in an admirable form when he declared that “success in science means to see what many people had seen, but to think what nobody else has yet thought”. Millions of people had seen an apple falling prior to Newton, but he was the first to make the connection with the moon falling continuously towards the earth. Thus Newton **discovered** the unity of terrestrial and celestial phenomena and formulated mathematically the law of universal gravitational attraction.

When a creative mind builds a device or conceives an idea and goes on to make it known to others, then this can be qualified as an invention. There are a few areas where invention is the norm, such as engineering and related sciences. Edison **invented** the electric light bulb and the phonograph, and Bell invented the telephone. Even the fact that similar inventions may be produced simultaneously by several people (as it happened with the two inventions mentioned above) does not make them discoveries, as they did not exist previously. Only previously existing entities are discovered. **Simultaneous discoveries or inventions** occur fairly often in science. One of the best known examples is that Newton and Leibniz invented independently differential and integral calculus.

Galileo Galilei **invented** the best telescope of his time in 1609, and with it he **discovered** four satellites of Jupiter, the phases of Venus, and the spots on the Sun. Alexander Fleming **discovered** serendipitously penicillin, and then Florey and Chain **invented** the practical method for producing and purifying it. Albert Szent–Györgyi, Axel Holst and Alfred Fröhlich **discovered** Vitamin C. Its industrial synthesis is based on Bertrand’s **invention** of a fermentative process followed by oxidation.

One should be aware, however, of the dangers and jealousies awakened by innovators, be they in art or in science, and expressed by somebody who knew well the human psychology: “There is nothing more difficult to take in hand, more perilous to conduct or more uncertain in its success than to take the lead in the introduction of a new order of things, because the innovator has for enemies all those who have done well under the old condition, and lukewarm defenders in those who may do well under the new” (Niccoló Machiavelli, in his book *Il Principe*, published in 1513).

1.5 Discovery and Invention in Mathematics, Physics, and Chemistry

Mathematics is a purely intellectual construction, yet it reflects fundamental aspects of knowledge, and is therefore regarded as the highest and the purest type of science, embodying the least material form. It is also much older than physics, which in turn is younger than chemistry. Life sciences are the youngest of all.

Does a mathematician discover or invent a theorem? This is an interesting topic for discussion and I would consider that all mathematics is an invention, but this is a quite subjective opinion. If an extraterrestrial civilization would contact us, it was argued that a test for intelligent reasoning would be the illustration of Pythagoras's Theorem or a sequence of prime numbers. Archimedes **discovered** why a solid is lighter when immersed in a liquid and in certain conditions can float, but he **invented** his spiral. Therefore I presume that Pythagoras's Theorem must be **invented** on Earth or anywhere else in the Universe.

The invention of particle accelerators and of nuclear reactors has allowed physicists to discover new elementary particles. By understanding how they are related to each other, physicists were able to predict the existence of unknown particles that were then discovered experimentally. History repeats itself in the physics of elementary particles as it had done with chemical elements more than a century ago. Mendeleev predicted the properties of three elements and he had the satisfaction to see them discovered during his lifetime: gallium, germanium, and scandium. We have become accustomed to the phrase "discovery of a chemical element", but I believe that the very short–lived radionuclides with atomic numbers higher than 100 deserve rather to be called "invented" in the light of the previous discussion.

My more familiar area is that of organic chemistry. According to Marcellin Berthelot, chemistry can be called the science that creates its object of study, and only mathematics shares this aspect. It is true that from the infinity of all possible chemical substances (and here organic compounds occupy a place of honor) quite a few have been **discovered** in nature, and continue to be found in the rich reservoir provided by living organisms, especially plants, insects, or inhabitants of oceans. However, among the more than 60 million of substances that until now have been obtained in pure state and are catalogued by *Chemical Abstracts*, the vast majority has been **invented** in the quest for new medicinal drugs, and then synthesized in laboratories. We shall come back to this topic in a subsequent section.

Here I would like to mention only one aspect that makes chemistry an exceptional science: *chemistry is the best documented among all sciences* if one wishes to know whether any chemical structure has ever been described in the chemical literature. By means of the structural formula and molecular graph (about which more will be mentioned later) one can retrieve in less than one minute all this information electronically (at a cost that is not unreasonable) from the *Chemical Abstracts On Line* , *SciFinder Scholar* or the *Beilstein* databases. However, for any other science, including chemistry, if one wishes to retrieve information that is contained in words and not in chemical formulas, *e.g.* about reactions, theorems, physical laws, biomedical terms, etc., then hard problems must be solved because words are not unique, and have no intrinsic metric.

The science of organic synthesis shares artistic aspects, and they are evident in the title of the book written by Anand, Bundra and Ranganathan, *Art in Organic Synthesis* [6]. If at the beginning of the 20th century, Emil Fischer (Berlin) was recognized as the most prolific among synthetic chemists, at the end of that century this title was conferred upon Robert B. Woodward. He invented really artistic pathways for reaching the synthetic goal of duplicating (with the crude organic chemist's tools and reactions known at the end of the 20th century) the structures that billions of years of biological evolution had taught living cells to produce via enzyme–catalyzed reactions. The spectacular synthesis of vitamin B_{12} involved more than 100 graduate students for over a decade till Woodward (Harvard University) and Albert Eschenmoser from the Eidgenössische Technische Hochschule in Zürich published their results in 1973. Chemists have still a long way to go and much to learn before understanding all nature's secrets in synthesizing such elaborate structures under mild conditions of temperature, pressure, and pH.

Roald Hoffmann, who was awarded the Nobel Prize for Chemistry in 1981, dealt repeatedly with the problem of chemistry as an art. In a series of four articles entitled “Molecular Beauty” published in *American Scientist* in 1988–1989 [7], he discussed problems on reaction mechanisms (“Frogs about to be kissed”), supramolecular chemistry (“As rich as can be”), and quantum chemical calculations (“towards an aesthetic theory of six–coordinate carbon”). R. Hoffmann and P. Laszlo (who taught organic chemistry at the University of Liège, Belgium) published a paper entitled “Representation in Chemistry” [8], in which in the fifth section “But is it art...” they stated: “Art or the reaction to it, the aesthetic response, has never been easy to define... Let us hazard a definition. While it is contestable in all its parts, perhaps it touches on most of the qualities of what we've chosen to call art. Then we'll examine representation in chemistry as it measures up against this definition....Let's call Art those symbolic acts of creation of human beings which aspire at the extraction from the complex realm of Nature, or the equally involved world of emotions, of some aspect of the essence of these worlds. Art functions by communication of a symbol, meant to convey information and/or to evoke an emotional response... To return to the question heading this section: are chemical structures art? It seems clear that they possess all the components of the “aesthetic system”. Structural formulas are symbols created by one chemist (or several) to communicate information to others. The drawing of the structure of camphor is certainly a symbolic motion, a communication of an essence – the arrangement in space of the atoms of this molecule. Some might call it just a sketch, an information–reducing stratagem by someone not able or willing to compute and show others the all–important electron density around the nuclei. *That* electron density is the real molecule; the structural formula – well, that's ‘just a poor representation’.”

2 PERSONAL RESEARCH IN THEORETICAL CHEMISTRY AND MATHEMATICAL CHEMISTRY

2.1 Chemical Applications of Graph Theory (A Branch of Mathematics)

When choosing a career, I had hesitated between chemistry, physics and mathematics but I decided to become a chemist because I knew about the research that Nenitzescu was carrying out at the Bucharest Polytechnic University. Immediately after graduating in 1953, I started to work for my Ph. D. degree under his supervision and I became one of his most productive coworkers, publishing with him 26 papers. In addition, two chapters in Olah's book *Friedel–Crafts and Related Reactions* have been coauthored by Nenitzescu and me, and were the direct outcome of results from my Ph. D. thesis. I would like to take this opportunity for mentioning that George A. Olah wrote several times in his publications [9] and in his autobiographical book [10] that among all scientists from East Europe he had the closest contacts with Nenitzescu. With Mircea Banciu as a co–author, I published in 1995 a book [11] about Costin Nenitzescu (1902–1970), and a paper entitled "Nenitzescu, the greatest Roumanian chemist" in Istvan Hargittai's journal, *The Chemical Intelligencer* [12].

In 1956–1957 I had the chance to compress in one year an intensive physics degree because there was a need to have rapidly a few hundred specialists in electronics, nuclear physics and radiochemistry, in connection with the cyclotron and nuclear reactor that were imported from USSR. As a radiochemist I was entrusted with the Laboratory of Labelled Organic Compounds in the Institute of Atomic Physics (IFA). I owe to the Director of IFA, Professor Horia Hulubei, as much as I owe to Professor Costin D. Nenitzescu, because the former created the first opportunity to carry on my own research in IFA. With a few coworkers, we prepared labeled compounds with ^{3}H, ^{14}C, and ^{131}I (the last ones to be used as radiopharmaceuticals). In addition, we could carry on research on organic chemical problems, and we benefitted from enough funds to obtain books and journals for an up–to–date library. Although I had a full job at IFA, I was also teaching Organic Chemistry and General Chemistry in the Bucharest Polytechnic.

I suspect that Professors Nenitzescu and Hulubei were strong supporters for my election as a corresponding member of the Roumanian Academy in 1963 when I was 32; for a long time I was the youngest person in this Academy, and I had to wait till 1990 to become a titular member.

Although I was primarily an experimental organic chemist, I remained interested in mathematics. Looking at organic chemical formulas, one cannot fail to recognize that they correspond to graphs studied by mathematicians, in which atoms are represented by vertices and covalent bonds by lines. In graph–theoretical parlance, graphs consist of a finite nonempty set of vertices together with a set of edges that are unordered distinct pairs of vertices. This association between molecules and graphs had even been one of the three sources for the birth of graph theory (due to Cayley and Sylvester, around 1860); the two other sources were electrical networks (Kirchhoff) and topology

(Euler). George Pólya proposed his fundamental enumeration theorem in 1937, and this has been a cornerstone for enumerating chemical isomers [13]. I became fascinated by the potential applications of graph theory in chemistry, especially since I had learned that the eigenvalues of the graph–theoretical adjacency matrix for conjugated chemical systems were Erich Hückel's electronic orbital energies in quantum chemistry.

My first graph–theoretical paper [14] was an attempt to predict all possible monocyclic aromatic systems by grouping together heteroatoms into three types according to their numbers of electrons in the non–hybridized atomic orbital, and by assigning relative electronegativity values using the cyclopentadienide anion, benzene, and tropylium as basis (with values –100, 0, and +100, respectively). This has led me to speculating about boron–containing aromatic heterocycles and to an exchange of correspondence with Michael J. S. Dewar before he had started to publish experimental data on borazaro compounds. Later I prepared boroxaropyrylium salts [15], but apparently the perchlorate anion is nucleophilic enough to connect via a covalent bond with this cation.

The general philosophy of applying graph theory to chemical problems is that thus one is able to explore all theoretical possibilities, and then one can select the gaps that can be filled most easily for answering the most interesting problems. This is actually the "Sherlock Holmes approach" that I quoted in one of my papers: 'when you have eliminated the impossible, what remains, no matter how improbable, must contain the truth.'

Since Nenitzescu was the first to obtain a valence isomer of an annulene, namely the so–called Nenitzescu's hydrocarbon $(CH)_{10}$, I developed an algorithm for enumerating and obtaining the structures of all possible valence isomers of annulenes, which correspond to planar cubic multigraphs [16]. These are graphs in which all vertices have degree three, *i.e.* they are the meeting points for three edges; in graph–theoretical parlance, a graph is planar if it can be represented in two dimensions without crossing edges. Later, I summarized with two co–authors the results scattered in several journal articles into a 3–volume book entitled *Annulenes*, *Benzo–*, *Hetero–*, *Homo–Derivatives and their Valence Isomers* published in 1987 by the CRC Press, Boca Raton [17]. My preoccupation with aromaticity continued both on theoretical and experimental planes, as will be mentioned later. I was invited several to present plenary lectures at international symposia on aromaticity: Dubrovnik, Croatia (1980) [18], Jerusalem, Israel (1982) [18] and Victoria, Canada (1992).

When I tried to contact Roumanian mathematicians specializing in graph theory, I failed to establish collaborations because they found my topics too trivial. However, on the advice of my mathematician friend, Silviu Teleman (who left Roumania before 1980 and taught mathematics till recently at the University of Puerto Rico), I wrote around 1965 to a well–known American graph theorist, Frank Harary. He was interested to collaborate on chemical problems, came to Bucharest on one of his European trips, and started a collaboration that resulted in ten joint papers. In 2001 the Dubrovnik symposium MATH/CHEM/COMP was dedicated to Frank's 80th anniversary and to my 70th. The first joint papers applied Pólya's theorem to various chemical systems [19]. Probably the most fruitful aspect of our collaboration was a paper on polycyclic aromatic hydrocarbons (PAHs) in which we introduced the notion of "characteristic graphs" (later renamed as "dualist graphs") formed by the centers of benzenoid rings, and by edges joining condensed rings that share a covalent bond [20]. Thus a simple classification of such PAHs emerged based on whether their dualist graphs are acyclic (catafusenes), have 3–membered rings (perifusenes) or larger rings (coronoids). Also, one can use these dualist graphs for coding and enumerating all possible PAHs, including those that have a so–called "bay–region" in their structure and are carcinogenic [21]. Another well–cited paper with Frank Harary [22] demonstrated that the characteristic polynomial of the adjacency matrix or its eigenvalues do not characterize a graph up to isomorphism, as it had been claimed earlier. More recently, two mathematicians from the University of Bucharest in Roumania became interested to collaborate with me on chemical–graph–theoretical topics, and I published several papers with Professors Solomon Marcus [23] and Ioan Tomescu [24].

In 1975, together with Oskar E. Polanski (Austria), A. Dreiding (Switzerland), and A. Kerber (Germany), I co–founded a new journal, *Communications in Mathematical Chemistry (MATCH)* which has continued to be published with A. Kerber as managing editor after Polansky passed away, and is now edited by Ivan Gutman in Kragujevac (Serbia) under the name *MATCH, Communications in Mathematical and Computer Chemistry*.

A book entitled *Chemical Applications of Graph Theory* that I edited was published by Academic Press, London, in 1976 [25]. It was the first book on this topic, and it contained chapters written by mathematicians (Frank Harary, Ronald Read and others) as well as by chemists (Ivar Ugi was one of them, I was another). I was invited to review the enumeration of isomers in a book chapter [26]. With Dennis Rouvray I contributed with another chapter in a book edited by Robin Wilson and L. W. Beineke [27]. The Division of Chemical Information of the American Chemical Society honored me in 1994 with the Herman Skolnik Award. Several lectures on chemical graphs were published in the official publication of the above Division (*Journal of Chemical Information and Computer Sciences*) [28], now having the title *Journal of Chemical Information and Modeling*. At the interdisciplinary symposium "Quo Vadis, Graph Theory" held at the University of Fairbanks, Alaska, I was asked to comment on open problems raised by chemistry [29].

2.2 Reaction Graphs in Chemistry, and Cages in Graph Theory

Starting from a chemical stepwise reaction that was studied in Nenitzescu's research group, I published in 1966 a paper [30] in which graph vertices were no longer atoms but molecular species, and edges symbolized elementary reaction steps. Thus were introduced the first *reaction graphs*. A particular case involved the rearrangements of ethyl carbocations with five different substituents.

When the two atoms of the ethyl group are labeled isotopically, one obtains a 20–vertex cubic graph but when one cannot discriminate between these two atoms, the 20–vertex graph becomes a 10–vertex graph that is known as the Petersen graph. This graph is also the unique 5–cage, *i.e.* the smallest graph having circuits with at least 5 vertices. It has a very high symmetry which will be discussed in a later section and it can also represent the isomerization graph for pentacoordinated phosphorus derivatives with five different substituents if one ignores enantiomerism. If stereoisomers are not ignored, one obtains the 20–vertex graph [30]. I have reviewed reaction graphs in a book chapter [31].

Between 1967 and 1970 I was appointed as Senior Research Officer in the Chemistry Section of the International Atomic Energy (IAEA) in Vienna. My duties were to edit books, to organize radiochemistry conferences in Latin America and to act as liaison officer with the World Health Organization in Geneva for radiopharmaceuticals [32]. Later I co–authored a book on radiopharmaceuticals [33]. I was no longer teaching during these three years of my appointment at the IAEA, but I maintained the connection with IFA and returned to Bucharest every second month for a few days to discuss with my coworkers in IFA. In my free time, I played with graphs, and I found a challenge in looking for the unknown 9–, 10–, and 11–cages. With the help of symmetry considerations, I obtained the first of the three possible 10–cages [34] and the unique 11–cage [35]. I was less lucky with the 9–cage because after I had found several cubic 60–vertex graphs with circuits having ≥ 9 vertices, N. Biggs devised a computer program and found that the real 9–cages had only 58 vertices; later it was proved by B. McKay that there are 18 such 9–cages and that they have low symmetry [36]. In a recent book ("*Pearls in Graph Theory*" by Nora Hartsfield and G. Ringel [36]) Balaban's 10–cage is reproduced there (and below in Figure 1) as a nice example, and Croatian authors were recently able to generalize its symmetry to other graphs under the name "generalized Balaban configurations" [37].

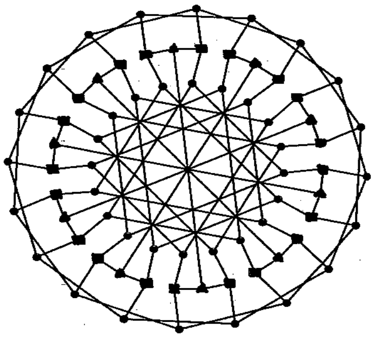

Figure 1. The Balaban 10–cage.

Paul Schleyer invited me and Ovidiu Ivanciuc to write in 1998 a monograph on "Graph theory in chemistry" in his *Encyclopedia of Computational Chemistry* [38]. In Roumania after 1970, I resumed my teaching position at the Bucharest Polytechnic University, but permissions for traveling abroad at scientific meetings were often denied. Through the Roumanian Academy's exchange program with the U.S. Academy of Sciences, in 1975 I came to the USA for lecturing at several universities. It happened that Dr. Milan Randić was in the audience when I talked about chemical graphs at Harvard University where he was a post–doc, and he became "converted" to redirect his research towards chemical applications of discrete mathematics. In turn, after returning to his native country, Croatia, he founded there a research school on chemical graphs, and among his collaborators there are several scientists who contributed to the further development of this field; one of them is Professor Nenad Trinajstić who authored a book entitled *Chemical Graphs* published in two editions [39].

2.3 Topological Indices, QSAR and QSPR, Design of Medicinal Drugs

The most recent application of graph theory is for topological indices that are useful for quantitative structure–activity or structure–property relationships (QSAR and QSPR, respectively). Molecules are discrete structures, whereas physical–chemical properties or biological activities are expressed by numbers that have an inherent metric. To establish correlations between structural formulas and properties or biological activities one needs to associate in an objective manner a number to each chemical formula. A simple way to do this is to use topological properties associated with the molecular graph. Till now a few hundreds of such numbers, called topological indices (TIs), have been devised starting with Wiener's and Hosoya's indices [40]. By compressing into a number the information contained in the adjacency or distance matrices that characterize uniquely a graph and can be used for retrieving the graph, some of the information from these matrices is lost, and one can no longer retrieve the graph from its TI; moreover, several graphs may yield the same TI, which is then said to be degenerate.

My involvement with TIs started in 1979 when I published a paper [41] defining centric TIs for acyclic graphs that have a unique center, which can be one vertex or a pair of adjacent vertices. At that time I had a graduate student (Ioan Moţoc, who died at an early age) with whom I published the first correlations between chemical structures and octane numbers of alkanes [42]. Then with Moţoc and two colleagues from Burgas, Bulgaria, we reviewed all the TIs known at that time [43]. The TI that was most employed was the "molecular connectivity"; it had been devised by Milan Randić [44], and then developed by him with L. B. Kier and L. H. Hall [45]. It was based on the *vertex degree* of hydrogen–depleted graphs, *e.g.* in hydrocarbons 1 for primary carbon atoms, 2 for secondary carbon atoms, etc. This type of local vertex invariant (LOVI) has a high degeneracy, because in a hydrocarbon there can be many chemically non–equivalent methyl groups. I reasoned that by using another LOVI, namely the *topological distance* between two vertices, a less degenerate TI can be obtained. Actually, vertex degrees and topological distances are derived analogously as sums over rows or columns from the symmetrical adjacency and distance matrices, respectively. By averaging over the number of edges and cycles in the graph, this new index denoted by J (average distance sum connectivity index) proved to be indeed useful in various

QSAR/QSPR studies [46]. It expresses the “topological shape” of a molecule, and for properties that are influenced also by the size of the molecule one should use multiparametric correlations.

At the International Symposium on Theoretical Organic Chemistry held in Dubrovnik, Croatia in 1982, I was invited to present a lecture on TIs that was printed in *Pure and Applied Chemistry* [47]. I went on to refine index *J* (this is now known as the Balaban index) by showing how one can include information on the presence of heteroatoms and on bond multiplicity [46]. An interesting property of index *J* is its asymptotic value (number $\pi = 3.14159\ldots$) for an infinite linear alkane, *i.e.* polyethylene [48]. Some applications of index *J* in multiparametric correlations have been demonstrated for normal boiling points of various classes of compounds [49], and for biological properties [50]. In 2000, I was invited to contribute with a monograph on “QSAR and computational methods in drug discovery” in the Wiley’s *Encyclopedia of Analytical Chemistry* [51]. An earlier book had presented steric fit in QSAR, and more recently I published a few personal views about TIs [52].

More recent applications of index *J* by other authors have been published for the analysis of chemical diversity [53], QSAR on sulfonamides as carbonic anhydrase inhibitors [54], and even for larger molecules such as polypeptides involved in the design of immunosuppressive compounds (Lahana and coworkers [55]), or the secondary structure of *Escherichia coli* transfer RNA [56]. In the last case, the Colombian authors added numeric information on hydrogen bonds between the two pairs of complementary purinic/pyrimidinic bases to the Randić and Balaban indices. Lahana’s paper [55] shows how with the aid of 13 molecular descriptors including four TIs (J and three Kier–Hall indices) one could reduce a library of over 279,000 possible decapeptides with potential immunosuppressive activity to only 26, one of which proved to possess a 100 times higher activity than the “leading compound”.

With my son, Teodor–Silviu Balaban, we pursued “inventing third–generation TIs” that are real numbers based on real–number LOVIs [57] and we developed two other classes of TIs, namely information–based TIs [58] different from those introduced earlier by Bonchev and by Basak, and a whole group of “triplet TIs” based on the idea that one can convert a matrix such as the adjacency or distance matrix into a system of linear equations by introducing two column vectors that contain chemical, topological, or other numerical information: one vector to furnish the main diagonal, and the other to afford the free terms of the equations [59]. The solutions of this system are LOVIs that can be combined into a TI by any of several mathematical operators, yielding hundreds of possible TIs that can be tested to see whether they reflect the property to be studied by QSAR/QSPR methods [60].

In 1999 I edited with James Devillers (Lyon, France) an 811–page book [61] on topological indices in which I wrote several chapters with my ex–Ph. D. student Ovidiu Ivanciuc, who now edits in Galveston the *Internet Electronic Journal of Molecular Design*.

2.4 Carbon Nets, Fullerenes, and Graphene Cones

In 1968 I published a paper discussing for the first time alternatives to the two allotropic forms of the element carbon: two–dimensional non–graphitic nets of sp^2–hybridized carbon atoms, and three–dimensional non–diamond lattices of sp^3–hybridized carbon atoms [62]. The discovery of fullerenes at the Rice University in Houston was honored by the 1985 Nobel Prize in Chemistry [63–65]. My association with the Texas A&M University at Galveston started in 1991. It was here that the "isolated pentagon rule" in fullerenes was formulated by Klein and coworkers [66] simultaneously with and independently from Kroto [67], one of the discoverers of fullerenes. I started to apply graph–theoretical ideas to infinite and finite carbon aggregates. With Roald Hoffmann, I published a paper on infinite nets having both sp^3– and sp^2–hybridized carbons [67]. With Douglas J. Klein and several other coworkers, I explored "block copolymers" from graphite and diamond [68], and the possibility of gradual interconversion of one of these two lattices into the other [69], as well as the possible presence of holes in these two nets [70]. We described for the first time cones from graphene sheets, and I communicated our results at a congress in Victoria (Canada) in 1992. Our paper on this topic was published in 1994 [71] and in the same year such "buckycones" were discovered experimentally [72], although they had been sighted earlier (as reviewed in a book chapter [73]).

Turning our attention to fullerenes, we explored various graph–theoretical invariants that can characterize uniquely all possible isomers of fullerenes with up to 100 carbon atoms [74]. Carbon nanotubes have dangling bonds at their non–capped ends but theoretically it may be possible to place O or N heteroatoms suppressing such dangling bonds, and possibly to bind charged metal ions by chelate bonds [75].

Istvan Hargittai invited me twice to contribute with a chapter in his volumes on Symmetry Unifying Human Understanding; in one chapter I reviewed the symmetry of graphs [76], and in the second one I discussed symmetry aspects of carbon nets [77]. An earlier account of graph symmetry was another book chapter [78]. A more recent review on finite and infinite carbon aggregates is a chapter in a book edited by Cyril Parkanyi [79]. The book entitled *From Chemical Topology to Three–Dimensional Geometry* that I edited in 1997 contains in about half of its chapters problems connected with fullerenes [80].

2.5 Symmetry and Beauty

In physical and mathematical sciences there are many associations between symmetry and aesthetics, but much less so in chemical sciences. Only a few books will be mentioned for mathematical symmetry associated with the Riemann Hypothesis about prime numbers [81–84]. The symmetry of conservation laws in physics was mentioned in Wigner's Nobel Prize lecture [85]; supersymmetries allowed the prediction and discovery of elementary particles, and the books about this topic are too numerous to cite; however, Weyl's [86] and Zee's books [87] on more general associations between physics and symmetry deserve to be mentioned.

In chemistry, the Jahn–Teller effect prevents geometries to be highly symmetric in certain cases, such as the hexaaquacopper(II) complex ion, $[Cu(OH_2)_6]^{2+}$: two axial Cu−O distances are 238 pm, whereas four equatorial Cu−O distances are 195 pm. However, many crystals astonish by their beautiful symmetry, which was understood after measuring dihedral angles, allowing Haüy, Schönfliess and Fyodorov to formulate the laws of crystallography based on symmetry.

Let us now recall the visual fascination of the convex regular polyhedra, due to their symmetry, as attested by the names of Plato (427–347 b. C.), Archimedes (287–212 b.C.), and Kepler (1571–1630). Even more striking are the stellated regular and semiregular polyhedra. When one considers that in a two–dimensional space one has an infinity of regular polygons, it is surprising than in our 3D space there are only five Platonic (regular) polyhedra whose faces are identical regular polygons: the tetrahedron which is self–dual, the dual pair of cube and octahedron, and the dual pair of dodecahedron and icosahedron. Also, there are only 13 Archimedean (semiregular) polyhedra whose faces are polygons of different types (not counting prisms and antiprisms, and ignoring that there are two pairs of enantiomeric snub semiregular polyhedra). All these polyhedra can be ordered in a series of increasing complexity and sphericity. In Table 1 the 5 regular and 13 semiregular polyhedra are ordered separately according to their solid angles at each vertex (the maximal solid angle is 2π = 6.28 steradians). The numbers in the column labeled "Notation" indicate the polygon size and the exponent shows the total number of each polygon; the next column shows how many polygons meet at a vertex [88]. The numbers of vertices (V), edges (E) and F (faces) obey the Euler equation: V + F = E + 2. The two snub semiregular polyhedra are chiral, each one existing as a pair of enantiomeric (mirror–image) solids in the 3D space.

Table 1. Data for Platonic and Archimedean polyhedra

Platonic regular polyhedron	Notation	Faces meeting at a vertex	V	E	F	Planar angle sum (°)	Solid angle (sterad)
Tetrahedron	34	3 triangles	4	6	4	180	0.55
Octahedron	38	4 triangles	6	12	8	240	1.36
Cube	46	3 squares	8	12	6	270	1.57
Icosahedron	320	5 triangles	12	30	20	300	2.63
Dodecahedron	512	3 pentagons	20	30	12	324	2.96
Archimedean semiregular polyhedron	Notation	Faces meeting at a vertex	V	E	F	Planar angle sum (°)	Solid angle (sterad)
Truncated tetrahedron	$3^4 6^4$	2 hexagons + 1 triangle	12	18	8	300	1.91
Cuboctahedron	$3^8 4^6$	2 squares + 2 triangles	12	24	14	300	2.47
Truncated cube	$3^8 8^6$	2 octagons + 1 triangle	24	36	14	330	2.8
Truncated octahedron	$4^6 6^8$	1 square + 2 hexagons	24	36	14	330	3.14
Small rhombicuboctahedron	$3^8 4^{18}$	1 triangle + 3 squares	24	48	26	330	3.48
Snub cube*	$3^{32} 4^6$	4 triangles + 1 square	24	60	38	330	3.59
Icosidodecahedron	$3^{20} 5^{12}$	2 triangles + 2 pentagons	30	60	32	336	3.67
Great rhombicuboctahedron	$4^{12} 6^8 8^6$	1 square + 1 hexagon + 1 octagon	48	72	26	345	3.95
Truncated dodecahedron	$3^{20} 10^{12}$	1 triangle + 2 decagons	60	90	32	348	3.87
Truncated icosahedron	$5^{12} 6^{20}$	1 pentagon + 2 hexagons	60	90	32	348	4.25
Small rhombicosidodecahedron	$3^{20} 4^{30} 5^{12}$	1 triangle + 2 squares + 1 pentagon	60	120	62	348	4.44
Snub dodecahedron*	$3^{80} 5^{12}$	4 triangles + 1 pentagon	60	150	92	348	4.51
Great rhombicosidodecahedron	$4^{30} 6^{20} 10^{12}$	1 square + 1 hexagon + 1 decagon	120	180	62	354	4.71

* Chiral polyhedra

Even more bizarre is the world of higher dimensions, which is inaccessible to our eyes but can be explored by our minds. Table 2 presents the six possible four–dimensional regular convex 4–polytopes consisting of regular polygons as faces and regular polyhedra as cells [89,90]. One may derive for them a third name (polychorons, a term that is equivalent to 4–polytope) from the numbers of cells. Thus, the first 4–polytope from Table 2 may be called pentachoron, the second octachoron, etc. Except for the octaplex which has 24 cells, all the other five regular polytopes are related to the five regular polyhedra and may also be called "hyperpolyhedra", as indicated in Table 2. In this Table, the last column presents the order of the symmetry group, and the Schläfli symbols indicate the numbers of edges (E), faces (F), and cells (C) meeting at each vertex. For 4–polytopes the Euler relationship becomes V + F = E + C. For five–dimensional and all higher–dimensional spaces, one can have only three regular convex polytopes, related to the tetrahedron, cube, and octahedron. If one divides the order of the automorphism group by the number of edges or faces, one obtains a normalized measure of symmetry which for each of the six 4–polytopes has values between 12 and 20.

Table 2. The six four–dimensional regular convex 4–polytopes with Schläfli's symbols

Polytope	Schläfli symbol	Vertices V	Edges E	Faces F	Cells C	dual	Order O	O/E
pentatope, hyperpyramid	{3,3,3}	5	10	10 triangles	5 tetrahedra	self–dual	120	12
tesseract, hypercube	{4,3,3}	16	32	24 squares	8 cubes	orthoplex	384	12
orthoplex, hyperoctahedron	{3,3,4}	8	24	32 triangles	16 tetrahedra	tesseract	384	16
octaplex, polyoctahedron	{3,4,3}	24	96	96 triangles	24 octahedra	self–dual	1152	12
dodecaplex, hyperdodecahedron	{5,3,3}	600	1200	720 pentagons	120 dodecahedra	tetraplex	14400	12
tetraplex, hypericosahedron	{3,3,5}	120	720	1200 triangles	600 tetrahedra	dodecaplex	14400	20

The symmetry of polyhedra and polytopes is reflected in their symmetry axes. Rotations around these axes lead to automorphisms showing that all their vertices and edges are equivalent. The graphs corresponding to polyhedra and polytopes have a higher symmetry because sequences of edges (paths) can also be taken into consideration; for instance, any two paths of length two of a regular polyhedron are equivalent (in graph–theoretical parlance they are transitive), but this is not true for paths of length three. However, the graphs corresponding to polyhedra can have higher transitivity. A graph that is transitive for a path of length n but not for a path of length $n + 1$ is called n–unitransitive (after Harary) or n–regular (after Tutte).

Now let us examine another class of strange graphs that may approach and even surpass the symmetry of polyhedra and polytopes. They are called cages, and have all vertices of the same degree (*i.e.* the same number of edges meeting at a vertex), and the same girth g (the minimal number of vertices in a circuit). The most representative cages have degree 3, and are called cubic cages. Table 3 presents all the cages with g = 4, 5, 6, 7, 8, which are unique (unlike the eighteen 9–cages and the three 10–cages), and may be seen in Figure 2. In Table 3 one can see that n–unitransitive cages can have n = 3, 4, or 5. The last case applies to the Levi graph of the Cremona configuration (also called the Tutte–Coxeter graph or simply the 8–cage). Higher cages have no such symmetries, and they have several vertex orbits, *i.e.* are not even vetex–transitive. As an interesting side remark, my 11–cage and the 12–cage (Benson graph) are also unique, and nothing has been proved so far for cages with higher girth ($g \geq 13$) which are still to be found. Of course, for all trivalent graphs $E = {}^{3}/_{2}V$. The order of their automorphism groups is $O = 3V \times 2^{n-1}$. A normalized measure of their symmetry is provided by O/V (last column in Table 3).

Table 3. Trivalent cages with g = 4 to 8

Trivalent cage	g	V	E	n	Order O	O/V
Thomsen graph	4	6	9	3	72	12
Petersen graph	5	10	15	3	120	12
Heawood graph	6	14	21	4	336	24
McGee graph	7	24	36	4	864	36
Levi graph	8	30	35	5	1440	48

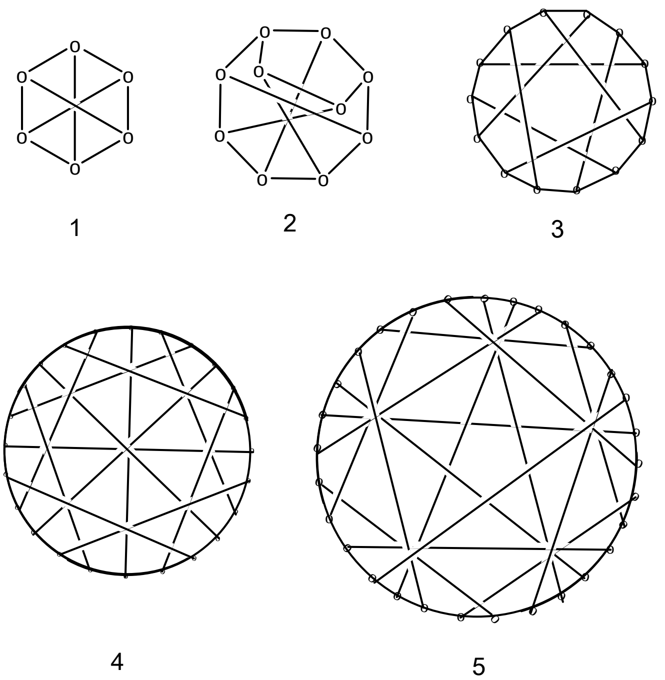

Figure 2. Trivalent cages with g = 4 to 8 having 6, 10, 14, 24, and 30 vertices, respectively.

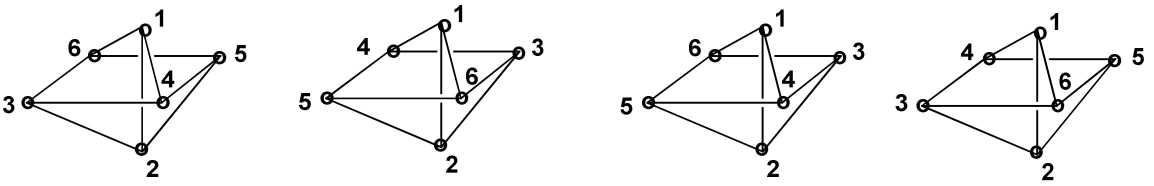

Figure 3. A 3D representation of the 4–cage (Thomsen graph) with isomorphic rearrangements around edge 1–2.

A comparison between the last column in Tables 2 and 3 shows that cages have higher normalized symmetries than polytopes. In both cases these beautiful and awesome symmetries cannot be seen visually, but have to be perceived intellectually by the mind’s eyes. If one could make toy models of cages with articulated straight edges that can cross freely, such toys (perhaps as computer games) could compete with Rubik's cube. Thus for instance the 4–cage (Thomsen graph, which is 3–unitransitive) can be viewed in our 3D–space as shown in Figure 3 – but imagine it in 4D !). The four views of Figure 3 are pairwise mirror images, and all maintain edge 1–2 in the same position. The analogous rearrangements of the 5–unitransitive 8–cage (Levi graph) should be truly spectacular!

3 CONCLUSIONS

An inescapable conclusion is that sciences such as chemistry and mathematics, which create or *invent* their objects of study, have a close similarity to arts (chemistry started by *discovering* the structures of natural minerals and organic compounds, but nowadays drug–design chemists *invent* new structures in the quest for new medicinal drugs).

Another conclusion is that symmetry certainly plays a role in appreciating objects visually or mentally. In addition to the bibliographic references indicated earlier on the topic of "chemical beauty" [7,8,76] a few other pertinent references are now cited [91–93].

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