Talkative Organic Molecules

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The 20th century has seen the birth of three Ages, called the Nuclear Age, the Electronic Age and the Chemical Age, each with profound social implications. Despite having a less dramatic impact, as a grandfather (beginning ca. 1930) the Chemical Age has more thoroughly and deeply permeated our day-to-day lives. Hence, we are now celebrating International Year of Chemistry 2011 (IYC-2011). Every single material in the universe is a chemical, and an impressive array of commonly used chemical “tools”, ranging from modern food and drugs to plastics and computers to specialized coatings, fire retardants, and heat-transfer gases/liquids have become essential ingredients of our society. While chemistry is a science in its own right, in concert with biology, physics, medicine, materials science and other core disciplines, it makes effective contributions to the solutions of problems facing the world today and to the improvement of the condition of mankind tomorrow. The world would be a far more mysterious and less advanced place to live, without the development of chemistry. In future, it promises to stimulate and support innovation in all other branches of science and technology.

As a giant branch of science, chemistry has the ability not only to create the molecules, but also manipulate their properties and promises to take an increasing role as a creator and enabler, in materials science and biology. In particular, learning from nature how she assembles molecules and how such molecules recognize each other, it promises to build up new molecular world, not yet even imagined. Two aspects of chemistry primarily confer the extraordinary power of this branch of science. On one hand it can generate a huge molecular diversity of small and medium-sized molecules, pre-organized supramolecular assemblies via non-covalent interactions as well as nano-sized entities. On the other hand, each of these is bestowed with a specific property, and perhaps more importantly, this can be tuned by subtle structural variations. The importance of these molecules/assemblies lies not in their existence or exotic structures, but because they can execute certain specific jobs and are functional. The molecules/assemblies in question cross-talk (hence termed ‘talkative’) with completely alien molecules and/or get triggered by physical/biological factors to block/augment certain functions, generating detectable and/

Fig. 1: Schematic description of talkative molecules
or measurable signals. Essentially, acting as a transducer, the molecules / assemblies exhibit the targeted functional property (Fig. 1).

**Organic functional materials: prospects & challenges**

Although traditionally well-known for their medicinal properties, the importance of organic molecules in seemingly unfamiliar areas such as nuclear and material sciences is increasingly being realized. Organic compounds offer the best potential for these due to the catenation property of the carbon atoms coupled with the possibilities of modulating their electronic properties as well as non-covalent interactions. Organic functional materials are also light-weight and can be processed easily, which offer distinct advantages especially in molecular electronics. The ease of tuning chemical structures and hence molecular properties can be appreciated from the following examples.

A simple phenol can be derivatized to a bioactive flavone to be used as a drug, or calixarene derivatives that form cage structures of different geometries and are excellent hosts for application in separation science. Indeed some of these molecules are crucial in sequestering Cs⁺-ions from the high level nuclear wastes. To cite another example, condensation of a pyrrole core with carbonyl compounds can furnish the bi-pyrroles (laser dyes and optical materials), calix-pyrroles (anions-specific ligands) or porphyrins/phthalocyanins (energy conversion and memory materials) (Fig. 2).

The idea of creating molecules with tailorable functions has fascinated chemists tremendously and the so called ‘functional or talkative molecules’ have become the buzzword in design and development of novel materials. Considering the large gamut of atomic energy research activities, the requirement of a diverse array of organic materials need not be overemphasized. Especially the success of the programmes with regard to back-end fuel reprocessing, development of advance technologies and health promotion hinges on the availability of a wide range of molecules with different attributes. Organic materials, useful to recover valuables from HLW as well as for its safe management, are crucial in the back end of the nuclear fuel cycle. On the other hand, photo- and electro-active organic molecules / assemblies are in great demand in various nuclear and non-nuclear applications such as tunable dye lasers and molecular electronics. Likewise,
development of new redox compounds is essential for harnessing the medical benefits of radiation technology as well as formulating new drugs against various kinds of pathogenesis, caused by radiation exposure and other factors related to stress, pollution and lifestyle changes. These are speciality materials, generally required in low volumes (except the solvents), but are of high value and purity, and often commercially unavailable. Hence development of their indigenous synthesis is essential.

Unfortunately, even at the height of maturity of organic synthesis, production, processing, and use of chemicals in modern society has been accompanied by global-scale environmental pollution, natural resource depletion, and adverse health impact. The depletion of the stratospheric ozone layer by chlorofluorocarbon chemicals (CFCs), bioaccumulation of several organic pesticides / toxicants in the food chain etc., demonstrate the need for more comprehensive consideration of the potential impact of chemical use in society. Many of these problems can be substantially reduced by innovative design of synthetic protocols that have high atom efficiency, are carried out with recyclable / biodegradable catalysts in environmentally-benign media using minimum energy, and produce the targeted materials preferably from renewable sources. The modern concept is innovation of green chemistry that produces what you want and no waste.

**Research & development of functional materials of societal relevance**

From the beginning of my research career, I have tried to focus on developing organic materials of societal relevance, including those required in various departmental programmes. Understandably the programme of such a wide dimension can be sustainable only by effective molecular design, creating molecular libraries, and evaluation of the targeted function. The conventional approach of synthesizing single compounds and screening would be inadequate to realize the objectives. Instead, availability of a large number of organic compounds, their screening and fine tuning for the designated activity by suitable modifications of the lead molecules would be essential. One of the major challenges associated with these, is that the molecules possess different complex structural motifs, and are often stereogenic. A large section of organic molecules are chiral, and their functional property is governed by the stereochemistry. Thus, a wrong stereomer of a target compound is a waste. Accordingly, development of asymmetric protocols is one of the major goals in organic chemistry research. Keeping in view of developing green synthesis, I have focused my research on (i) biocatalysis, (ii) asymmetric synthesis, and (iii) use of benign solvents (room temperature ionic liquids/H$_2$O) and/ or energy efficient techniques (microwave irradiation), to realize the goals, as are highlighted below with only a few examples.

**Solvent engineering with biocatalysts**

Enzymes are biodegradable agents that can catalyze most of the organic reactions under ambient conditions with high selectivity and turnovers. Hence, these are best suited for developing efficient green protocols for organic transformations with minimum side products and wastes. However, contrary to the conventional wisdom of enzymatic reactions in water medium, we have shown the feasibility of using enzymes even in organic media and even controlling the reaction course by subtle changes in the polarity / hydrophobicity of the reaction media. Such a strategy, known as ‘solvent engineering’ is very efficient and economic, compared to the typical biotechnological protocols. The advantages of using organic media are: better solubility of the substrates / products, easy product isolation, no / less enzyme deactivation and inhibition, reuse of the enzyme without immobilization, high temperature reaction etc. Together, these factors help in downstream processing and better turnovers. However, most importantly, this technique offers the possibility of designing new reactions as well as modulation of enantioselectivity and substrate-specificity. To cite some examples, enantio-selective esterification of (±)-3-hydroxybutyric acid (3-HBA) was
carried out at room temperature in toluene medium using *Candida rugosa* lipase (CRL) as the catalyst, and the enantioselectivity could be inverted by changing the chain length of the nucleophilic alcohol from *n*-butanol to *n*-hexanol. Likewise, the difficult task of entropically disfavourable macrolactonization can also be achieved enantioselectively, via a lipase catalyzed intramolecular trans-esterification of suitable α,ω-hydroxysters, in an organic solvent. Conventionally, the reaction requires high dilution conditions and expensive reagents to activate the reacting groups, but still produce the racemic macrolide. Another lipase-catalyzed lactonization was also innovatively devised, to control the stereochemistry of three stereogenic centres in one step. These are schematically depicted in Fig. 3.

**New asymmetric synthesis strategies**

Majority of the natural and non-natural chiral organic molecules owe their chirality to the presence of a methyl branching and/or carbinol function. Further, the stereogenic carbinol moiety can be transformed to various other complex structural motifs. Hence, we have introduced various new protocols for the syntheses of chiral methyl-branched and/or carbinol synthons (Fig. 4) and used them for the syntheses of a large array of complex organic compounds of departmental and societal relevance. For example, the asymmetric syntheses of methyl-branched chiron were developed starting from the naturally available terpene, pulegone, as well as a diosgenin-derived waste material, available in huge quantities from the pharmaceutical industries. The key step for the synthetic routes was a Pb(OAc)₄-catalyzed decarboxylation, to furnish the alkene in the presence of Cu(OAc)₂ as an co-oxidant or the alkane, in its absence.

With regard to creating the chiral carbinol moiety and its derivative, both biocatalytic as well as various substrate controlled strategies were developed. Thus, the lipase-catalyzed esterification, trans-esterification, alcoholysis and
aminolysis as well as oxynitrilase-mediated hydrocyanation were developed, to furnish a wide range of chiral carbinols. On the other hand, using a sugar-derived chiral aldehyde as the template, an efficient enantioselective synthesis of tertiary alcohols was also achieved, via sequential addition of two Grignard reagents to suitable intermediates.

New media & techniques for efficient synthesis

Development of energy-efficient process, especially in safe reaction media is a major challenge in organic synthesis. We used [bmim][Br] as a new Room Temperature Ionic Liquid (RTIL) for asymmetric Barbier-type allylation reactions of γ-substituted allylic halides with a chiral aldehyde. This strategy enabled us to address the issue of chirality in an environmentally-benign solvent to furnish chirons, possessing both the above mentioned stereogenic centres. Another important aspect of the protocol was the metal-mediated stereoselectivity tuning. For example, while the Ga-mediated crotylation was found to produce the anti, anti-product with a diastereomeric ratio (dr) of 3:5:92, the Bi-mediated reaction altered the diastereoselectivity in favour of the anti, syn-product with a dr of 10:83:7. The reactions failed in other media, establishing the role of the RTIL in metal activation.

Microwave-Assisted Organic Synthesis (MAOS) is a useful method for fast reaction, with better control on the product distribution. We have employed the MAOS route for regio-selective alkylation of the calix[4]arenes, and used some of the products to synthesize several calix[4]-crown compounds as potential metal-ions selective host molecules.

Talkative molecules of societal relevance

Materials for the back-end nuclear fuel cycle

Separation science plays a pivotal role at different stages of the nuclear fuel cycle, and techniques such as solvent extraction and ion-exchange are the backbones of this science. This warrants the development of novel metal ions-selective extractants and / or membranes that can be used to recover valuables from HLW as well as confine other toxic and hazardous radioactive metal ions of HLW, for their safe management / disposal. Besides showing high metal ions-selectivity, the materials need to be stable under highly acidic, oxidizing and radiolytic conditions. The low degradability, high selectivity and coordinating ability of the solvents would reduce their inventory, while good stripping parameters would increase their reusability. In my career, I have developed the syntheses of CMPO and a pentaalkyl malondiamide as actinide(III)-specific solvents and the process was transferred to the Heavy Water Board. More recently, one of the calix-crown derivatives, was found to be an efficient solvent for selective removal of the Cs⁺-ions from HLW. We also demonstrated that in the presence of a suitable plasticizer and additive, the same calix-crown derivative can be used as an Ion Selective Electrode (ISE) for the Cs⁺-ions with a linear response at concentration range (10⁻⁷ to 10⁻² M) over the pH range of 4 to 11, and a detection limit of 8.48 × 10⁻⁸ M for the Cs⁺ ions (Fig. 5). The lifetime of
the electrode was ~10-12 months, which is the highest for any membrane based Cs-ISE developed so far.

Regarding molecular electronics, we developed molecular diodes based on donor-acceptor bilayers consisting of fullerene (C-60) and a tetraphenyl porphyrin derivative (TFPP), grafted on Si. The diodes were synthesized in by electrografting of a ~ 3.5 nm C-60 layer on H-terminated Si, followed by self-assembly of TFPP layers on the C-60 layer. The current rectification ratio (defined as: $RR = \left| \frac{I_{-1.8V}}{I_{+1.8V}} \right|$) for the diode was ~1500, which could be rationalized using ab initio molecular-orbital theoretical calculations. Using a novel concept, a Si-wafer containing a bilayer of two different PM molecules was prepared, by first electro-grafting of one PM-moiety (containing a terminal olefin group) on Si-surface, followed by supramolecular attachment of the other PM molecule. The resultant molecular aggregate showed Negative Differential Resistance (NDR) property. This is the first report of a PM-based NDR system and is promising for its potential application in memory devices (Fig. 7).

**Bio-materials for therapy**

Oxidative Stress (OS), caused by intra-cellular and external stress (including radiation exposure) has been implicated for various pathogenic conditions such as gastric ulceration, cardio-vascular disease, cancer etc. At the same time, targeted creation of stress using chemicals and ionizing / non-ionizing radiation are the only non-invasive option for cancer management. Given that the commercial synthetic drugs against these diseases are often toxic and expensive, we have explored various dietary factors as potential alternatives. To this end, three phenolics, isolated from the indigenous edible plants, *Piper betle* (pan) and *Myristica malabarica* (a spice) showed excellent anti-ulcer activities, while the pan-phenolic can be used against microbial skin infection. Contrary to the popular belief of gastro-toxicity of tea, our group has established the gastric ulcer healing property of various tea (green, black and
The health benefit of the kombucha tea could be ascertained due to the reduction of its caffeine level during fermentation.

The clinical use of the grape-derived hydroxystilbene (HST), resveratrol against various oxidative stress-related diseases, is restricted due to its gastro-toxicity. Hence, we synthesized several of its analogues, and established better potency of one of these congeners as a chemopreventive agent against several human cancer cell lines than resveratrol. The HST also could heal indomethacin-mediated gastric ulceration in mice. In another approach, we have established the photo-dynamic action of a combination of coralyne, an alkaloid and UV-A light (CUVA) against lung and skin cancer cell lines, irrespective of their p53 status. The efficacy of CUVA was superior to that of psoralene and UV-A combination, that is used clinically for photo-dynamic therapy (Fig. 8).

**Conclusions**

Over the years, I have humbly tried to combine basic research in organic synthesis, chemical biology and supramolecular chemistry, to make molecules, that can talk with their environments and perform specific functions for which they have been designed. The synthetic strategies were formulated following the principles of green chemistry, wherein biocatalysts, ionic liquids, metallo-organics and micro-wave conditions were used, to develop comparatively clean protocols. The targeted deliverables viz. solvents and chemo-sensors, electronic materials, laser dyes and redox drugs were designed carefully for applications in various programmes (energy, separation science, health and advanced technology) of societal benefits. All these, perhaps, emphasize the utility of organic chemistry research, in building tomorrow’s new world.