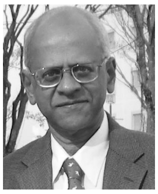
# Chemistry: The Middle Kingdom

*Gautam R Desiraju*



**Gautam R. Desiraju has made seminal contributions to the development and worldwide growth of the subject of crystal engineering, especially with reference to the properties of novel interaction types such as the weak hydrogen bond. He has been at the University of Hyderabad since 1979.**

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*Current Science*, Vol. 88, No 3, pp.374–380, 10 Feb. 2005.

**Chemistry occupies a unique middle position between physics and mathematics on the one side and biology, ecology, sociology and economics on the other. It is said that chemistry is reducible into physics and finally mathematics. However, in moving from the covalent to the non-covalent world we obtain a new chemistry, one that is a starting point for the emergence of the soft sciences. This article argues that this new chemistry represents a paradigm shift in the way in which chemists think about their subject today. Biology may be considered as emerging out of this new chemistry, which in itself cannot be reduced into physics and mathematics as was the case for chemistry thus far practiced. This dualistic nature of chemistry, reducible and irreducible, is a new development but one that ensures that the subject will remain alive and well in the foreseeable future.**

> *"... so chemistry can be no more than systematic art or experimental teachings, indeed never real science, because its principles ... do not lend themselves to the application of mathematics."*
>
> *Immanuel Kant*§

## Introduction

The position of mathematics on the scientific grandstand is indisputable and indeed nearly axiomatic to all practitioners of science [1]. One accepts, without any argument, that mathematics provides a template for rational thought and for the logical development of scientific discourse. The subject defines order and discipline, furnishing protocols to establish relationships between cause and effect. It is impossible to conceive of any science without the mathematical underpinning. I have yet to come across a good scientist who disliked mathematics. I will not dwell further on the primary role of mathematics in the natural

**Keywords**
Supramolecular chemistry, non-covalent interactions, complexity and emergence.

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§ Kant, I. *Metaphysische Anfangsgründe der Naturwissenschaft*, Riga, 1786. In the German original: "... so kann Chymie nichts mehr als systematische Kunst, oder Experimentallehre, niemals aber eigentliche Wissenschaft werden, weil die Principien derselben ... der Anwendung der Mathematik unfähig sind."

sciences, namely as an aid to organised thought. It is the second role of mathematics, as a subject into which all other scientific disciplines may be reduced, that is far more alluring to a chemist.

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According to reductionist thinking, all science can ultimately be reduced into mathematics. Reductionism would have it that biology is reducible into chemistry, chemistry into physics and, ultimately, physics into mathematics. This "unreasonable effectiveness" of mathematics [2] in explaining natural phenomena confer upon it almost mystical qualities. In keeping with these qualities, and also because mathematics has been termed a language, one may draw analogies between it and Sanskrit, the language of the Gods. Both these languages are precise and accurate, and yet remain aloof. They seem to describe the reality that surrounds them only too well, and yet they remain tantalisingly apart from this very reality. Wigner said that the appropriateness of mathematics for the formulation of laws that govern physical phenomena is "a wonderful gift which we neither understand nor deserve" [2]. Might I add that the same could be said about the appropriateness of Sanskrit to an understanding of the workings of the mind?

## The Origins of Chemistry

During antiquity and medieval times, Western science was based on the holistic thinking of Aristotle. Modern science, with its emphasis on reductionism, came into being with the Renaissance, [3] and astronomy and physics were the first sciences to feel the impact of mathematics. Chemistry, however, was curiously resistant to these developments for nearly two centuries. With its origins in alchemy and the black arts and with the frenzied attempts of its practitioners to transmute base metals into gold, chemistry retained its qualitative character. It is curious, even amusing, to note today that the great Newton was a closet alchemist who felt at the time of his death that his work in alchemy would eventually be recognized as prominently as his contributions to mathematics, astronomy and physics. The first winds of change came from the work of Boyle who sensed the

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concept of the modern chemical elements and demolished the Aristotlean concept of "four elements and three principles". The real break with the past, however, came with Lavoisier who emphasized the importance of quantitative experimentation. He and, independently, Dalton provided the first framework of atomic theory and were the earliest of the great chemists. Still, it is worthwhile to ponder a little on why chemistry resisted quantification for so long. The subject is deliciously qualitative even today and this dichotomy of character between the quantitative and the qualitative, the reducible and the irreducible, is what I wish to highlight in this article.

## The Nineteenth Century

Friedrich Wöhler's synthesis of urea from ammonium cyanate in 1828 triggered two important developments. Until that time, urea was only obtainable from animal matter, and yet ammonium cyanate is a salt of indisputably inanimate origin. Wöhler's experiment signalled the beginning of the end of vitalism as a scientific dogma [4].

Secondly, organic chemistry emerged as a separate subject within the chemical domain. The philosophy of vitalism went back to 1600 with its roots in the distinction that was perceived to exist between organic and inorganic compounds. This distinction had to do with the behaviour of these compounds upon heating. Inorganic compounds could be recovered upon removing the heat source, or so this argument went, whereas organic compounds appeared to undergo mysterious and irreversible transformations when heated. This led to the thought that organic compounds were imbued with a special vital force and in turn to the belief that while organic compounds might obey the same physical and chemical laws as inorganic compounds, life could not be governed by just these laws. The synthesis of urea, an organic compound, from ammonium cyanate, an inorganic compound, sounded the death knell of the vital force theory, and the letters between Wöhler and his teacher Berzelius, a staunch advocate of vitalism, make for fascinating reading even to this day.

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From then onwards, chemistry in the nineteenth century was one unbridled run of synergistic analysis and synthesis. A vast amount of empirical data mostly on organic compounds were painstakingly accumulated, especially in Germany, and in the hands of grandmasters like Kekulé, Liebig, Baeyer and Willstätter, rational and reductionist thought assumed a nearly art form in chemistry. For, reductionism is nothing other than analysis and synthesis coupled together, when cause can be used to predict effect or when, and with equal validity, effect may be used to decipher cause. The object of study of these German organic chemists was the isolated molecule, and gradually there arose a considerable body of work in support of the notion that all the physical and chemical properties of a substance are characteristic of, or contained within, its molecular structure. This dogma was to persist for more than a hundred years. In my view, though, the high noon of reductionism in nineteenth century chemistry did not belong to organic chemistry but to Mendeleev and his periodic table of elements [5]. The appeal of this table to students of chemistry even today is palpable. Which novitiate has not marveled at the fact that the properties of bromine are nearly the mean of the corresponding properties of its congeners chlorine and iodine? When Mendeleev asked Lecoq to check the specific gravity of the newly discovered gallium once again because it was lower than what he had predicted, and when this value was revised upwards from 4.8 to the predicted 5.9 after careful purification of the sample, we have before us one of the most impressive examples of the success of reductionism.

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All this synchronized well with other developments in the natural and social sciences. The late nineteenth century saw the zenith of the industrial revolution, the emergence of capitalism and colonialism as economic doctrines and the importance given to the individual in relation to the group. Aristotle's holistic thinking finally gave way to the reductionism of Darwin [6]. Even in chemistry, it was recognized that there were areas of the subject that were even more amenable to reduction into physics and mathematics than organic chemistry, however systematized the latter had become, and the work of Ostwald, van't Hoff and Arrhenius led to the demarcation of physical chemistry as a separate field of study [7]. This was an exciting and new subject in the late 19th century, the molecular biology of its time. Studies of aqueous solutions and chemical thermodynamics transformed scientific knowledge of chemical affinity. This emergence of a new discipline at the boundaries of physics and chemistry wrought deep-seated changes throughout chemistry. In turn, physical chemistry was eclipsed by its own offspring, quantum chemistry and for this we need to consider the contributions of the most outstanding chemist of all time, Pauling.

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## The Al(l)chemist

Linus Pauling was of the greatest significance to the growth and development of chemistry as a subject because it was he who showed conclusively the distinction between chemistry and physics. From wave mechanics to quantum chemistry is but a subtle step but the consequences are fundamental and deep-seated. Pauling's essential contribution, the concept of the covalent bond, meant that chemistry did not need physics any longer in its day-to-day functioning and operation. This articulation of chemistry as an independent subject was the handiwork of this great scientist [8].

Pauling's contributions were important and varied, and extended across disciplines like crystallography, mineralogy, biology, medicine, anaesthesia, immunology but above all, structural chemistry. The basic theme that runs through his work is that one can explain the structures and properties of molecules with an understanding of the chemical bond, especially the covalent bond [9]. His influence may be assessed by the fact that at the time of the first edition of *The Nature of the Chemical Bond*, in 1939, less than 0.01% of today's structural information was available and yet the generalizations and conclusions he drew then on molecular structure are largely valid even today. His impact on inorganic chemistry was immediate in that he could explain the magnetic properties of transition metal coordination compounds.

Curiously, however, Pauling was silent about organic chemistry even after enunciating its most basic feature, namely that a sharing out of electrons evenly among equivalent energy states, or what chemists call hybridization of bond orbitals, leads to an explanation for the tetrahedral valences of the saturated carbon atom. This silence has been ascribed to various reasons of a non-scientific type, but I feel that his reluctance to come to terms with organic chemistry arose from his realization that his reductionist approach could only be taken so far in this most qualitative branch of the subject. Pauling's ideas apply well to structure, reactivity and analysis but not as easily to dynamics and synthesis.

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## Supramolecular Chemistry – beyond Pauling

Pauling's work elevated the molecule to the high altar and it was taken as the delimiter of all the important physical and chemical properties of a substance, to the extent that there was no world outside it. His formidable influence on chemistry in general might have accounted for the relatively late take-off of the subject of supramolecular chemistry, nearly seventy years after Emil Fischer enunciated his famous lock-and-key principle of enzyme action [10]. The scope and possibilities of this new subject were clearly enunciated by Jean-Marie Lehn [11]. Supramolecular chemistry literally means chemistry beyond the molecule and the main idea here is that if molecules such as **A** and **B** were to form an aggregate of the type [**A**.**B**] using weak non-covalent interactions, the properties and more significantly the functions of the aggregate need not be readily derivable from the individual properties of **A** and **B**.

This type of thinking is especially appropriate to biological systems because some of the most important biological phenomena do not involve the making and breaking of covalent bonds – the linkages that connect atoms to form molecules. Instead, biological structures are usually made from loose aggregates that are held together by weak, non-covalent interactions. Because of their dynamic nature, these interactions are responsible for most of the processes occurring in living systems. Chemists were slow to recognize the enormous variety – in terms of structure, properties and functions – offered by this more relaxed approach to making chemical compounds [12].

Fischer's lock-and-key mechanism proposed that an enzyme interacts with its substrate as a key does with its lock [13]. This elegant mechanism contains the two main principles of supramolecular chemistry – molecular recognition and supramolecular function. The idea of molecular recognition is that it takes place provided there is compatibility between the interacting partners **A** and **B** with respect to both the geometry and the non-covalent interactions. In turn, specific recognition leads to useful and specific supramolecular functions. For example, it is important that an enzyme works only on the appropriate substrate and not on any other compound. A key without its own lock or a lock without its own key is quite useless. **A** without **B**, or **B** without **A**, is meaningless in a functional context.

The implications are profound as far as the reductionist approach to chemistry is concerned. Reductionism in chemistry, that is the explanation of chemical phenomena in physical and mathematical terms, began with Wöhler and progressed through Pauling until the present time. But with the arrival of supramolecular chemistry, chemists looked more closely at the reduction of biology into chemistry. Can biology be really reduced into chemistry? If so, what are the implications? How do life processes work at a molecular level? How does one differentiate life from non-life? The fantastic levels of specificity achieved by biological machines may still, in principle, be reduced to the chemistry of weak interactions [14]. Yet, a reductionist approach is simplistic beyond the extreme. One may apply reductionist arguments in going from biology to chemistry but one would lose so much detail that it would be impossible to reconstruct the original from the reduction. Living and non-living matter differ not in content but rather in organizational complexity – and our understanding of this theme may well turn out to be the biggest breakthrough in modern chemistry.

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## Complex and Complicated – Emergence

Supramolecular chemistry provides a convenient introduction to chemists about the notion of complexity. At the outset, it is necessary to distinguish between the terms *complex* and *complicated.* A complicated system, like a high precision Swiss chronometer, consists of many components each of which is well understood in isolation. The functioning of such a system is also fully understood and derivable from the functions of the individual components. A characteristic of a complicated system is that if one of the components stops working, the whole system can quickly grind to a halt. Therefore when one designs a complicated system, one builds in redundancy. A complex system is, however, quite different. Complexity is well illustrated by the continuous flow of traffic through an intersection of many roads, such as is seen in large American cities. There may be as many as ten roads approaching the intersection and any vehicle may approach from any road and proceed onwards through the intersection onto any other road, all this taking place without any vehicle ever stopping at the intersection. The functioning of a complex system is not easily understood from the functioning of its individual components. For example, a traffic intersection of ten roads is not easily designed or derived from an intersection of say, four roads. Returning to chemistry, a 20-step synthesis of a natural product with several stereocenters is an example of a complicated system. A supramolecular synthesis as exemplified by the crystallization of a small organic molecule or the folding of a protein, [15] or the spread of cancer in living tissues [16] are examples of complexity. If functional complicated systems need to incorporate redundancy (many doctoral students working on the natural product synthesis and all doing essentially the same things), complex systems are characterized by adaptability (crystal polymorphism, [17] biological signaling pathways [18] in the spread of cancer). Unlike a complicated system, a complex system does not necessarily break down because one of the components is not present or working. It merely modifies or mutates. If one of the roads leading to the busy traffic intersection were to be blocked, traffic on the

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other roads would continue to move largely unimpeded. If one were to change the solvent in a crystallization experiment, one might obtain another polymorph, [19] and when one tries to fight cancer with a new drug, the disease adapts itself so that it attacks the cell using another pathway.

Emergent phenomena are structures, behaviours, events or patterns that arise only when a large number of individual agents somehow aggregate.

Closely allied to the notion of complexity is the idea of *emergence* [20]. Emergent phenomena are structures, behaviours, events or patterns that arise only when a large number of individual agents (molecules, cells, water droplets, musical notes, ants, birds, people, stars) somehow aggregate. Unless a critical number of agents act together, the phenomenon does not occur. An emergent property is created when something becomes more than the sum of its parts. The whole is difficult to predict from the properties of individual parts and it is no surprise then that supramolecular chemistry is full of emergent phenomena. Crystallization, for example, is a process of complex pattern formation arising from cooperative behaviour between components, and is still very hard to predict [21].

Emergence and reductionism are nearly antithetical. Reductionism implies the ease of understanding one level in terms of another. Emergent properties are, however, more easily understood in their own right than in terms of lower level properties. This suggests that emergence is a psychological property and not a metaphysical absolute. A property is classified as emergent based at least in part on the difficulty of an observer deducing the higher level property from the lower level property. Conversely, an increase of knowledge about the way certain effects are obtained in a system may reveal that they are decomposable into the effects contributed by the subcomponents of that system. In the mid-19th century, the reaction of sodium hydroxide (NaOH) and hydrochloric acid (HCl) to give NaCl and $H_2O$ was quoted as an emergent property, as it was held that the properties of NaCl and $H_2O$ are not understandable from the aggregate of the properties of NaOH and HCl (for instance NaOH and HCl are both corrosive while NaCl and $H_2O$ are harmless) [22]. After the electronic structure of atoms was known, the above reaction became easily understandable. In the end, complexity is a temporal attribute. What is complex today might become merely complicated tomorrow, or even trivial, like the acid–base neutralization reaction given above.

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A useful way of looking at mathematics and its relationship to the physical and natural sciences is in terms of emergence. Rather than say that biology can be reduced into chemistry, which can then be reduced into physics and finally into mathematics, one could say that biology emerges out of chemistry, which emerges out of physics, which emerges out of mathematics, which emerges out of the mind contemplating the Absolute, like Sankara's doctrines of *advaita*. We note that each level of investigation (mathematics, physics, chemistry, biology) has its own explanatory relationships, and yet if we check carefully there is no 'added extra' coming in from anywhere. There are no mysterious ingredients added as we proceed from a lower level to a higher level. The only place from which these value additions can emerge is the mind. Hence one concludes again that emergent phenomena are psychological in nature.

An analogy from the world of music is appropriate here. From the twelve notes in geometric progression that are used in the well-tempered scale of Western music, one progresses to the 22 microtones or *srutis* within an octave in Indian music [23]. *Ragas*, or musical forms/moods, are characterized by the use of particular microtones that occur within smaller frequency ranges located around the twelve notes [24]. But if this were all, a raga would be reducible into srutis. This is clearly not the case. In the Carnatic system, one obtains pairs of ragas like Darbar and Nayaki, Aarabhi and Devagandhari, or Surati and Kedaragaula wherein the microtones are practically identical but their structuring, scaffolding and emphasis (*raga svarupa*) are so different that even a non-expert can distinguish between the ragas in any pair. In the Hindustani system, one has the raga trio of Puriya, Marwa and Sohini where again one perceives a similar effect. So rather than say that Darbar and Nayaki can be reduced to Kharaharapriya (the parent scale of microtones which is one of 72 possibilities called *melakartas*) [24], one could more constructively say that Darbar and Nayaki emerge out of Kharaharapriya. The value addition again arises from within the mind, and ragas then surely emerge out of srutis.

## Emergent Properties

In supramolecular chemistry, one makes higher level aggregates (supermolecules) from lower level entities (molecules) using weak intermolecular interactions as a glue.

***(a) Crystal Structure Prediction:*** Crystallization is the ultimate supramolecular reaction, just as the crystal is the ultimate supermolecule. A molecule may be said to consist of several functionalities or functional groups [$F_1$, $F_2$, … $F_n$] and during crystallization, these functionalities come together through a process of molecular recognition and utilizing weak interactions to generate supramolecular synthons [$S_1$, $S_2$, … $S_N$].$^{25}$ The conjunction of particular supramolecular synthons uniquely defines a crystal structure. However, there are two serious problems that arise when one attempts to predict the outcome of crystallization.

(i) The number of possible supramolecular synthons is large because the intermolecular interactions are weak.

$$
\begin{array}{lll}
S_1 = F_1\ldots F_1 & S_4 = F_1\ldots F_4\ldots F_5 & \\
S_2 = F_1\ldots F_2 & S_5 = F_2\ldots F_3 & \\
S_3 = \begin{array}{c} F_1\ldots F_2 \\ \backslash\ / \\ F_3 \end{array} & S_6 = \begin{array}{c} F_2\ldots F_3\ldots F_4 \\ | \\ F_2 \end{array} & \text{and so on \ldots .}
\end{array}
$$

From this it is obvious that the number of possible supramolecular synthons quickly becomes very large, even though the appearance of some supramolecular synthons will preclude the formation of others.

(ii) Interference from remote functionalities may be unpredictable. One notes that instead of say, $S_1$ appearing from the association of $F_1$ and $F_1$, it may associate preferentially with $F_2$ to give $S_2$ because of the presence (or absence) of some $F_i$ in another location of the molecule, with $F_i$ seemingly unrelated or unconnected with either $F_1$ or $F_2$.

Both these problems are endemic and it is for good reason that the prediction of a crystal structure of a small organic molecule (higher level property) from the structural formula (lower level property) has been deemed to be one of the most challenging scientific problems of the 21st century [21, 26].

**(b)** ***Hydrogen Bridges. Water Aggregates:*** The hydrogen bridge, or hydrogen bond, is an interaction X–H…A wherein an electropositive H-atom acts as a bridge between two electronegative atoms X and A. There are many varieties of hydrogen bond and the energies associated with X–H and H…A may be widely different to nearly the same [27, 28]. Although the phenomenon has been studied extensively for a century, it is surprising that there are no rules that allow the chemist to estimate the geometry and energetics of the hydrogen bridge from the formulas of the interacting molecules. This indicates that chemists have so far not been able to understand the hydrogen bridge phenomenon in all its complexity [29]. While this is, in general, true of all intermolecular interactions, the hydrogen bridge is the most important interaction in molecular recognition, supramolecular chemistry and biology and therefore it merits special mention as an emergent property.

In this connection, hydrogen bond arrangements that involve water are most fascinating. Water is almost a philosophical abstraction. Hardly a molecule in the usual sense, its surface is composed entirely of strong hydrogen bond donor and acceptor regions. It is small but supramolecularly very potent. Therefore it plays a crucial role in molecular association and aggregation – and indeed for life itself. Water is found associated with other molecules, and with itself, in many ways. The study of liquid water is fascinating and there are 'different' types of water molecules present [30]. These are characterized by different

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geometrical coordinations (supramolecular synthons), by different dynamical properties (slow, fast) and different locations (surface, bulk). In crystals water occurs in a myriad environments, bound to itself or to other molecules. The amazing feature of these patterns is that new ones are constantly being discovered [31]. There seem to be no limit to the variety of water…water association patterns. Clearly this is an important example of an emergent property of fundamental importance.

**(c)** ***Fluorinated Compounds:*** The supramolecular behaviour of the halogens (fluorine, chlorine, bromine, iodine) is still very difficult to understand [32]. Reference has already been made to the periodic law in connection with Cl, Br and I. However, this law breaks down more or less regularly in supramolecular chemistry and the properties of Br are not the mean of the corresponding properties of Cl and I. In supramolecular chemistry, Br behaves more or less like Cl, or more or less like I, *depending on the system under consideration*. Accordingly, Br-atom interactions are emergent properties.

Fluorine is even more complex. If one takes a hydrocarbon and successively replaces the H-atoms by F-atoms, the boiling point rises (as it is expected to) for a while but after the extent of fluorination crosses a critical value, the boiling points begin to fall. The boiling point of the perfluoro derivative may even be lower than that of the original fully hydrogenated compound. For example, the boiling point of methane and its fluorinated derivatives are as follows: $CH_4$ (–161.5 °C), $CH_3F$ (–78.4 °C), $CH_2F_2$ (–51.7 °C), $CHF_3$ (–82.2 °C), $CF_4$ (–128.0 °C). Such behaviour is not seen in the other halogens. For example, the boiling points of the corresponding chloromethanes are: $CH_3Cl$ (–24.2 °C); $CH_2Cl_2$ (39.5 °C); $CHCl_3$ (61.2 °C); $CCl_4$ (76.0 °C). No one has been able to explain such anomalies satisfactorily. Fluorine is also unusual in that the so-called "fluorous" compounds with many C–F bonds (say, teflon) are neither hydrophilic or hydrophobic. But a fluorous molecule is not simply a fluorine-rich molecule – perfluorohexane is fluorous but hexafluorobenzene is not. So a new concept of fluorophilicity/fluorophobicity is invoked [33], but no one has really been able to quantify this. Many drugs that are in active clinical use today contain fluorine but no one knows just why the F-atom is so ubiquitous in medicinal chemistry. As a sampling, one might mention Allergan, Cifran, Clinoril, Dalmane, Diflucan Haldol, Lescol, Orap, Prozac and Uftoral (all registered trademarks). Again, the C–F group is unable to accept hydrogen bonds like the C–O and C–N groups, although fluorine is more electronegative than oxygen and nitrogen. Truly, fluorine chemistry is one of the last frontiers in chemical research and emergence is more or less rampant [34].

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To summarise, universality in the behaviour of complex systems often reveals itself in forms that are essentially independent of the details of microscopic dynamics. A representative paradigm of complex behavior in nature is cooperative evolution, seen in structural and supramolecular chemistry as self-assembly and crystallisation (chemical sociology). The interaction of individuals gives rise to a wide variety of collective phenomena that strongly differ from individual dynamics such as demographic evolution, cultural and technological development, and economic activity. Each human is part of a family of six billion members.

## The Middle Kingdom

Chemistry is poised midway among the sciences, straddling the space between physics and mathematics on the one side, and biology, ecology, sociology, economics and the higher sciences on the other. The history of chemistry from the early 19th to the late 20th centuries represents the consolidation of reductionist and Paulingesque thought, the triumph of inductive and deductive logic in synthesis as seen in the work of Woodward, Corey and others [35], and defines a tightly knit body of work that, in the end, is more or less reducible into physics and finally mathematics [36]. Much of this chemistry was built with concepts and models like acidity/basicity, electronegativity/electropositivity, oxidation/reduction, hardness/softness, enthalpy/entropy, kinetics/thermodynamics, reactivity/selectivity, electrophilicity/nucleophilicity, hydrophobicity/hydrophilicity and chirality/achirality.

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Although most of these models cannot be rigorously derived from physics and mathematics, they still constitute a continuum with these more exact sciences. This continuity was established through physical chemistry, which enjoyed a dominant role in the development of chemistry as a whole during the 20th century. Chemistry is oceanic with respect to factual information, but it has always been contained with respect to the number of concepts and models that were required to understand all these facts.

In contrast, the reduction of biology to chemistry has always been problematic [37]. The appearance of supramolecular chemistry on the scene in the late 20th century stimulated new thinking about the relationship of chemistry with biology. This new chemistry is less about structure and more about organization, less about reactivity and more about dynamics, less about synthesis and more about association. All this represents a paradigm shift in the way in which chemists think about their subject today [38]. The argument is that biology and the other higher sciences may be considered as emerging out of this new chemistry, *which in itself cannot be reduced into physics and mathematics* as was the case for chemistry as it has been practiced thus far. An entirely new set of properties can emerge from the interplay of macrosystems that are not related directly to their component atoms and molecules [39,40]. The idea of emergence is being linked to biological pathways and this approach is being used to explain the evolution of complex self-organizing systems in a way that opens up a huge discontinuity from physics and 20th century chemistry. Living systems are viewed as autonomous self-reproducing entities that operate upon information, that originates at the molecular level by covalent chemistry, transferred and processed through non-covalent chemistry, expanded in complexity at the system level and are ultimately changed through reproduction and natural selection [41].

This new chemistry then promises to be the language of biology in the same way that mathematics is the language of physics and the older chemistry [1]. As a language, the new chemistry shares much with mathematics. While biology cannot exist without chemistry, (supramolecular) chemistry seems to develop well without biology [42, 43]. When chemistry is used in biology, it is only a small fraction of the totality of chemistry that is so used. In other words, there is a large surplus of chemistry that is not even relevant to biology. This is a characteristic of a language. To paraphrase Jean-Marie Lehn, chemistry is all about diversity [11] but biology does not need all this diversity. Biology is about complexity and in the process of emerging from (supramolecular) chemistry, complexity builds itself around the chemical core.

Chemistry then occupies a unique middle position in the scientific arena. Its development thus far may be traced as an emergence from the harder sciences, physics and mathematics. In moving from the covalent to the non-covalent world, however, it enters totally different territory, a domain that is a starting point for the development of the softer sciences. This dualistic nature of chemistry is a new development but one that ensures that the subject will remain robust in the foreseeable future. It has been bemoaned that most of the important problems in chemistry have been solved and that all that remains now is to fill in the details. Nothing could be further from the truth. Almost imperceptibly, and in silent revolution, the subject has evolved so dramatically that future possibilities for the Middle Kingdom appear almost limitless.

***Acknowledgements:*** I thank the Institute of Advanced Study, University of Bologna (Prof. R. Scazzieri, Prof. D. Braga) for the award of a Senior Visiting Fellowship during which tenure this article took shape.

*Address for Correspondence*
Gautam R Desiraju
School of Chemistry
University of Hyderabad
Hyderabad 500 046, India.
Email:
desiraju@uohyd.ernet.in

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