The World Behind the Word 'Structure'

In Crystallography, Chemistry and Elsewhere

P Venugopalan

Structure determination is an important aspect in chemistry. However, the answer to the primary question, 'what do we mean by structure in chemistry?' is often not that clear. This article tries to answer this question by considering different aspects of structure such as connectivity, conformation/configuration and packing in crystals. Structure is intimately linked with property; hence the effects of small structural changes on the property variations of various compounds are discussed briefly with closely related examples.

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The commotion and murmuring faded away quickly. In a few seconds, there was almost pin-drop silence in the classroom as I stood in front of first year MSc students to teach X-ray crystallography. To most of them, X-ray crystallography is something unfamiliar – a not-yet-studied subject – curiosity prevailed to listen to what I had to say and what it is all about. Indeed, the first lecture is difficult to teach, even for an experienced teacher, as it inscribes an everlasting memory into the minds of the students about the subject and the teacher. I wrote on the blackboard:

'Structure: There is a world behind every word.'

I began:

The word 'structure' is familiar to all of us; in fact, it has different meanings and connotations depending upon the situation/circumstance in which we are using it. Think about the words 'elephant', 'mouse' and 'energy'. There is an instantaneous buildup of a 'world' in our minds with these words – the first two, so tangible and familiar – the last one, not so simple to comprehend. We know the structure of an elephant and a mouse, that of a building and a car, indeed, a 'world' opens up the moment we hear the word, depending upon who uses it and in what context. Then,

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Structure, connectivity, conformation, configuration, crystal packing.

"Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world. Science is the highest personification of the nation because that nation will remain the first which carries the furthest the works of thought and intelligence."
– Louis Pasteur

what is the world behind the word 'structure' in Chemistry? Seems simple, seems obvious … ask to put it in words, immediately haziness engulfs the obvious! The operational approach is to express what you know, correctly and convincingly. Let us begin with the question, 'what is the structure of benzene'? Seems trivial, doesn't it? The hexagon with three alternating double bonds or the one with a small circle inscribed within the hexagon will figuratively represent benzene. Everyone knows it; hundreds of such structures are at the fingertips of those of us who deal with science, especially Chemistry or Biology. The next corollary to this question, 'why is it important to know the structure?' is tougher than the first question, but certainly there are answers to put across, depending upon one's understanding, articulation and even imagination.

The whole world looks forward to a better tomorrow and we are all well convinced that only science can spearhead such an endeavor. We want paints on our cars which will never fade, jet-plane nozzles that never wither away, electric wires with 100% transmission, total solar energy capture, and many other 'dream-things'. That is, *Homo sapiens* is fervently dreaming of unprecedented control over properties of materials. He is also well aware that his mastery over this dream-craftsmanship hinges on a pivotal theme: the relationship between structure and property. Any understanding towards the question of 'what do we mean by structure in Chemistry?' must take into account the relationship between structure and property in a way that the functional part of it is also conveyed in a tangible way. Let us ponder over structures-in-chemistry in this direction.

Structure and Connectivity

It is interesting and that the liquid that is most consumed by man after water is the so-called 'booze material', ethanol, with the molecular sum formula C_2H_6O.

Indeed, there are many chemicals with the same sum formula; a familiar alternative being dimethyl ether. While the use of etha-

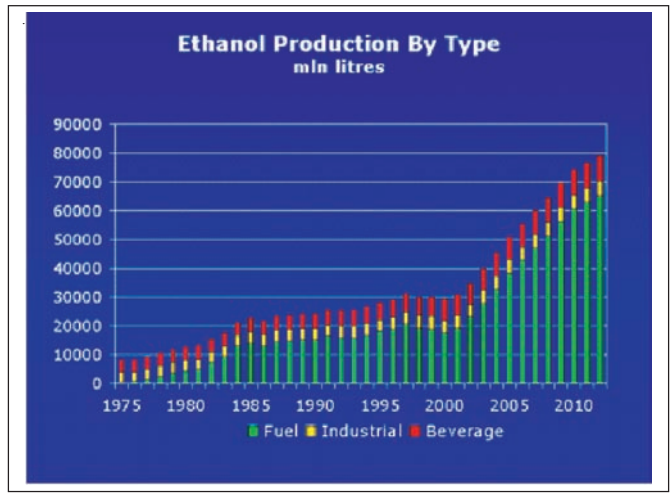


Figure 1. Graph showing the production of ethyl alcohol and its use in the world.
Source: http://www.distill.com/World-Fuel-Ethanol-A&O-2004.html

nol is increasing widely across the globe, with a multitude of applications as shown in *Figure* 1, dimethyl ether, as known, is very ordinary. It can be child's play, even at the high school level, to draw their respective structures (of course in the bookish way that all of us have learned). For brevity, let us draw them in *Figure* 2.

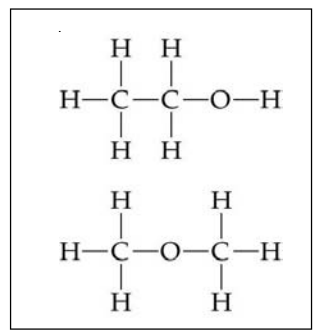


Figure 2. Connectivity pattern in ethanol and dimethyl ether.

What one observes immediately is that there is an entirely different bonding pattern of atoms in these two compounds. The correlation between the difference in their properties and that of their structures also becomes obvious: their structures are very different and so are their properties. I want you to pause for a moment here; look at the structures again (*Figure* 2), as an important aspect of the 'structure' is emerging. A molecular structure can be discerned based on the specific connectivity of the atoms within the molecule. Let us put this in a different way. Any structure at a molecular level can be construed based on the unique connectivity of atoms that constitute the molecule. If there is even a single change in the connectivity of atoms, then, obviously structure also changes. Thus, in a simple way, (yet at a fundamental level), understanding any structure is knowing its connectivity. Now, carefully examine the figure below (*Figure* 3).

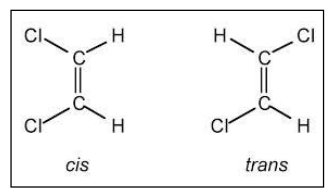


Figure 3. *cis* and *trans* isomers of 1,2-dichloroethene. The double bond restricts C-C rotation.

The compound with molecular formula $C_2H_2Cl_2$ has the same connectivity pattern, both are 1,2-dichloroethenes, but they are two entirely different chemical entities with a multitude of differences in their chemical and physical properties. The left one in the figure is the *cis* form with a dipole moment of 1.9D and boils at 60.2 ºC whereas the *trans* form has a zero dipole moment and boils at 48.5 ºC. Though their connectivity pattern is identical,

their structures are different and so also are their properties. We are at a juncture of consolidating two important concepts about 'structure' here: a) the simple description of connectivity pattern alone does not suffice to describe a structure, b) the structure can be perceived at a different hierarchical level of complexity, depending upon the molecular constitution. Thus, the structure can be perceived at different levels, but before discussing those aspects, let us ponder a little more deeply into connectivity.

Keto-enol Tautomerism

A perusal of molecular diagram of acetylacetone (**1** in *Figure* 4) will enable us to predict that 2 peaks can appear in a ^{1}H-NMR spectrum, one for the methyl protons and one for the protons of the methylene group. But the proton NMR of acetyl acetone shows 4 signals consistent with the keto-enol tautomerism in this molecule (*Figure* 5), that is, in the 'eye of NMR' there are two

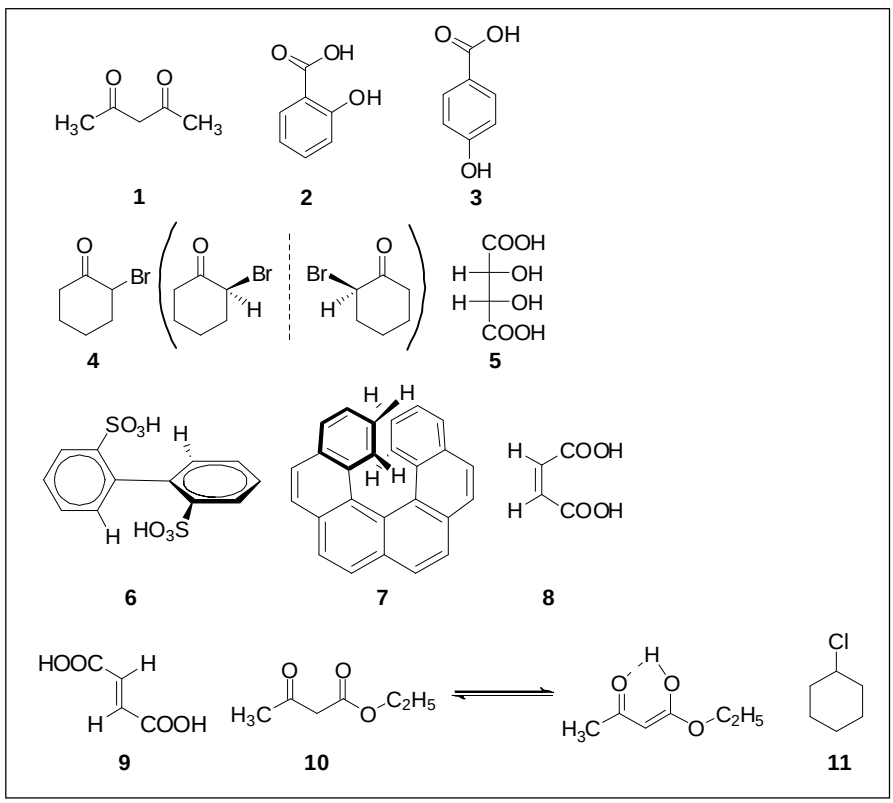


Figure 4. Structural formulae of compounds used in this article.

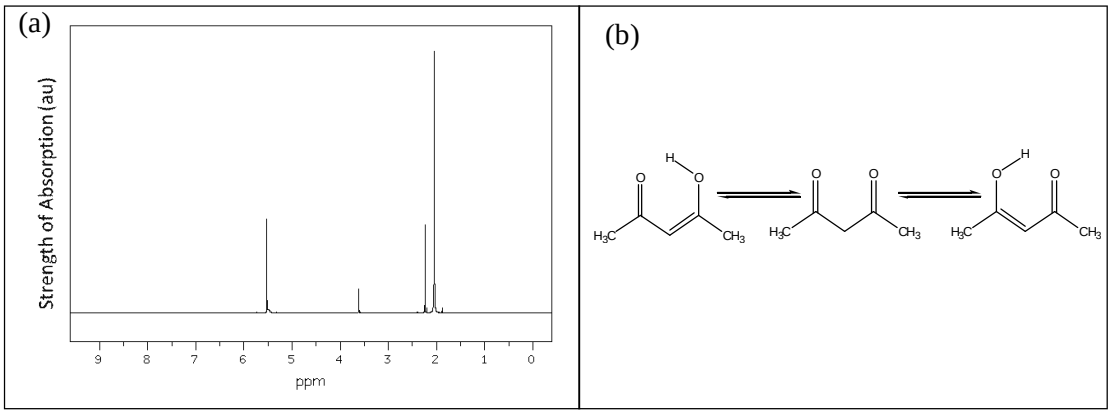


Figure 5.
(a) ^{1}H-NMR spectrum of acetylacetone.
(b) Keto-enol tautomerism.

distinct species with different connectivity patterns for this molecule.

Interestingly, for a sample of this compound, only a single boiling point (140.2ºC) and density (0.98g/mL) can be measured. Distillation or weighing cannot distinguish between the two species, but NMR can. This cautions us that there is not always a single, static connectivity pattern describing a molecule. Depending upon their intrinsic nature, dynamic changes are possible even without the explicit influence of an external agency. Certain experimental techniques such as chromatography, will consider them deceptively as a single entity but others like NMR can distinguish between the different forms.

There is an important corollary to this observation. The connectivity change in acetylacetone described above does not need an external reagent, but there are also dynamic processes induced by external reagents, which alter the connectivity pattern to the extent that it can be recorded by some analytical techniques. Pure ethanol gives a ^{1}H-NMR spectrum which faithfully follows the (n+1) rule of splitting pattern, but addition of a trace of acid or even water alters this pattern substantially as shown in *Figure* 6.

The reason for this change is well known. In the structural perspective, in the presence of acid, NMR cannot 'cope' with the rapid exchange of hydroxyl protons and the spectrum becomes simple. Look at compounds **2** and **3** in *Figure* 4. A solution state

Nuclear Magnetic Resonance (NMR) is a nuclei (nuclear) specific spectroscopy technique that can be applied to solids, liquids and gases for kinetic and structural studies. Indeed, its importance becomes obvious as researchers in this field have already won six Nobel Prizes.

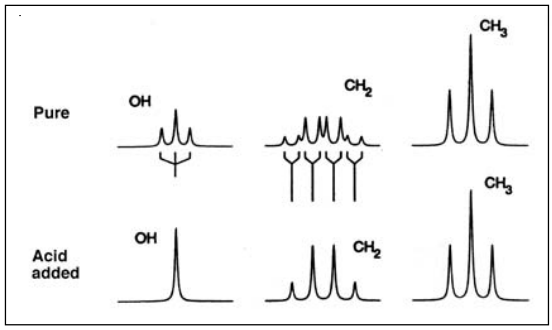


Figure 6. ^{1}H-NMR spectrum of ethanol. Note the disappearance of splitting when acid is added.

IR with different concentrations of **2** will have very little effect on the stretching frequencies, but there will be a substantial change for **3**. We are not changing any connectivity pattern of these compounds by dilution. However, the external solvent used is affecting the structure in **3**, but has very little effect in **2**. The reason behind such a change is the difference in the hydrogen bonding patterns of these molecules with the solvent.

From the above mentioned observations, it is clear that even if one can assign a well defined connectivity pattern to a compound, this pattern may not encompass all the structural aspects of a compound. Structure in chemistry is certainly beyond connectivity.

Structure and Configuration

Let us do a thought experiment. Imagine that we have synthesized 5 grams of compound **4** shown in *Figure* 4 without the use of any chiral reagents or any special means. Now, with a magical gesture, we command the molecules of **4** that have identical structures to sit at their place (bottle A) and all others to step into another bottle B. Accordingly, exactly half of the molecules (2.5 g), move to bottle B. By checking with any physical means like boiling point, specific gravity, solubility, dipole moment, NMR, IR, etc., we will observe that the difference between them is nil except for their specific rotation in a polarimeter[1]. Interestingly, the absolute value of the specific rotation is exactly the same, but their direction is opposite. For example, if bottle A shows +52.8°, bottle B will show -52.8°, but curiously, we can never predict which bottle will show which sign for these compounds. One thing is very clear – the structure of molecules in bottle A is different from that in bottle B, at least for some experiments. Now look at again, see the two diagrams in the brackets. They are the two enantiomers of α-bromocyclohexanone. Their structures in the 'connectivity world' are exactly the same, but in the 'configurational world', they are different. This effect, grossly called

[1] A polarimeter is used to measure the angle of rotation caused by passing polarized light through an optically active substance. It can also be used to identify which isomer is present in a sample and the ratio of enantiomers in solutions.

'handedness' of molecules, is observed when a molecule lacks a mirror plane or center of inversion. Such molecules are called chiral; the relationship between a chiral molecule and its mirror-related sibling (for example, the bracketed structures in *Figure* 4) is called enantiomerism and the members of the pair are called enantiomers. They will have identical chemical formulae and connectivity patterns but will behave differently in specific environments such as that provided by the polarized light. Extreme care is needed here since a molecule is not necessarily chiral just because it has a chiral center or that it is necessarily achiral because it lacks a chiral center. These are not the criteria for molecular chirality. The necessary and sufficient criterion for chirality in a molecule is the 'nonsuperimposability' of the molecule on its mirror image. Examine the molecules **5**, **6** and **7** in *Figure* 4. **5** is the well-known tartaric acid, but its meso form shown here, despite having two chiral centers, is optically inactive. 2,2'-diphenyldisulphonic acid (**6**) can exist as a pair of enantiomers due to steric crowding although it has no chiral center; the same is true for the famous hexahelicene (**7**).

We have seen that the structure at the molecular level can differ very subtly, only a simple configurational change can alter certain properties such as the optical rotation. Indeed, the chiral nature of molecules is manifested profoundly in the biological world of amino acids, sugars, proteins, DNA, steroids etc., which are all chiral. Biological receptors (for drugs, taste-inducing chemicals, biopharmaceuticals, agrochemicals) are chiral and will therefore recognize and bind enantiomers differently, as shown in *Figure* 7, where the receptor has a perfect fit with the R enantiomer, but a mismatch with the S enantiomer. Such a difference markedly affects the activities (efficacy, taste, toxic nature) of the two mirror images of chiral molecules in the human

> "Biology is now bigger than physics, as measured by the size of budgets, by the size of the workforce, or by the output of major discoveries; and biology is likely to remain the biggest part of science through the twenty-first century."
>
> *– Freeman Dyson*

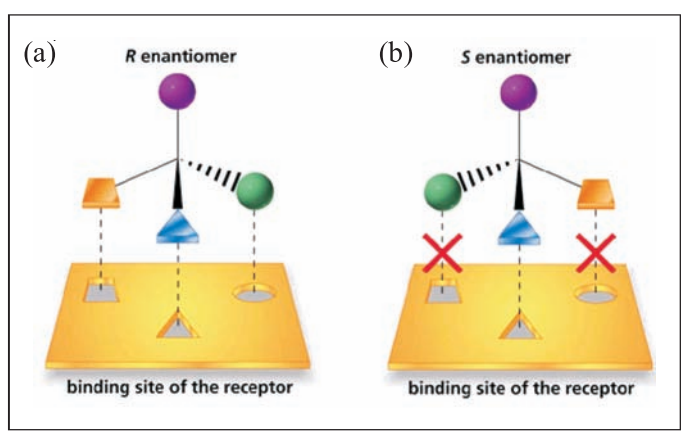


Figure 7. Interacting modes of enantiomers with a receptor. (b) S enantiomer interaction is much weaker due to mismatch.

Source: http://www.kshitij-iitjee.com/Discrimination-of-Enantiomers-by-Biological-Molecules.

body. There are dramatic examples of this, such as, racemic (R,S) thalidomide, a drug to alleviate the morning sickness of pregnant women. Its consumption led to disabilities in new born babies to such a tragic level that it is known as the 'Thalidomide Tragedy'. In this case, the R enantiomer was effective whereas, the S enantiomer was poisonous.

There are many more such instances. (S, S)-aspartame is 160 times sweeter than sugar but the (R,R)-isomer evokes a bitter sensation in our chiral taste buds; S-(+) ketamine is 4 times more potent than R-(-) ketamine in anaesthesia applications, S-(+) ketoprofen is an analgesic with anti-inflammatory activities, whereas, the R-isomer is devoid of such activity, but toxic to cells.

Structure-property relationships from the chiral world teach us that certain structural aspects that are very intricate and unseen by many physicochemical methods may get unraveled by special and specific experimental techniques. These structural aspects have to be considered very carefully and astutely to take full control over the properties in a predestined way.

Structure and Conformation

We have already seen that although the *cis* and *trans* forms of 1,2-dicholoroethene (*Figure* 3) have the same connectivity pattern, they are different compounds due to the spatial arrangement of the atoms within the two molecules. Such configurational rigidity can also manifest itself in differences in chemical reactivity; for example maleic acid (**8**) with the *cis*-orientation of the carboxyl groups undergoes dehydration by gentle heating to form the corresponding anhydride, whereas its *trans* isomer (**9**) is inert to this reaction at moderate temperatures (the two carboxyl groups are not at the requisite proximity to induce dehydration see *Figure* 4. It has been mentioned earlier that acetylacetone **1** shows the signals of both the tautomers in NMR due to the coexistence of the keto and enol forms, directing us to mull over the relevance of structural homogeneity at a given temperature. A related

compound, acetoacetic ester (**10**, *Figure* 4) which can also exhibit keto-enol tautomerism, also shows distinct signals for both the tautomers in NMR. In contrast to **1** acetylacetone, the two tautomers can indeed be separated by a low-pressure distillation in quartz apparatus. In the case of the above mentioned molecules, we surmise that their connectivities and/or configurations vary, hence their structures do too. This leads to different properties and reactivities.

In this context, it is worthwhile to examine the ^{13}C-NMR spectral behavior of a simple cyclohexane derivative, namely chlorocyclohexane (**11**, *Figure* 4). It has a mirror plane and hence should show only four signals and this is seen at room temperature.

However, there are two C-Cl stretching frequencies in the IR[2] spectrum in agreement with the equilibrium shown in *Figure* 8; this clearly shows that chlorocyclohexane is a mixture of two chemical structures. In agreement with this conjecture, ^{13}C-NMR at –100ºC shows 8 peaks validating that, below the coalescence temperature, NMR can also 'see' these two species. For most observations like distillation, chemical reaction and even chromatography, the compound will appear as a homogeneous one. However, at –150ºC, it is possible to isolate these two species. Thus, it is a matter of the technique used for the observation and the conditions of the experiments that will decide whether one can put one's hands on these types of different molecular entities. Let us try to get an insight into the equilibrium shown above in terms of the structure at the molecular level and try to correlate structure with properties, a premise that we set at the beginning. Even at the undergraduate level, we come across the equilibrium shown in *Figure* 8. There is rotational freedom of C–C single bonds (though restricted), which will allow the flip of a cyclohex-

[2] Infrared spectroscopy (IR) is the analysis of interactions of infrared light with a molecule. Functional group analyses of a molecule are more convenient with this technique. It is curious that no two molecules can have the same IR spectrum.

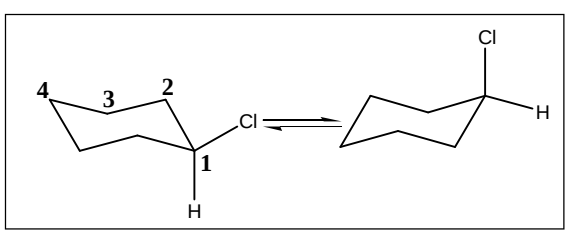


Figure 8. Ring flipping in chlorocyclohexane, the numbers 1 to 4 indicate the unique carbon atoms.

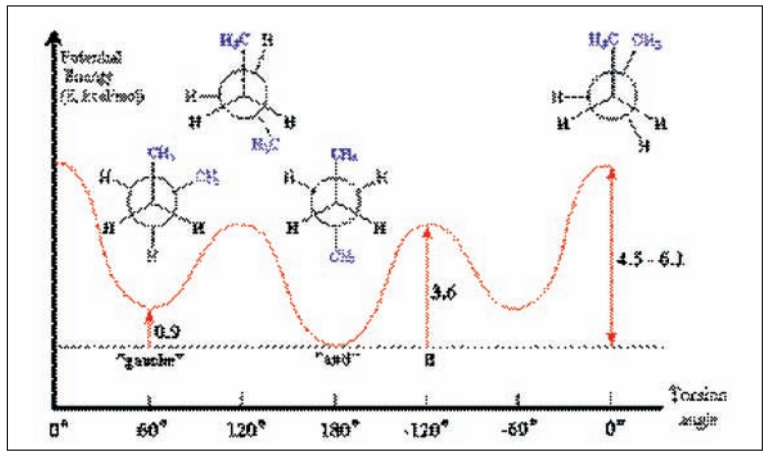


Figure 9. Potential energy variation as a function of torsion angle in n-butane. Source: http://tigger.uic.edu/~kbruzik/text/chapter6.htm

ane ring to generate another structure with a Cl atom in the axial rather than in the equatorial position. We link these types of molecular shape alteration with the word *conformation* which describes the 3D structure or shape of a molecule. Rotation about a single bond alters conformation.

The demarcation between conformation and configuration also needs to be distinguished. Change of conformation does not need any bond breaking whereas change of configuration is associated with at least one bond breaking and bond making process. The relative positions of attached atoms with respect to a bond can be expressed by a torsion angle and this parameter is central to conformation. Due to steric crowding, there can be barriers to rotation, a classical example being that of n-butane (*Figure* 9). At room temperature about 72% of all molecules are in the most stable antiperiplanar conformation.

From a structural perspective, every conformation can be considered as a new structure but their isolation and the measurements of their physicochemical properties become a function of temperature. If the steric crowding becomes substantial, conformer(s) may get locked at some appropriate temperature and can then be isolated. The conformational differences also affect chemical reactivity, for example, the base-induced ester hydrolysis of *trans*-cyclohexyl ester (**A**) proceeds 19.8 times faster than that of the cis-isomer (**B**) (*Figure* 10). The reaction of the axial ester **B** is

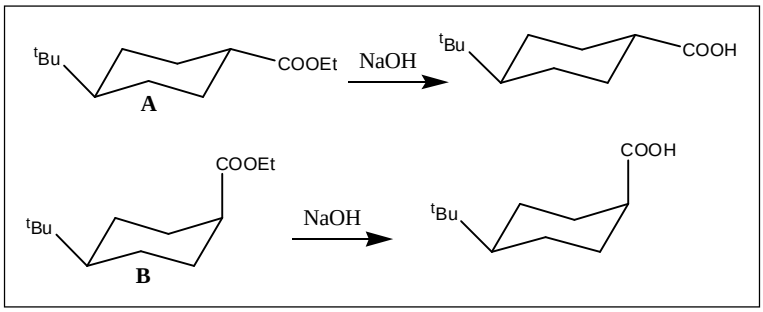


Figure 10. Base induced hydrolysis of cyclohexyl derivatives. Flipping cannot convert **A** to **B.**

decelerated due to the development of destabilizing 1,3-diaxial interactions in the transition state. Similarly, the S_N2 substitution reactions of *cis* and *trans* chlorocyclohexane derivatives proceed with a marked difference in their reaction kinetics. In organic chemistry, the conformational analysis of molecules and its influence on chemical reactivity is an area of active research.

It is to be mentioned that compounds **A** and **B** shown in *Figure* 10 differ in configuration and their ring-flipped forms, (not shown here, but they are similar to those shown in *Figure* 8), also differ in configuration. In the ring flipping process, axial substituents become equatorial ones and *vice versa*. However, **A** and its ring-flipped structure have the same configuration (no bond is broken) but differ in conformation only. That is, a compound with a given configuration can have different conformations. Thus, in the understanding of a structure (and consequently its reactivity), one has to consider configurational and conformational features jointly or separately, wherever deemed appropriate.

Structure and Packing

When atoms, molecules or ions condense, solids result, which can be either crystalline or amorphous, the former one having long range order which is lacking in the latter. So far, we have seen that to understand 'what is meant by structure in chemistry' precisely, one needs to take into account connectivity, configuration and conformation of the molecules (wherever applicable) and their ramifications. There is also another dimension to structure, which is concerned with the packing[3] of atoms, molecules or ions in the condensed state of matter. Describing and understand-

[3] Stereochemistry, in general, describes how the atoms of a molecule are arranged in 3D space. In particular, stereoisomers are molecules that have identical connectivity but differ in 3D structure. Stereoisomers differ from one another in configuration at one or more atoms. Conformations are the various shapes that are available to molecules by single-bond rotations and other changes that do not involve bond breaking.

ing this aspect is an arduous task as it implies understanding a multitude of parameters, interaction forces, thermodynamic and kinetic aspects, symmetry considerations etc. Hence, only some glimpses about packing in terms of structural diversity and their consequences are given here.

Allotropism

Atoms and mono-atomic ions of elements are generally treated as spherical objects for describing their 3-D periodic arrangements in crystals. Their packing is controlled by size, charge, etc. Although they may be viewed simply as balls of varying size, they can take a rich variety of arrangements in the crystalline state, each one displaying different properties. The different packing arrangements exhibited by an element is called allotropism, a typical example being that of elemental carbon existing as diamond, graphite, fullerenes and nanotubes. Phosphorus occurs as P_4 molecules that stack in different ways to form several allotropes, the major ones being white, red, violet and black phosphorous (*Figure* 11).

Phosphorous allotrope can be interconverted and their properties are much different. White phosphorous is so reactive that it ignites spontaneously in contact with air, the red allotrope needs flame or friction to burn and the black one is the thermodynamically stable form. What is important in a structural perspective is that, seemingly simple elements can show remarkable structural diversity in the solid state.

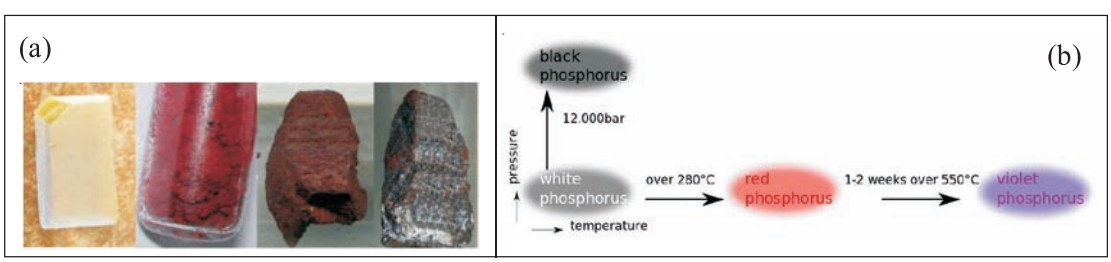


Figure 11. (a) Four major allotropes of phosphorous. (b) Conditions of phase transition.
Source: http://en.wikipedia.org/wiki/Allotropes_of_ phosphorus.

Polymorphism

Polymorphism is a similar phenomenon, but related to molecules.

It is defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements or conformations of molecules in the crystal lattice. As a result, polymorphic crystals exhibit different physical or chemical properties such as solubility, melting point, stability, mechanical strength, reaction rate etc. At the applied level, polymorphism takes a pivotal role in those areas where the results of full characterization and fine tuning of the properties determine the ultimate use of polymorphs. This is the case for pharmaceuticals, agrochemicals, pigments, explosives and other fine chemicals. There are very many examples of compounds connected with multimillion dollar sales for which polymorphism is an important feature to consider. A typical example is that of aspirin (world production of this drug is around 40,000 tons per year) which can exist as different polymorphic forms (Form-I and Form-II).

In the context of our discussion about structure, the relevance of allotropes or polymorphs is the fact that different packing of atoms or molecules can generate different structures with substantially different properties.

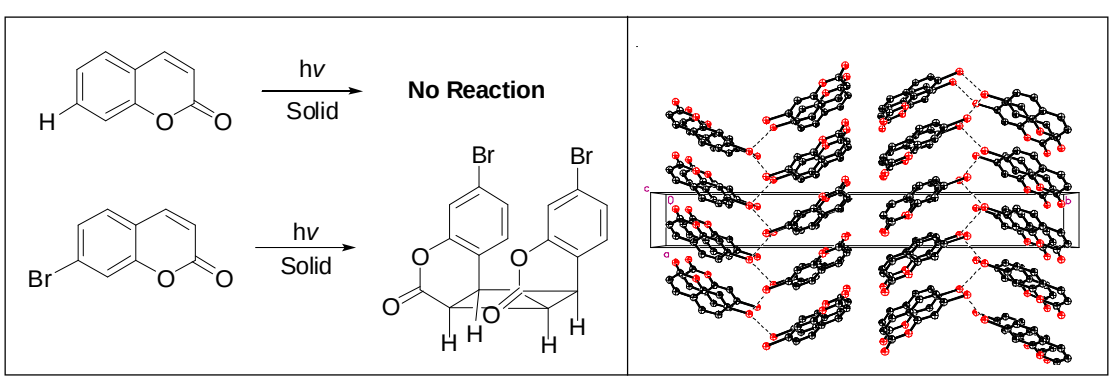
The word 'solid' also evokes the concept of strength in our mind. Look at the expression 'the lawyer's argument was solid' (remember, there is a world behind every word). The atoms or molecules are tightly packed in a solid that give strength to it, but, interestingly, it is possible to change their packing arrangement, generating a different type of solid. This phenomenon is called phase transition. Generally temperature or pressure or their combination induces such transformations (see *Figure* 11). Phase transitions are found for a wide variety of systems, from metals and alloys to complex organic and inorganic materials. A striking example of property difference associated with phase transformations is that of metallic tin. At ambient temperature (above 18ºC), it exists as β-tin which is metallic (the tin globules that we see in laboratory bottles), but at sub-zero temperatures, it can transform to a nonmetallic form, α-tin. The pleasant smell of solid camphor is also due to a phase transition called sublimation.

Topochemical reactions take place more selectively in solid than in the fluid phase. Indeed, solid state reactions have become an 'efficient green' route to targeted molecules, polymers, and solid-state materials that are less available by conventional synthesis.

Structure–Reactivity Correlations

We have learned that energy-input into crystals can change their packing, thus the structure. Not only that. Heat and light, the wonderful energy sources of nature can induce chemical transformations in many crystals. Solid State Chemistry itself has become a field of active research, stimulating many researchers to fathom and unravel the subtleties of molecular arrangements that permit molecular transformations in crystals. As mentioned at the outset, we want to take control of the behavior of materials; solid state chemistry has seen leaps and bounds in this direction. There are new methods, methodologies, reviews and books appearing in this prolific area. The fundamental question, how to engineer molecules to arrange themselves in a specific way and to undergo reactions has been deeply studied by many incisive minds. In this context, let us examine the solid state reaction shown in *Scheme* 1, which is a typical [2+2] photocyclodimerization reaction.

The famous topochemical principle states that if reactive double bonds are far apart in the crystal lattice (more than 4.8 Å), reaction cannot take place. The principle is truly followed during the solid state irradiation of coumarin shown at the top of *Scheme* 1 (double bond separation = 5.68 Å). However, an appropriate bromo substitution brings the reactive partners much closer (4.31 Å) and there is almost a quantitative yield of the photodimerization product. This example shows that we can engineer molecules towards adopting a reactive arrangement. Steering groups such as halogens, sulfur, methylenedioxy, etc



Scheme 1. Effect of bromo-substitution on the photoreactivity of coumarins. See the lattice stabilizing Br…Br interactions (dotted line) in the packing diagram shown on the right side.

have shown their potential to induce many crystalline state chemical reactions. In addition, it has been shown that the products of solid state reactions can differ from those of solution state reactions in terms of number and nature of products and their reaction kinetics. From this base level of understanding about the preorganization of molecules in the solid state, much deeper insights into the type and nature of weak intermolecular interactions also started unraveling, eventually leading to a very active area of research called 'crystal engineering'. As has been put succinctly, 'crystal engineering is the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties'.

Conclusions

So far we have discussed many aspects related to the fundamental question, what do we mean by 'structure' in chemistry and to the implication of this question on observed properties/reactivities. Structure is one of the central themes in chemistry. The meaning of the intricacies of the hierarchical levels of any structure, starting from connectivity in a molecule to its packing in the crystalline state, depends upon the requirement of the researcher and the power of the analytical tool. Every researcher at some stage or other will say something like this, "I could do the NMR finally, my IR matches expectations, this X-ray structure shows disorder, the fluorescence quenching was unexpected...." In fact these words are all pointing towards the means for finding the structure of a compound. There are innumerable analytical methods in chemistry to unravel some/many structural features of a compound. When it comes to crystalline materials, X-ray crystallography cannot be matched. As the idiom goes, 'seeing is believing' and we can 'see' atoms with X-rays. X-ray crystallography can provide information about connectivity, conformation, configuration and packing in crystals in unambiguous ways. No other technique can match this consolidation of information. That is the power of X-ray crystallography.

Suggested Reading

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