Dynamic Equilibrium: Is it an Important Concept in Chemical Biology and Drug Discovery?

Dhevalapally B. Ramachary[1] and Indresh Kumar[2]*

Abstract | Dynamic equilibrium is one of the important aspects of study, because its existence can be observed in the infinitesimally small cells within the body to the huge adversities of the nature. In organic chemistry, a single compound having dynamic equilibrium states gives a driving force to create diversity-oriented synthesis of library of products from the same single compound. In chemical biology, the protein/nucleic acids are in constant equilibrium with their changing conformations/folds, which is responsible for the biological activity with a very small level of energy barrier for the conformational/folds inter-conversion. In medicinal/pharmaceutical chemistry, a drug having dynamic equilibrium states plays an important role in the delivery of the drug on the active site across the cell membrane in a dynamic fashion and also acts as self-protection for the active drug molecule. Herein, we present a brief account on the existence and application of dynamic equilibrium states in chemical and biological chemistry as well as its existence in other inorganic complexes. Information regarding the existence of exact 1:1 ratio of the two dynamic equilibrium forms of chemical entities in the chemical reaction from organic, inorganic and biological perspectives have been discussed. We believe that this review is the first of its kind to discuss the importance of dynamic equilibrium states in chemical and biological systems, addressing the question to the scientific community as and the importance of the concept for further study.

[1]*School of Chemistry, University of Hyderabad, Hyderabad 500 046, India*
**ramsc@uohyd.ernet.in*

[2]*School of Biology & Chemistry, College of Sciences, Shri Mata Vaishno Devi University, Katra 182 320 (J&K), India*

1. Introduction

One important question that arises when highly functionalized molecules are used as biologically active products or drugs is that, what is the secondary or pro-active structure before the action on the active site of the cells? (Or) whether the given primary structure is really the actual acting drug? Some drugs like the warfarin (anticoagulant) drug, which exists in two forms, is active in the open form but also exists in the cyclic form. Is it really true that these types of drug molecules exist in more than one form *in vivo*? If only one form, like the open form, is the active form, then why does it exist in the cyclic form or *vice-versa*? It is an important task to understand the role of secondary structure of the drug molecules, which is in equilibrium with the *parent* one. We are looking into this important yet still unexplored process in the drug action, along with some of our recent results in this direction, which allows us to realize the importance of the dynamic equilibrium states in biology and drug discovery. Herein, we are explaining the importance of the new concept 'dynamic equilibrium states' to

understand the dynamic behaviour of chemical species existing in more than one form. In this context, we are taking together some of the recent drug molecules and biologically active organic/inorganic species present in dynamic equilibrium for the discussion.

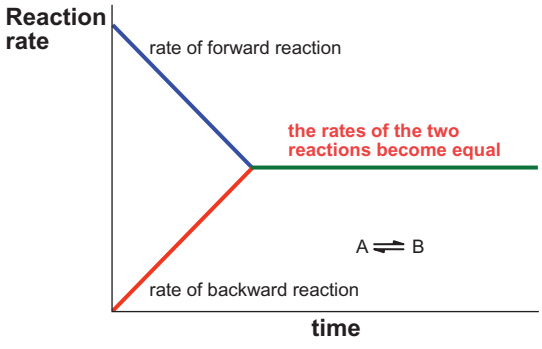
In general understanding of the dynamic equilibrium from the static point of view, a system is in a steady state if the forward reaction and the backward reaction occur at the same rate.[1] A saturated solution is considered to be in dynamic equilibrium because there is solid to liquid phase change occurring in opposite directions at the same rate, such that there is no net observable change. In a reversible reaction, chemical equilibrium is reached when the rates of forward and the backward reactions are equal and the concentrations of the reactants and products no longer change. In kinetic equilibrium, the equilibrium exists towards the kinetically stable product whereas the equilibrium exits towards the thermally stable product in thermodynamic equilibrium. In dynamic equilibrium, concentrations of the reactants and the products remain constant.

Present topic of "dynamic equilibrium" is different compared to the well defined dynamic combinatorial chemistry (DCC), because DCC depends on the library of different starting materials in equilibrium, whereas dynamic equilibrium deals with single compound in many equilibrium states.[1b] In DCC, the inter-conversion of library members into one another is through a reversible process that may be involve covalent or non-covalent interactions. The existence of some of the basic problems of the dynamic chemical equilibrium, and the fractional life-time of the participating species and the relaxation time of the system have been explained earlier by Michael Szwarc *et al.*[2]

Dynamic combinatorial chemistry (DCC): It is defined as combinatorial chemistry under thermodynamic control. In a dynamic combinatorial library, all constituents are in equilibrium. The inter-conversion of library members into one another is through a reversible process that can involve covalent or non-covalent interactions.

Multi-catalysis cascade (MCC): A multi-catalysis cascade reaction is a consecutive series of intermolecular/intramolecular organic reactions which often proceed via highly reactive intermediates through catalyzed by many different catalysts in one-pot.

Figure 1: Graphical representation of the dynamic equilibrium (A ⇌ B).



From a chemical point of view, when the rates of the forward and backward reactions are equal, the system is in dynamic equilibrium, because individual molecules are in action continuously as it is shown in Figure 1. It is important to study the existence of dynamic equilibrium in chemical and biological reactions as there are prominent applications in the biological systems. The role of the kinetic-dynamic interaction in the evolution of the drugs has been explained earlier by Campbell *et al.*[3] Recently, a review article on the dynamic personalities of the proteins as described by D. Kern *et al.*[4] provides an insight into the dynamic behaviour of the proteins. However, to our surprise we could not come across any concrete discussion regarding the application of dynamic equilibrium states at the interface of chemistry, biology and drug discovery. With our recent study in this direction, we present a brief discussion on the dynamic equilibrium and its existence at the interface of chemistry and biology.

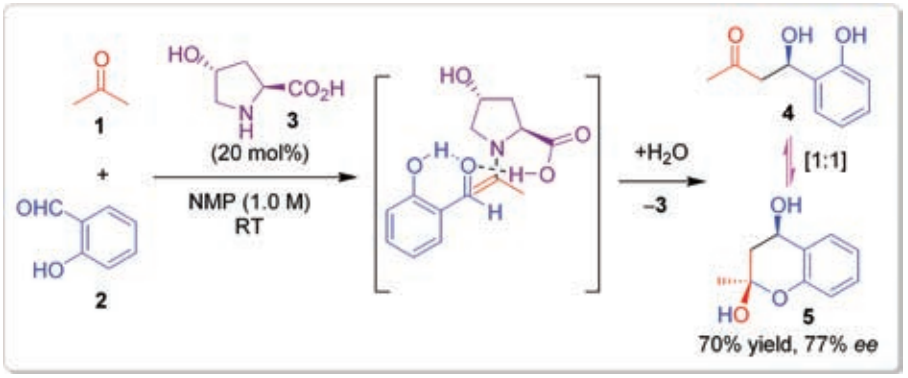
2. Observation of Dynamic Equilibrium States During the Development of Asymmetric BLA and BMA Reactions

The ever increasing demand for environmentally and economically friendly synthetic processes promote the development of sequential one-pot combination of multi-catalysis cascade (MCC) and multi-component reactions (MCR) to provide the desired products in the most efficient ways.[5] Thus, the sequential one-pot combination of MCC/MCR's is an emerging area in organic chemistry that ensures reduction in cost of the process and makes it more economic, which subsequently fulfils the requirement for green chemistry. Over the last few years, we have showed our interest in developing amine/amino acid-mediated MCC reactions from multi-component and multi-catalysts for the generation of several highly functionalized scaffolds, having biological activity directly or indirectly via C-C, C-H, C-O, and C-N bond formation in one-pot.[6] Recently we studied *trans*-4-OH-L-proline **3** as organocatalyst for the Barbas–List aldol (BLA) reaction of several *o*-hydroxy-benzaldehydes **2** with acetone **1** for direct catalytic asymmetric synthesis of functionalized chromans, an important class of heterocycles that display a very large spectrum of biological activities and are widely used as drug intermediates and ingredients in pharmaceuticals.[7] During the course of this study, we observed an interesting phenomenon of *rapid dynamic equilibrium* between the expected 4-hydroxy-4-(2-hydroxyphenyl)-butan-2-one **4** as the aldol product and its corresponding cyclic

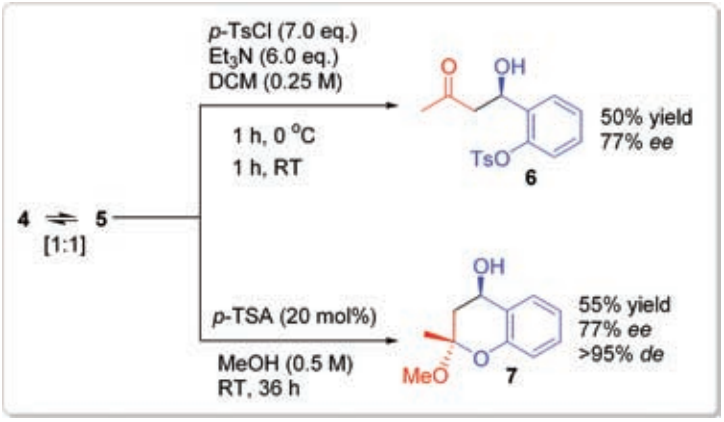
lactol, 2-methylchroman-2,4-diol **5** as shown in Scheme 1. Under normal reaction conditions, the aldol product **4** and the corresponding lactol **5** existed in exact 1:1 ratio through a fast dynamic equilibrium, which was further confirmed by NMR and HPLC analyses. For further understanding and application of this dynamic equilibrium states, the 1:1 mixture of aldol **4** and lactol **5** on treatment with *p*-TsCl and Et_3N in one-pot operation furnished selectively the tosylated product (±) **6** in 50% yield with 77% *ee* as shown in Scheme 2. In a similar manner, treatment of BLA reaction products (**4**↔**5**) with *p*-TSA in MeOH at 25°C in one-pot furnished selectively the *trans*-2-methoxy-2-methylchroman-4-ol (+)-**7** in 55% yield with 77% *ee* and >95% *de* as shown in Scheme 2. This is one of the best demonstrations for the complete trapping of both the open and the cyclic forms of a dynamic equilibrium in individual single forms with good yields as shown in Scheme 2.

Recently, we developed the 9-amino-9-deoxyepiquinine **9**/Ph_2CHCO_2H-catalyzed asymmetric Barbas-Michael/acetalization (BMA) reaction of acetone **1** with 2-(2-nitrovinyl)-phenols **8** under ambient conditions to furnish the functionalized chiral chromans as shown in Scheme 3. During our asymmetric investigation on the BMA reaction, we observed the concept of fast dynamic equilibrium between 4-(2-hydroxyphenyl)-5-nitropentan-2-one **10** and 2-hydroxy-2-methyl-4-nitromethylchromans **11/12** in 1:1:1 ratio, the products of the BMA reaction of **8** with **1** as shown in Scheme 3.[8] Rapid dynamic equilibrium between the BMA open

Scheme 1: Observation of fast dynamic equilibrium during the development of asymmetric BLA reaction.



Scheme 2: Application of the dynamic equilibrium states in the functionalized chromans synthesis.



product **10** and the lactols **11/12** in solution was confirmed by NMR and HPLC analyses, and finally ascertained by acetalization with methanol. For clear understanding and utilization of the fast dynamic equilibrium between **10** and **11/12**, we transformed the crude 1:1:1 mixture of **10/11/12** into two easily separable cyclic BMA products *cis*-**13** and *trans*-**14** in 1:1 ratio with 92% yield and 82% *ee via p*-TSA-catalyzed acetalization reaction in MeOH at 25°C for 2 h. However, treatment of 1:1:1 mixture of **10/11/12** with 6 equiv. of basic methylenetriphenylphosphorane in benzene (0.1 M) at 25°C for 3 h furnished the open product, phenol (−)-**15** in 95% yield with 82% ee as shown in Scheme 3. In this project, we have shown the application of fast dynamic equilibrium [chiral δ-hydroxyketone↔lactol products **10/11/12**] as basic platform for the high-yielding asymmetric synthesis of highly functionalized pharmaceutically important chiral phenols and chroman molecules from single component.[8]

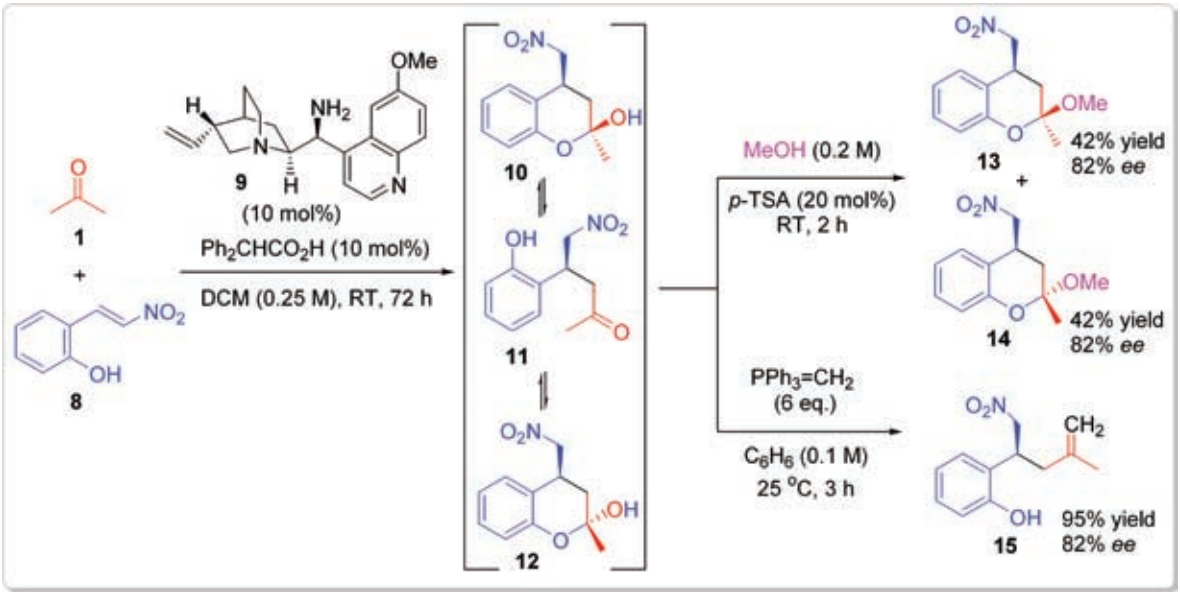
3. Observation of Fast Dynamic Equilibrium States in Warfarin Drug

Warfarin (coumadin) is one of the most widely used *anticoagulant drug* that has been prescribed as a racemate for more than 40 years and it is well known that the *anticoagulant* activity of the (*S*) enantiomer is about 5–8 times higher than that of the (*R*) enantiomer and also having different half-lives in human body.[9] Warfarin exists as two forms, open (δ-hydroxy-ketone) and cyclic (hemiketal) forms in fast dynamic equilibrium; however the conspiracy regarding the bioactive forms of warfarin being open or hemiketal remains unresolved, but scientists suggest that the hemiketal must hydrolyze to 4-hydroxy form for warfarin to be active. The structure of warfarin in solution was studied earlier and found to in a *dynamic equilibrium* between the open **19** and the diastereomeric cyclic forms **20**.[10a] In 2003, Jorgensen and co-workers[10b] published the first organocatalytic asymmetric synthesis of warfarin through the Michael addition of 4-hydroxycoumarin **16** to benzylideneacetone **17**, and also observed the existence of the rapid dynamic equilibrium between the open **19** and the cyclic ketal **20** form of warfarin as shown in Scheme 4. The structure of the cyclic ketal form **20** of warfarin was further confirmed by the ^{1}H-NMR followed by the single crystal X-ray structure of the ketal **20** as shown in Figure 2. *This preliminary data suggests that the secondary structure **20**, having dynamic equilibrium with the primary structure **19**, resembles a pro-drug or self-protection before the in situ hydrolysis, and further studies are needed to prove the importance of this dynamic equilibrium states on drug action*. We strongly believe that probing the warfarin drug action through controlling/locking dynamic equilibrium states via designed molecules

Anticoagulant: Any agent used to prevent the formation of blood clots.

Pro-drug: A precursor (forerunner) of a drug. A pro-drug must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent.

Scheme 3: Observation of fast dynamic equilibrium states during the development of asymmetric BMA reaction.



Scheme 4: Dynamic equilibrium has been observed during the organocatalytic asymmetric synthesis of warfarin.

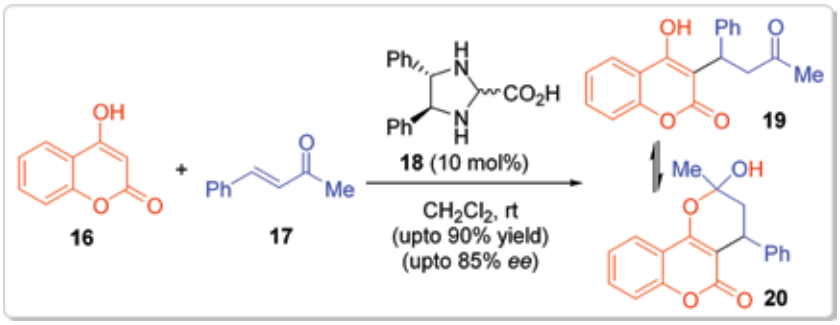
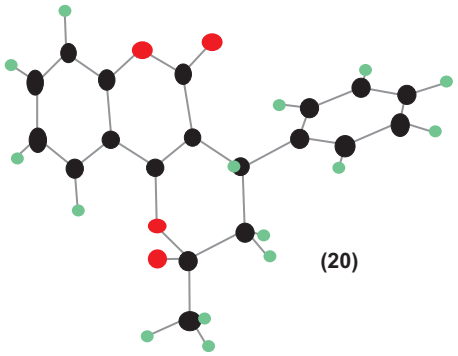


Figure 2: Cyclic ketal form of warfarin [grey = carbon, red = oxygen, aquamarine = hydrogen].



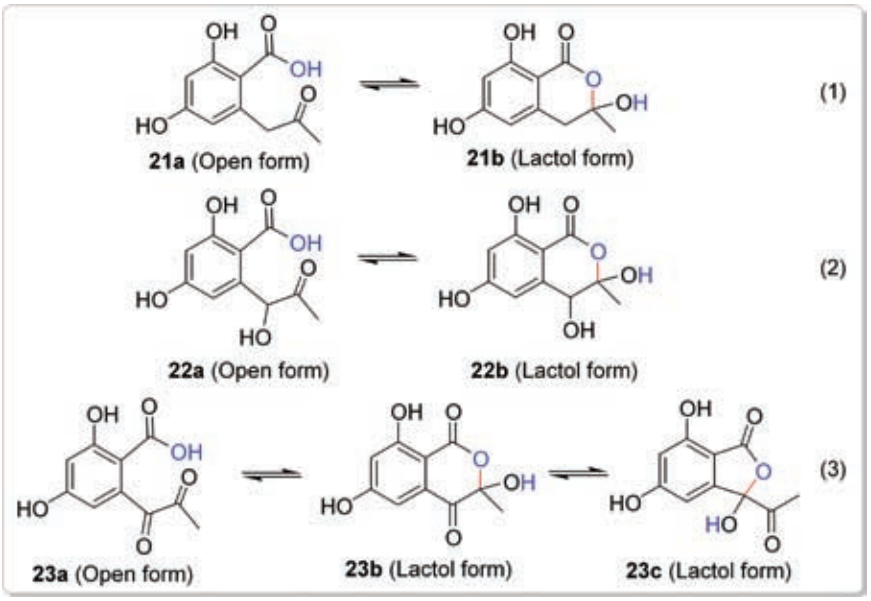
may give important information to support the statement like "*biological consequences of molecules unable to cooperate without equilibrium states*".

4. Observation of Dynamic Equilibrium States in Fungal Metabolites

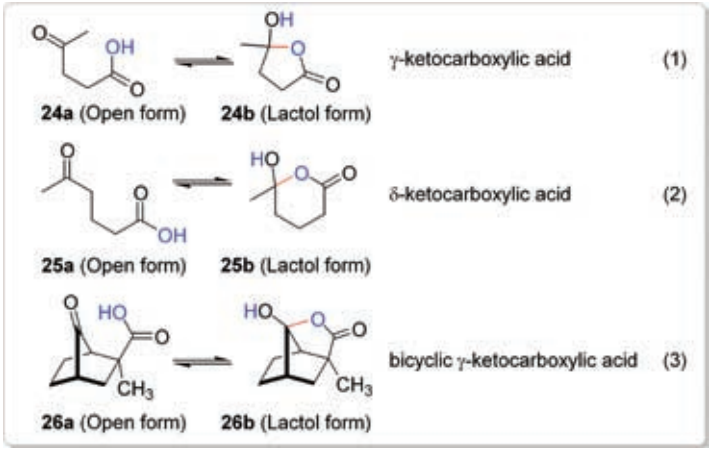
Dynamic equilibrium states were observed in fungal metabolites also as shown in Scheme 5. B. Anderson observed a consistent production of fungal secondary metabolites from *Penicillium brevicompactum*, which he further purified and identified as the raistrick phenols [2,4-dihydroxy-6-(2-oxopropyl)benzoic acid **21**, 2,4-dihydroxy-6-(1-hydroxy-2-oxopropyl)benzoic acid **22**, and 2,4-dihydroxy-6-(1,2-dioxopropyl)benzoic acid **23**] as presented in Scheme 5.[11a] These compounds are known to exist separately as rapid equilibrium mixture in aqueous solution. It was earlier reported by Grove and Pople that both the ketone **21a** and the ketol **22a** exist as a solid in their lactol forms **21b** and **22b,** and that the diketone **23a** exists as a five-membered ring lactol **23c** as shown in Scheme 5.[11b] It was also mentioned that the diketone **23a** in organic solvent is present as the open chain tautomer, and that the ketone **21a,** in both the solid state and in solution, exists in the lactol form. Further studies on the application/existence of rapid dynamic equilibrium of fungal secondary metabolites **21–23** may furnish answers to the chemotaxonomic characterization of the fungus, and certainly will highlight the importance of *equilibrium states* in fungus.

The existence of γ-keto carboxylic acid **24** and δ-keto carboxylic acid **25** in equilibrium with their corresponding cyclic lactol-form through the ring-chain tautomerization have been well discussed in literature.[12a] In the case of bicyclic γ-keto carboxylic acid, the equilibrium between the open and cyclic lactol-form is not only through ring tautomerization but also driven by relief of the angular hybridization strain of the bridged carbon from sp^2 to sp^3 hybridization. A recent report in this direction by Lalancettte and co-workers showed that the racemic 2-*exo*-carboxy-2-*endo*-methyl-7-oxobicyclo[2.2.1]-heptane **26a** exists preferentially, even in solution, as the ring closed tricyclic lactol **26b** as shown in Scheme 6.[12b] The 7-oxobicylco[2.2.1] heptanes **26a** have internal carbonyl angles at C-7 of 97–98°,[12c] and are thus strained by some 22–23° relative to the natural carbonyl angle. Therefore, the cyclic lactol form **26b** provides the relief of the angular hybridization strain of the bridged carbon from sp^2 to sp^3 hybridization. The existence of the equilibrium between the open and cyclic lactol forms was further supported by the single crystal X-ray structure of **26b**.[12b] The analogous molecules in the biological systems will give interesting properties due to the equilibrium states, which need to be studied further.

Scheme 5: The fungal secondary metabolite like raistrick phenols [2,4-dihydroxy-6-(2-oxopropyl)benzoic acid **21**, (2,4-dihydroxy-6-(1-hydroxy-2-oxopropyl)benzoic acid **22**, (2,4-dihydroxy-6-(1,2-dioxopropyl)benzoic acid **23**] existed in dynamic equilibrium in aqueous solution.



Scheme 6: Existence of *dynamic equilibrium* in δ- and γ-ketocarboxylic acids and driven by relief of angular hybridization strain in bicyclic γ-ketocarboxylic acid.

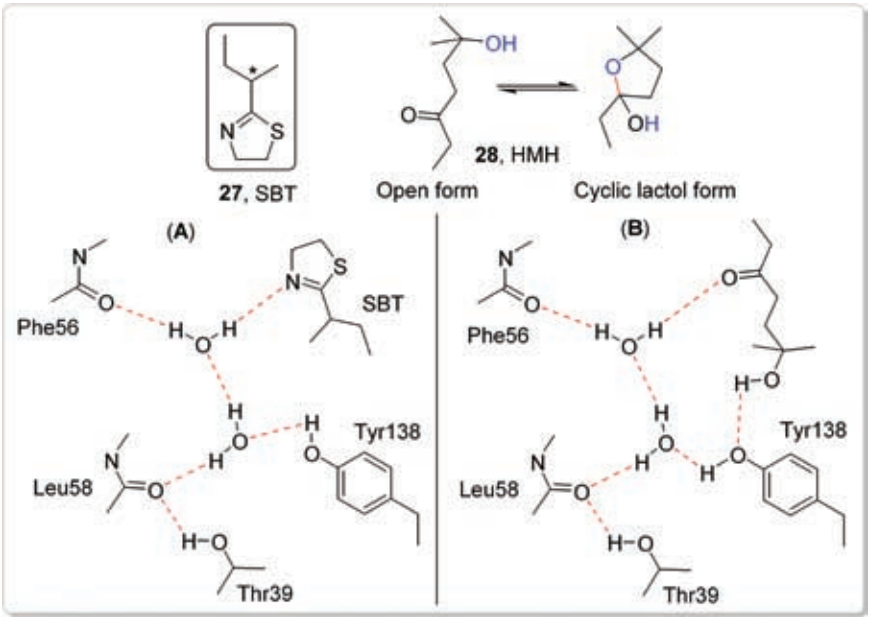


5. Observation of Dynamic Equilibrium States in Mouse Pheromones

In 2001, David E. Timm *et al.* reported that the mouse major urinary proteins (MUPs) bind a variety of volatile pheromones and also function as carriers of volatile pheromones that affect aspects of mouse physiology and behaviour.[13a] Although initially accepted that MUPs act as a binding protein for 2-*sec*-butyl-4,5-dihydrothiazole (SBT) **27**, later on it has been observed that the MUPs are also capable of binding additional pheromones like γ-hydroxy ketone of 6-hydroxy-6-methyl-3-heptanone (HMH) **28**. Interestingly, HMH exists in *dynamic equilibrium* between the open chain and the lactol form; it is the most abundant volatile constituent of male mouse urine and induces puberty acceleration in female mice.[13b] In 2001, David Timm and co-workers further supported this result by the crystal structure study at high resolution and showed how different classes of pheromones can be accommodated with the MUPs. The interaction of MUP-I with HMH was carried out in the open form that is suitable for binding through the hydrogen-bonding as shown in Scheme 7.[13c]

The MUP-I/SBT complex comprises a five-membered ring structure, but it was surprising to find that the HMH **28** binds as the open hydroxyl-ketone structure with the ketone group nearer to the entrance to the active site and the dimethyl/hydroxy moiety located near the center of the β-barrel as shown in Scheme 7. Binding of the open structure would presumably stabilize the pheromone against dehydration to give cyclic vinyl ethers. These biologically inactive products of the furan ring tautomer were readily detected in the analyses of the urinary fractions showing puberty-accelerating activity. The open hydroxyl-ketone form will be less susceptible to dehydroxylation reaction. Therefore, this result provides support for the role of MUP-I

Scheme 7: Chemical structures for two synthetically derived pheromones (A) SBT (2-*sec*-butyl-4,5-dihydrothiazole) **27** and (B) HMH (6-hydroxy-6-methyl-3-heptanone) **28** and their interaction with the mouse major urinary protein (MUP-I).



in protecting the pheromones against the chemical decomposition and further studies are needed to prove the importance of dynamic equilibrium states in HMH to behave like a pheromone.

6. Observation of Dynamic Equilibrium in Quorum Sensing (QS) Signals of Autoinducer-2

Recently, Kim D. Janda *et al.* reported "dynamic equilibrium states" of (4*S*)-4,5-dihydroxy-2,3-pentanedione (*S*-DPD) to be a very important phenomenon in autoinducer-2 (AI-2) based quorum sensing (Scheme 8).[14] Bacteria have developed a cell-to-cell communication system, termed as quorum sensing (QS), which allows for the population-dependent coordination of their behaviour through the exchange of chemical signals. Quorum sensing is used by the bacteria as a means to rapidly coordinate gene expression patterns in response to environmental cues. AI-2 has been revealed as a universal signaling molecule in a variety of bacterial species, and is believed to be generated by the conversion of the ribose moiety of *S*-ribosylhomocysteine into (4*S*)-4,5-dihydroxy-2,3-pentanedione (*S*-DPD) **33** by the protein LuxS. Recent report shows that *Salmonella typhimurium* is it signalling process requires only (2*R*,4*S*)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuran (*R*-THMF) **35a**, a hydrated form of the precursor *R*-DHMF **34a**.[14a] The study from Kim Janda group presented that the furanosyl-carbonate shows positive effect on signalling through the formation of an orthocarbonate structure (2*S*,4*S*)-2-methyl-2,3,3,4-tetrahydroxytetrahydrofuran-carbonate (*S*-THMF-carbonate) **35b** as shown in Scheme 8.[14b] This study was further supported by the recent results from the same group about the designing and synthesis of several alkyl (R = alkyl) precursors of 4,5-dihydroxy-2,3-pentanedione **33**, which also exist in dynamic equilibrium states and show similar activity as the DPD-based analogues for modulation of AI-2 based QS as shown in Scheme 8. The synthetic precursor **33** is in dynamic equilibrium between *R*-DHMF and *S*-DHMF through open-ring tautomerisation, a very important phenomenon for QS singnals.[14c]

Recently, controlled experiments by Janda group on analogous DPD studies shed light on the interaction between the heterocyclic oxygen atom and the receptor proteins as well as the importance of the open form and dynamic equilibrium states of DPD as crucial requirements for the activation of AI-2 based QS signals.[14d]

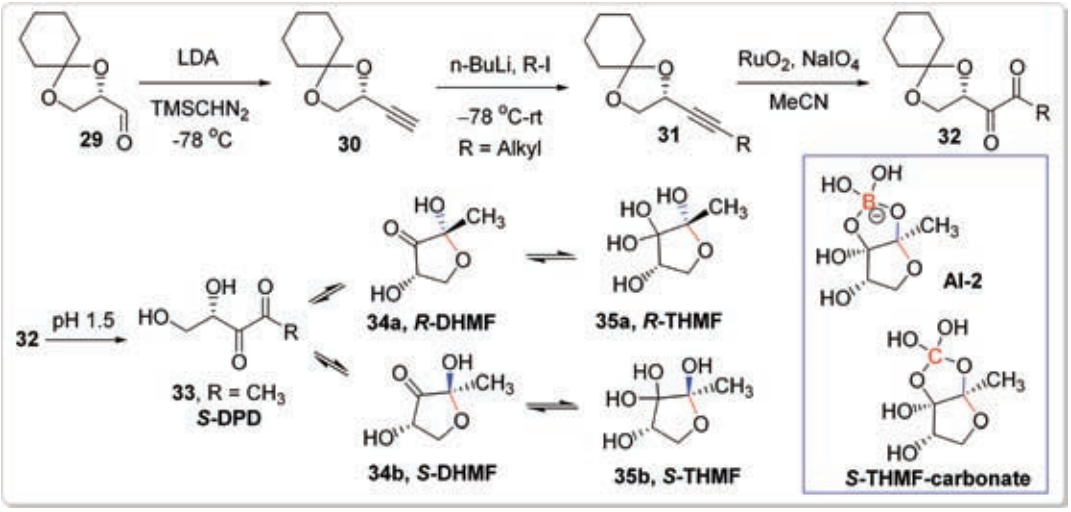
7. Observation of Dynamic Equilibrium in Steroids for Hormone Chemistry

The importance of dynamic equilibrium states was also observed in the function of steroids in

Quorum sensing (QS): Quorum sensing is a system of stimulus and response correlated to population density. Many species of bacteria use quorum sensing to coordinate gene expression according to the density of their local population.

Autoinducer-2 (AI-2): A furanosyl borate diester, is a member of a family of signaling molecules used in quorum sensing. AI-2 is unique in that it is one of only a few known biomolecules incorporating boron. First identified in the marine bacterium *Vibrio harveyi*, AI-2 is produced and recognized by many Gram-negative and Gram-positive bacteria.

Scheme 8: Observation of dynamic equilibrium in quorum sensing (QS) signals of autoinducer-2 (AI-2).



hormone chemistry as shown in Schemes 9 and 10. Aldosterone **36** is the naturally occurring sodium-retaining hormone of the adrenal cortex.[15] For years, it has been recognized that a very potent sodium-retaining substance is present in extracts of adrenal glands. Aldosterone **36** is synthesised in the adrenal zona glomerulosa and bound to specific mineralocorticoid receptors located in the cytosol of target epithelial cells. Recent studies have shown major therapeutic benefits of mineralocorticoid receptor antagonism in cardiac failure, which emphasise the importance of aldosterone in causing adverse cardiovascular pathophysiological effects. Additional evidence demonstrates that aldosterone levels predict development of high blood pressure in normotensive subjects, while it is now clear that increased aldosterone action contributes to hypertension and cardiovascular damage in approximately 10% of patients with established hypertension. All these properties of aldosterone **36** are due to the existence of dynamic equilibrium states between the two-three tautomeric forms of hemiacetal **36b/c** and aldehyde **36a** as shown in Scheme 9. This dynamic structure gave aldosterone with unique properties, both chemically and biologically, and this was clear when its metabolism was studied.[15]

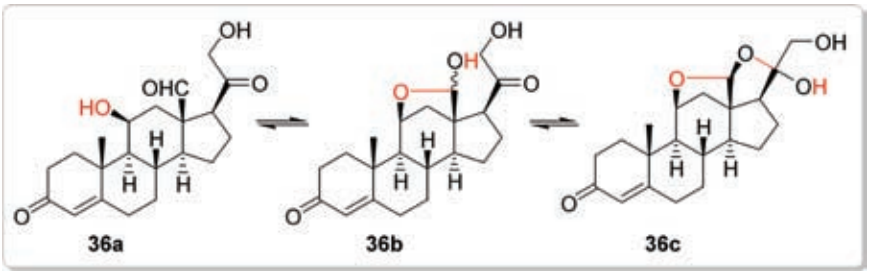
The equilibrium driven 18-hydroxyl group in the hemiacetal structure is available for metabolism in humans as in the formation of aldosterone 18-glucuronide. Interestingly, the 11–18 hemiacetal formation actually self-protects the 11β-hydroxyl group in aldosterone from metabolism. According to the current theories, aldosterone remains the dominant mineralocorticoid because other potentially competing 11β-hydroxy steroids binding to the same receptor are converted to the corresponding inactive 11-oxo steroids, such as cortisone, by an 11β-dehydrogenase. However, the 11β-hydroxyl group of aldosterone is self-protected as the hemiacetal structure. Therefore, the 18-hydroxyl of aldosterone is available for metabolism but the 11β-hydroxyl group is self-protected only due to the dynamic equilibrium.[15]

Similarly, the formation of the cyclic nitrone **38** from the oxime of aldosterone 21-acetate **37a** can be explained through the dynamic equilibrium of two consecutive ring open-chain tautomerization with **37a** ↔ **37b** as shown in Scheme 10.[15b]

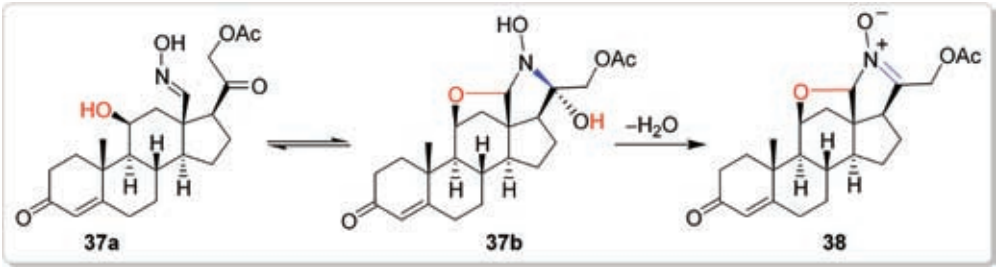
8. Observation of Dynamic Equilibrium in Potent Inhibitors of InhA and MabA Reductases

Tuberculosis (TB), a leading cause of bacterial infectious disease mortality, is observed with increasing incidence in both developing and industrialized countries. Isoniazid (INH) **39** is an anti-tuberculosis prodrug that is activated by mammalian *lactoperoxidase* and *Mycobacterium tuberculosis* catalase peroxidase (*Mt*CP), and is still the drug most widely and efficiently used in antituberculosis regimens. Recently, a study by Bernadou and co-workers showed that the closest model of the INH–NADP adduct **41,** is existing as ring (major) **41b** and chain (minor) **41a** tautomers in dynamic equilibrium.[16a] The ratio of the tautomeric forms involved in the equilibrium of this system is also influenced by the polarity of

Scheme 9: Aldosterone exits in dynamic equilibrium between three forms (open **36a** and two lactol **36b/c**).



Scheme 10: Observation of consecutive ring-chain tautomerization via dynamic equilibrium states.



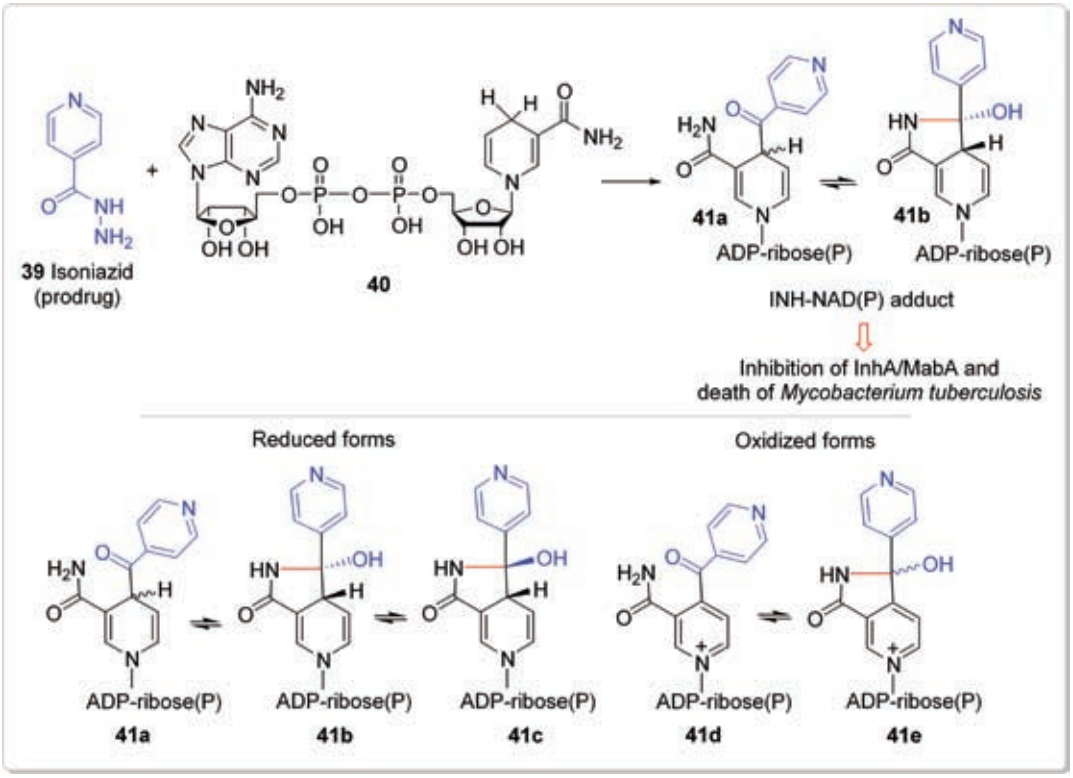
the solvent with a shift towards the ring tautomer when the polarity of the solvent is increased. Complementary computational studies were performed by using quantum chemical calculations (B3 LYP/6–31G) and frontier molecular orbital analyses, which allowed the understanding of key structural factors involved in the ring–chain tautomeric equilibrium. It was concluded that the design of simplified analogues of these biologically relevant species should either favour compounds with a chain structure or consider derivatives in a cyclized form as prodrugs that are able to release the bioactive chain molecule *in vivo* through the ring–chain tautomeric equilibrium states as shown in Scheme 11.

Recently, Singh and co-workers carried out the enzyme assays involving INH, and the crystal structure of the complex of bovine lactoperoxidase (LPO) with INH to shed light on the binding properties by highlighting the dynamic equilibrium states. The INH activation as well as the mode of diffusion and interactions together with the structural and functional comparisons with *Mycobacterium tuberculosis catalase peroxidase* (*Mt*CP) was studied in detail. The results indicate that the size and chemical nature of the binding sites in peroxidases on the distal heme side allow the substrates of the size of INH to be able to orient in more than one way. Therefore, the substrates, such as INH, can generate two-three forms through dynamic equilibrium in the binding site of peroxidases.[16b]

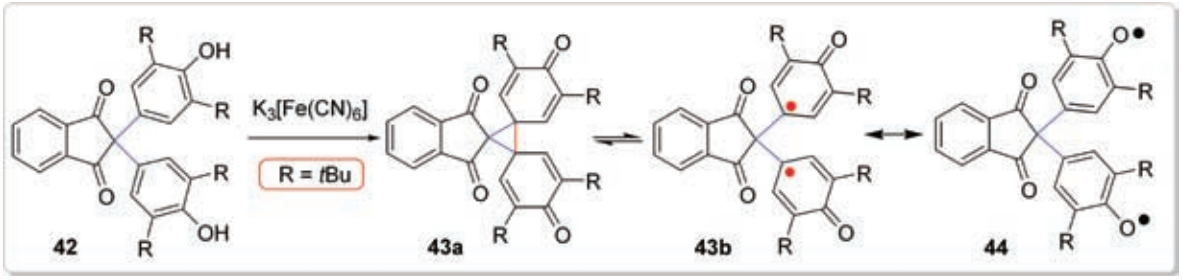
9. Observation of Dynamic Equilibrium between Cyclopropane Ring and Biradical Species

Formation of radicals and their stability through equilibrium in biological species is one of the interesting concepts, especially in biological ageing. Recently, Kobayashi and co-workers reported the oxidation of 2,2-di(3,5-di-*t*-butyl-4-hydroxyphenyl)indan-1,3-dione **42** by potassium hexacyanoferrate(III) to yield trispiro-conjugated cyclopropane compound **43a** via bond formation between the ipso-carbons.[17] Further, they found existence of fast *dynamic equilibrium* behaviour of the cyclopropane ring in solution through ring opening and closing between **43a** and the biradical species **43b/44** as shown in Scheme 12. These results were further confirmed by the NMR-study at different temperatures and also by the dissociation of the C-C bond, which was as long

Scheme 11: The observation of dynamic equilibrium states in potent inhibitors of InhA and MabA reductases.



Scheme 12: Dynamic equilibrium exists between the cyclopropane ring **43a** and the biradical species **43b**.



as 1.594 Å, as confirmed by the X-ray crystal analysis.

10. Observation of Dynamic Equilibrium States in the Degenerate Prototropy

Whether in biology or organic chemistry, rapid intra- and intermolecular proton transfer reactions and their dynamic equilibrium states would make an interesting to study due to their various applications, which is called as *degenerate prototropy*.[18d] Recently, Maciel and co-workers reported the observation of dynamic equilibrium states in rapid proton exchange of tropolone **45** (2-hydroxy-2,4,6-cycloheptatrien-1-one) between **45a** and **45b** as a function of temperature, which was confirmed by the new NMR data.[18a] The proton transfer in pure solid tropolone **45** occurs very rapidly via a tunneling mechanism as observed in matrix-isolated molecules; this was also confirmed through the X-ray analysis.

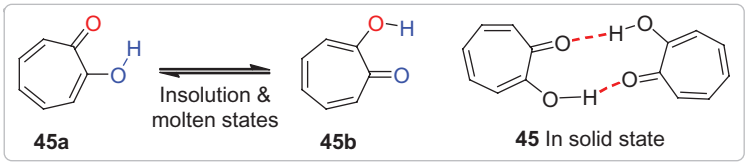
However, earlier the 2D-NMR experimental data showed that tropolone **45** interconverts between two equivalent structures in solid state.[18b] In the solution state too tropolone **45** has been known to be in a fast dynamic equilibrium system showing the averaged four signals in the NMR as shown in Scheme 13.[18c]

Very recently, Yamabe and co-workers reported the existence of the dynamic equilibrium in thiotropolone **46**, where the proton exchange occurs very fast even in the solid state, and the ratio of the two tautomeric forms are almost equal (58:42).[19] This thiotropolone **46** in solid state behaves entirely different from the solid state of tropolone **45**. The thiotropolone **46** contains two unequivalent tautomeric forms of the thione **46a** and enethiol **46b** as shown in Scheme 14. The solid-state of **46** is a crystallographically isolated system displaying an extremely fast equilibrium even at low temperature. This would be a novel example of an undegenerate tautomeric system exhibiting dynamic equilibrium.

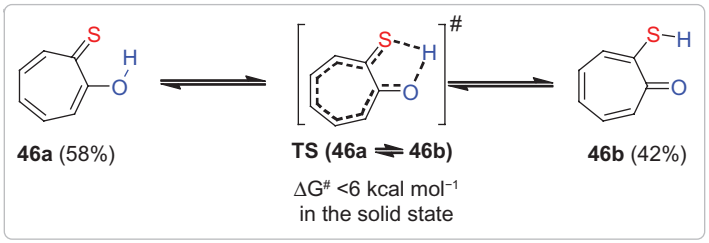
In continuation of the discussion on the proton-induced dynamic equilibrium states, we herein discuss one important aspect of the proton-induced dynamic equilibrium between the cyclometalated ruthenium rNHC (remote *N*-heterocyclic carbene) tautomers with an NAD^+/NADH function. Very recently, Tanaka and co-workers[20] synthesized the cylcometalated ruthenium (II) complexes **47** containing 2-(pyridine-2yl)acridine (pad) and 2 equivalents of 2,2'-bypiridyl (bpy) as ligands $[Ru(pad)(bpy)_2]PF_6$ ($[\mathbf{47}(bpy)_2]PF_6$). Protonation of the pad containing ruthenium(II) complexes were found to not only cause the dynamic equilibrium with remote *N*-heterocyclic carbene Ru=C complexes but also generate the NAD^+/NADH redox function driven by a proton-coupled two electron transfer accompanying a reversible C-H bond formation in the pyridinium ring. The dynamic equilibrium between the Ru-C bond (**A**) and Ru=C (**B**) coordination was also supported by the temperature-dependent ^{1}H-NMR of $[\mathbf{47}(bpy)_2]PF_6$ with the addition of one equivalent of HCl. The signal of the adjacent proton to the coordinated carbon center undergoes a shielding effect with a lowering of the temperature, signifying an increase in the Ru=C-type contribution as shown in Scheme 15. A similar study shows that a dynamic equilibrium exists between the achiral lanthanide shift reagent and partially resolved alkyl amine substrate by ^{1}H NMR with the ratio of 1:1 (seven-coordinate) and 1:2 (eight-coordinate) adducts.[21]

The importance of dynamic equilibrium states was also observed in classical organic chemistry like in the ion pairs of aromatic [9] annulene anion,[22] organometallic compounds,[23] self-assembled multi-porphyrin systems,[24,25] photochemical conversion of 1,3,6,8-tetraphenylcyclooctatetraene,[26] and Pt-coordinated supramolecular rhomboid and the hexagon.[27]

Scheme 13: Fast dynamic equilibrium between the two tautomeric forms of tropolone.



Scheme 14: Observation of dynamic equilibrium between the two different forms **46a** and **46b** of thiotropolone.

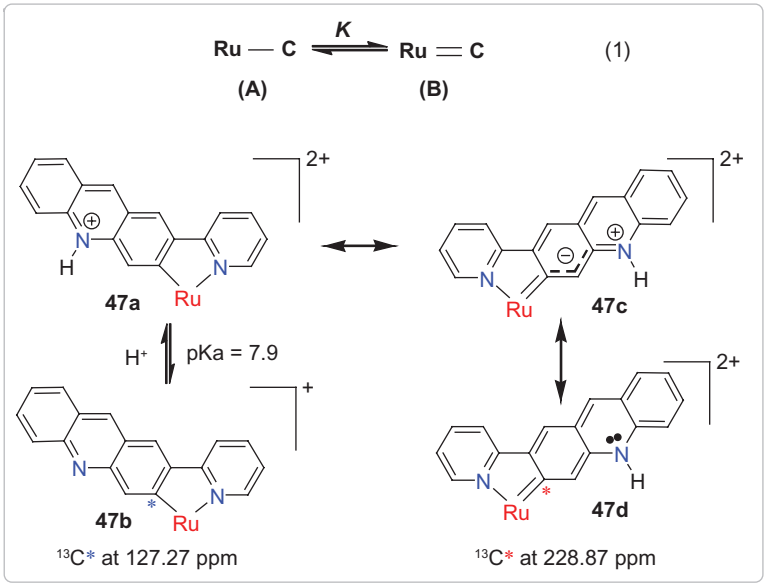


11. Observation of Dynamic Equilibrium States in the Proteins/Nucleic Acids

Understanding and exploration of dynamic equilibrium states in chemical biology will be a revolutionary step towards advance went in the subject. As proteins and nucleic acids are central to the cellular function, researchers have sought to uncover the secrets of how these complex macromolecules execute such a fascinating variety of functions. Although static structures are known for many proteins/nucleic acids, the functions of proteins/nucleic acids are governed ultimately by their dynamic character. Many protein/nucleic acid molecules in solution can exist as equilibrium of different conformations/folds, but the sizes and shifts of these populations cannot be determined from the static structure.

RNA sequences can adopt different co-existing folds on the level of secondary and/or tertiary structure. The underlying folding and refolding processes cover a wide temporal range. Recently, for

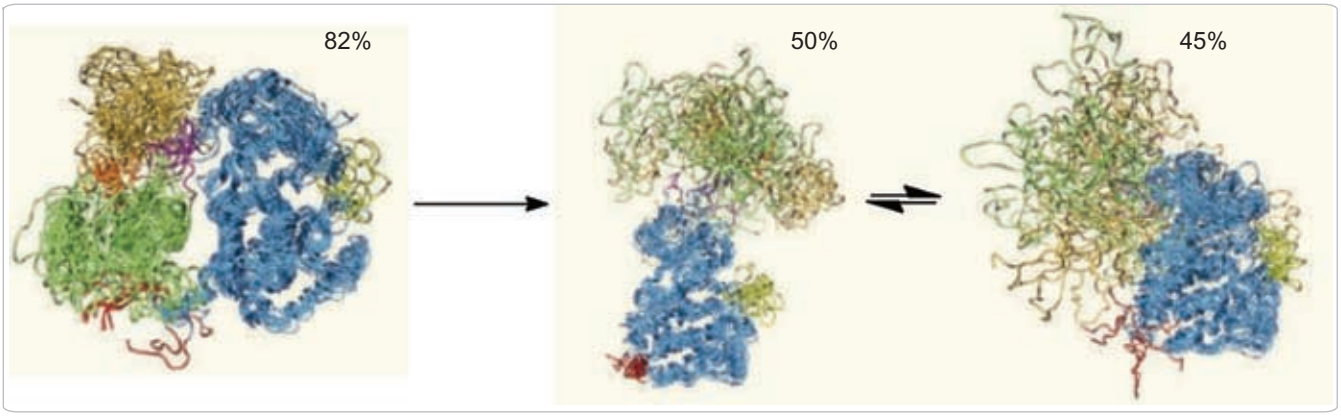
Scheme 15: Dynamic equilibrium between the Ru–C bond (A) and Ru=C (B) confirmed by NMR analysis.



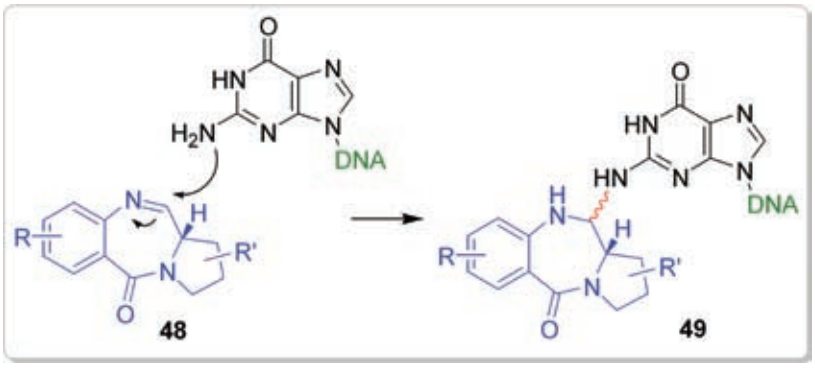
the first time, Stefan Pitsch and co-workers reported the refolding kinetics of a thermodynamically stable 34 mer RNA sequence and the molecule was found to exist in an unperturbed dynamic equilibrium, upon implementation of a new $^{1}H/^{15}N$-heteronuclear exchange-sensitive NMR method.[28] Further studies on these kinds of equilibrium states can reveal the secrets beyond the function of 34 mer RNA. In a similar manner, recent advancement in the technology have helped in determining the protein structure approaches towards understanding of the molecular biology with three dimensional models at atomic resolution and explain the molecular basis of physiologically important interactions between biochemically active molecules.[29] Recent report from Yang *et al.* described methods with the combination of the computational simulations and X-ray scattering data, which could provide the observation of shifts in the equilibrium population of protein conformational states.[30] The authors also found that the Hck enzyme was predominantly in the inactive, assembled conformation (82% of enzyme molecule), but in dynamic equilibrium with partially and fully disassembled states as shown in Scheme 16. The use of the experimental data in solution and structural biology together can provide an insight into the multi-dimensional conformation of proteins existing in dynamic equilibrium, which can deliver more information beyond complexity.[31]

The existence of a dynamic equilibrium between covalent 1:1 hairpin and 2:1 duplex DNA adducts of a pyrrolobenzodiazepine (PBD) minor groove binding agent (**48**) was observed for the first time by Thurston *et al.*[32] It is well established that PBD is highly selective in its requirement for duplex DNA structure and a minor groove environment to bond covalently with 1:1 stoichiometry to C2-NH_2 functionalities of guanine bases via their C11-position as shown in Scheme 17. The equilibrium is interesting from energetic perspectives due to the well known DNA stabilizing effect of PBDs. This observation could have significance in the *in vitro* and *in vivo* biological activity of PBDs, as DNA hairpin and loop structures are known to be important in cellular processes such as transcription and replication. These novel observations could be of great relevance for the future design of gene-targeted agents including novel anticancer drugs.

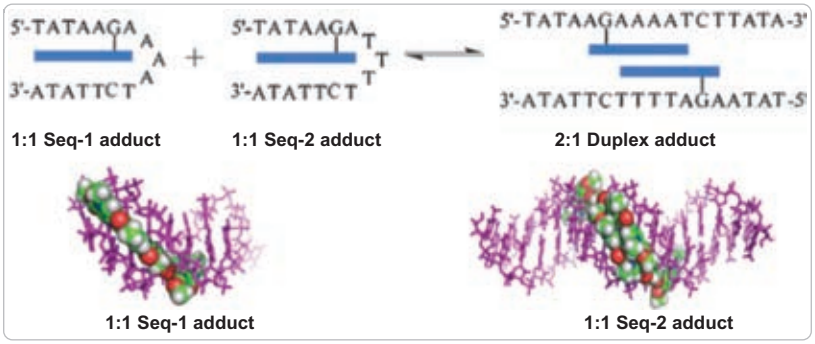
Scheme 16: Dynamic equilibrium of partially and fully disassembled states of Hck enzyme in solution.



Scheme 17: (A) Covalent binding of a PBD to the C2-NH_2 of guanine *via* its C11-position and (B) observed dynamic equilibrium between 1:1 hairpin and 2:1 duplex DNA adducts.



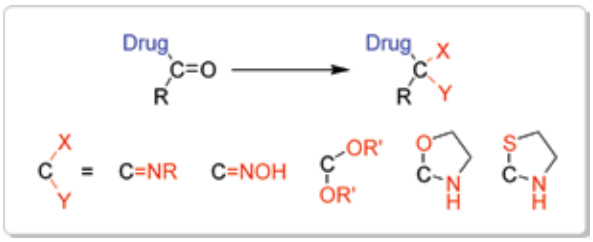
(A)



(B)

Studies by Kanner *et al.* show that the coupled and uncoupled modes of a neuronal glutamate transporter in brain also exist in a dynamic equilibrium.[33] In a similar manner, recent study by Hendzel *et al.* showed that the β-actin exists in a dynamic equilibrium between the low-mobility polymeric species and the rapidly diffusing populations.[34] β-Actin, once thought to be an exclusively cytoplasmic protein, is now known to have important functions within the nucleus. The interaction of the B7–1 and the B7–2 with the receptor CD28 on the T-cell surface has been studied by Bhatia and co-workers, and they concluded that the B7–2 molecule is present as a monomer on the T-cell surface, whereas B7–1 is present as the monomer–dimer form through an unique dynamic equilibrium and further suggested that the B7–1 monomer-dimer equilibrium is very much important for modulating signaling through the TCR/CD28 pathway and the regulation of T-cell activation.[35] These important unexplored observations on the secondary structure of the biomolecules through dynamic equilibrium will lay have many secrets beyond life itself, and we hope this will become a novel tool to create great properties in the near future.

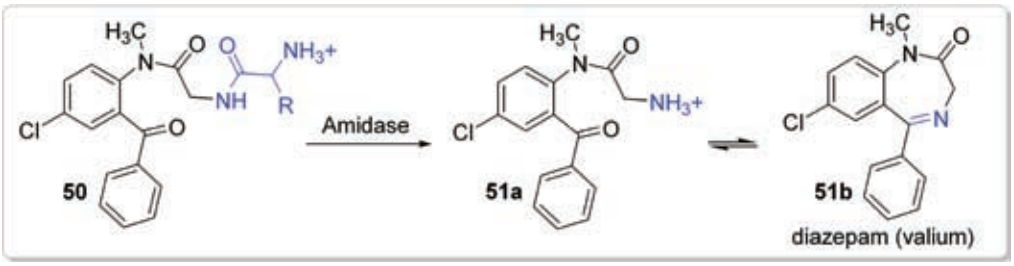
Figure 3: Pro-drug analogues of the carbonyl compound drugs.



12. Importance of Dynamic Equilibrium States in the Drug Discovery

We strongly believe that in drug discovery, dynamic equilibrium can become one of the novel techniques as self-protection or pro-drug. A pro-drug can be defined as a drug substance that is inactive in the intended pharmacological actions and must to be converted into the pharmacologically active agent by metabolic or physico-chemical transformation. Pro-drugs can exist naturally as many phytochemicals/botanical constituents and

Scheme 18: Dynamic equilibrium between the open **51a** and the chain **51b** forms of diazepam.



endogenous substances, or they can result from synthetic or semi-synthetic processes, produced intentionally as a part of a rational drug design or unintentionally during drug development.[36]

The dynamic equilibrium can serve as the self-protection (defence) of the drug molecules for the proper action on the active site. The drug molecule may be active in one form; however it gets transported in to another form which is thermodynamically more stable, before reaching to target. Once the pro-drug reaches the active site/target it opens-up/or forms ring structure and works as the actual drug. Most of the carbonyl group containing drug molecules is transported in the form of the pro-drug analogue like cyclic ketal/imine forms, which on *in situ* hydrolysis produce the active drug molecule as shown in Figure 3.

For example, diazepam **51** is a benzodiazepine derivative, which has low water solubility but the open chain amino-acid pro-drug **50** has very good water-solubility. Peptidases (*in vivo*) hydrolyze the pro-drug **50** to an intermediate **51a**, which spontaneously cyclise to provide the actual drug **51b** in the ring form having dynamic equilibrium with the open form **51a**. Therefore, this example confirms that the dynamic equilibrium can serve as the self-protection (defence) of the drug molecule before reaching the target as shown in Scheme 18.

A number of mechanisms exist for the passage of drugs across the plasma membrane, including passive diffusion, facilitated diffusion, and active transport systems. Passive diffusion of drugs through the bilayer lipid structure of the plasma membrane is a function of its size, lipid solubility, and charge on the drug molecule. If the extracellular drug concentration is constant, then drug accumulation within the cell will continue until the rate of drug uptake from the extracellular space is equal to the rate of drug efflux from the cell. At this point, a dynamic equilibrium is reached as the intracellular and the extracellular drug concentrations are equal.[37]

13. Summary and Future Prospects

In conclusion, we have given a brief discussion on the existence and the importance of the dynamic equilibrium in chemical biology and drug discovery. Several drug molecules existing in dynamic equilibrium with open and cyclic form depends on the mode of action at the active site as well as the mode of transportation. Moreover, several protein/nucleic acids are known to be the dynamic personalities as their structure are in dynamic equilibrium with the several conformations/folds through the slight movement/flipping in different biological environment. Furthermore, the importance of dynamic equilibrium in drug release in biological systems have been discussed here. The question to be addressed is, are drug molecules really in dynamic equilibrium when they exist in more than one form. If it is the case, then dynamic equilibrium may be working as a self protector for the drug, before it acts as the actual drug. However, we believe that this review article presents very important concepts like 'dynamic equilibrium states' in chemical biology and pharmaceutical chemistry and we believe that a better understanding will appear in the near future.

Dynamic equilibrium states of a molecule can be compared to a person having many skills; internally those skills make the person to be ideal, strong and more adventurous in sociological chemistry. In a similar manner, single molecule containing many equilibrium states will become famous in all aspects of molecular chemistry.

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References:

1. a. H. C. Corben and P. Stehle, *Classical Mechanics*, Courier Dover Publications 113, p. 1994.
   b. P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J.-L. Wietor, J. K. M. Sanders and S. Otto, *Chem. Rev.,* **106**, 3652 (2006).
2. M. Szwarc, *J. Mole. Liquid*, **76**, 111 (1998).
3. D. B. Campbell, *Psychopharmacology*, **100**, 433 (1990).
4. K. H. Wildman and D. Kern, *Nature*, **450**, 964 (2007).
5. For recent reviews on general cascade and multi-component reactions, see:
   a. E. Cane, *Chem. Rev.*, **90**, 1089 (1990).
   b. L. F. Tietze, *Chem. Rev.*, **96**, 115 (1996).
   c. L. F. Tietze and A. Modi, *Med. Res. Rev.*, **20**, 304 (2000).
   d. L. F. Tietze and F. Haunert, *Stimulating Concepts in Chemistry*, Eds.: F. Vogtle, J. F. Stoddart and M. Shibasaki, Wiley-VCH, Weinheim, 2000, p. 39.
   e. S. F. Mayer, W. Kroutil and K. Faber, *Chem. Soc. Rev.*, **30**, 332 (2001).
   f. K. C. Nicolaou, T. Montagnon and S. A. Snyder, *Chem. Commun.*, 551 (2003).
   g. W. Notz, F. Tanaka and C. F. Barbas III, *Acc. Chem. Res.,* **37**, 580 (2004).
   h. J. C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, **105**, 1001 (2005).
   i. D. J. Ramon and M. Yus, *Angew. Chem., Int. Ed.*, **44**, 1602 (2005).
   j. N. T. Patil and Y. Yamamoto, *Synlett*, 1994 (2007).
   k. D. M. D'Souza and T. J. J. Mueller, *Chem. Soc. Rev.*, **36**, 1095 (2007).
   l. C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, **2**, 167 (2010).
   m. D. B. Ramachary and S. Jain, *Org. Biomol. Chem.*, **9**, 1277 (2011).
6. For the development of multi-catalysis cascade reactions for drugs and drug-like molecules, see:
   a. D. B. Ramachary, M. Kishor and K. Ramakumar, *Tetrahedron Lett.*, **47**, 651 (2006).
   b. D. B. Ramachary, M. Kishor and G. B. Reddy, *Org. Biomol. Chem.*, **4**, 1641 (2006).
   c. D. B. Ramachary and G. B. Reddy, *Org. Biomol. Chem.*, **4**, 4463 (2006).
   d. D. B. Ramachary and M. Kishor, *J. Org. Chem.*, **72**, 5056 (2007).
   e. D. B. Ramachary, G. B. Reddy and M. Rumpa, *Tetrahedron Lett.*, **48**, 7618 (2007).
   f. D. B. Ramachary, K. Ramakumar and V. V. Narayana, *J. Org. Chem.*, **72**, 1458 (2007).
   g. D. B. Ramachary, M. Kishor and Y. V. Reddy, *Eur. J. Org. Chem.*, 975 (2008).
   h. D. B. Ramachary, Y. V. Reddy and B. V. Prakash, *Org. Biomol. Chem.*, **6**, 719 (2008).
   i. D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.*, **6**, 2488 (2008).
   j. D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.*, **6**, 4176 (2008).
   k. D. B. Ramachary, Y. V. Reddy and M. Kishor, *Org. Biomol. Chem.*, **6**, 4188 (2008).
   l. D. B. Ramachary, V. V. Narayana and K. Ramakumar, *Eur. J. Org. Chem.*, 3907 (2008).
   m. D. B. Ramachary, K. Ramakumar and V. V. Narayana, *Chem. Eur. J.*, **14**, 9143 (2008).
   n. D. B. Ramachary and Y. V. Reddy, *J. Org. Chem.*, **75**, 74 (2010).
   o. D. B. Ramachary and M. Shiva Prasad, *Tetrahedron Lett.*, **51**, 5246 (2010).
   p. D. B. Ramachary, M. Shiva Prasad and R. Madhavachary, *Org. Biomol. Chem.*, **9**, 2715 (2011).
   q. D. B. Ramachary, Y. V. Reddy, A. Banerjee and S. Banerjee, *Org. Biomol. Chem.*, **9**, 7282 (2011).
7. D. B. Ramachary and R. Sakthidevi, *Chem. Eur. J.*, **15**, 4516 (2009).
8. D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.*, **8**, 4259 (2010).
9. a. A. Robinson, H.-Y. Li and J. Feaster, *Tetrahedron Lett.*, **37**, 8321 (1996).
   b. H.-Y. Li and A. Robinson, *US patent* **5**, 856, 525 (1999).
10. a. E. J. Valente, E. C. Lingafelter, W. R. Porter and W. F. Trager, *J. Med. Chem.*, **20**, 1489 (1977).
    b. N. Halland, T. Hansen and K. A. Jørgenson, *Angew. Chem. Int. Ed.*, **42**, 4955 (2003).
11. a. B. Andersen, *Antonie van Leeuwenhoek*, **60**, 115 (1991).
    b. J. F. Grove and M. Pople, *J. Chem. Soc., Perkin Trans* 1, 337 (1979).
12. a. a. i) P. R. Jones, *Chem. Rev.*, **63**, 461 (1963); ii) D. J. Chadwick and J. D. Dunitz, *J. Chem. Soc. Perkin Trans* 2, 276 (1979); iii) M. D. Soffer, R. A. Stewart, J. C. Cavagnol, H. E. Gellerson and E. A. Bowler, *J. Am. Chem. Soc.*, **72**, 3704 (1950).
    b. J. K. Wong, R. A. Lalancette and H. W. Thompson, *The Open Cryst. J.*, **1**, 56 (2008).
    c. J. K. Wong, R. A. R. Macalintal, A. P. J. Brunskill, R. A. Lalancette and H. W. Thompson, *Acta Cryst. C*, **56**, 371 (2000).
13. a. A. Bacchini, E. Gaetani and A. Cavaggioni, *Experimentia*, **48**, 419 (1992).
    b. M. V. Novotny, W. Ma, D. Wiesler and L. Zidek, *Proc. R. Soc. Lond. B. Biol. Sci.*, **266**, 2017 (1999a).
    c. M. V. Novotny, B. Jemiolo, D. Wiesler, W. Ma, S. Harvey, F. Xu, T. M. Xie and M. Carmack, *Chem. Biol.*, **6**, 377 (1999b).
    d. D. E. Timm, L. J. Baker, H. Mueller, L. Zidek and M. V. Novotny, *Protein Science*, **10**, 997 (2001).
14. a. S. T. Miller, K. B. Xavier, S. R. Campagna, M. E. Taga, M. F. Semmelhack, B. L. Bassler and F. M. Hughson, *Mol. Cell*, **15**, 677 (2004).
    b. K. M. McKenzie, M. M. Meijler, C. A. Lowery, G. E. Boldt and K. D. Janda, *Chem. Commun.*, 4863 (2005).
    c. C. A. Lowery, J. Park, G. F. Kaufmann and K. D. Janda, *J. Am. Chem. Soc.*, **130**, 9200 (2008) and references therein.
    d. K. Tsuchikama, C. A. Lowery and K. D. Janda, *J. Org. Chem.*, **76**, 6981 (2011).
15. a. J. O. Davis, *J. Nat. Med. Assoic.*, **49**, 42 (1957).
    b. D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **83**, 4083 (1961).
    c. P. R. Jones, *Chem. Rev.,* **63**, 461 (1963).
    d. S. A. S. Tait, J. F. Tait and J. P. Coghlan, *Molecular and Cellular Endocrinology* **217,** 1 (2004).
16. a. T. Delaine, V. B.-Génisson, J.-L. Stigliani, H. Gornitzka, B. Meunier and J. Bernadou, *Eur. J. Org. Chem.*, **10**, 1624 (2007).
    b. A. K. Singh, R. P. Kumar, N. Pandey, N. Singh, M. Sinha, A. Bhushan, P. Kaur, S. Sharma, and T. P. Singh, *J. Bio. Chem.*, **285**, 1569 (2010).
17. S. Kiyohara, K. Ishizuka, H. Wakabayashi, H. Miyamae, M. Kanazumi, T. Kato and K. Kobayashi, *Tetrahedron Lett.*, **48**, 6877 (2007).
18. a. N. M. Szeverenyi, A. Bax and G. E. Maciel, *J. Am. Chem. Soc.*, **105**, 2579 (1983).

b. N. M. Szeverenyi, M. J. Sullivan and G. E. Maciel, *J. Magn. Reson.*, 47, 462 (1982).
c. L. Weiler, *Can. J. Chem.*, **50**, (1975).
d. P. K. Baruah, R. Gonnade, U. D. Phalgune and G. J. Sanjayan, *J. Org. Chem.*, **70**, 6461 (2005).
19. T. Machiguchi, T. Hasegawa, H. Saitoh, S. Yamabe and S. Yamazaki, *J. Org. Chem.*, **76**, 000 (2011).
20. S. K. Padhi, K. Kobayashi, S. Masuno and K. Tanaka, *Inorg. Chem.*, **50**, 5321 (2011).
21. K. Ajisaka and M. Kainosho, *J. Am. Chem. Soc.*, **97**, 1761 (1975).
22. G. Boche and F. Heidenhain, *J. Am. Chem. Soc.*, **101**, 738 (1979).
23. M. T. Caudle and J. W. Kampf, *Inorg. Chem.*, **38**, 5474 (1999).
24. A. Tanaka, A. Ryuno, S. Okada, A. Satake and Y. Kobuke, *Israel Journal of Chemistry*, **45**, 281 (2005).
25. L. A. Bottomley and J.-N. Gorce, *Inorganic Chemistry*, **27**, 3733 (1988).
26. E. H. White, R. L. Stern, T. J. Lobl, S. H. Smallcombe, H. Maskill and E. W. Friend, *J. Am. Chem. Soc.*, **98**, 3247 (1976).
27. T. Yamamoto, A. M. Arif and P. J. Stang, *J. Am. Chem. Soc.*, **125**, 12309 (2003).
28. P. Wenter, G. Bodenhausen, J. Dittmer and S. Pitsch, *J. Am. Chem. Soc.*, **128**, 7579 (2006).
29. a. J.-M. Chandonia and S. E. Brenner, *Science,* **311**, 347 (2006).
b. Q. Zhang, A. C. Stelzer, C. K. Fisher and H. M. Al-Hashimi, *Nature*, **450**, 1263 (2007).
30. S. Yang, L. Blachwicz, L. Makowski and B. Roux, *Proc. Natl. Acad. Sci. USA*, **107**, 15757 (2010).
31. P. Bernado and M. Blackledge, *Nature*, **468**, 1046 (2010).
32. K. M. Rahman, V. Mussa, M. Narayanaswamy, C. H. James, P. W. Howard and D. E. Thurston, *Chem. Commun*., 227 (2009).
33. L. Borre, M. P. Kavanaugh and B. I. Kanner, *J. Bio. Chem.*, **277**, 13501 (2002).
34. D. McDonald, G. Carrero, C. Andrin, G.-de. Vries and M. J. Hendzel, *J. Cell. Biol.*, **172**, 541 (2006).
35. S. Bhatia, K. Sun, S. C. Almo, S. G. Nathenson and R. J. Hodes, *J. Immunol.,* **184**, 1821 (2010).
36. K. –M. Wu, *Pharmaceuticals*, **2**, 77 (2009).
37. A. Goldstein, L. Aronow and S. Kalman, *Principles of Drug Action*, 2nd ed.; John Wiley & Sons: Hoboken, NJ, USA, (1974).

Dhevalapally B. Ramachary has been an Associate Professor at the School of Chemistry, University of Hyderabad, Hyderabad, since 2007. After Ph. D. work on natural product synthesis with Prof. A. Srikrishna at the Indian Institute of Science, Bangalore, he did postdoctoral studies in the Prof. Carlos F. Barbas III laboratories of The Scripps Research Institute as Skaggs Postdoctoral Fellow working with small molecular catalysts. In 2005 he joined the faculty of the School of Chemistry, University of Hyderabad as an Assistant Professor and moved to his current position in 2007. He was awarded the INSA Young Scientist Medal in 2006, Member of The National Academy of Sciences, India in 2009, Associate Fellow of the Andhra Pradesh Academy of Sciences in 2010 and Anil Kumar Bose Memorial Award of the INSA in 2010. His research focuses on the design and implementation of bio-mimetic one-pot strategies for the synthesis of biologically important drugs and drug-like molecules, in addition to the development of new synthetic methods including asymmetric catalysis and multi-catalysis cascade processes.

Indresh Kumar is Lecturer in School of Biology and Chemistry, College of Sciences at Shri Mata Vaishno Devi University, Katra (J&K) since 2009. He completed his Ph. D. degree with Dr. C. V. Rode at National Chemical Laboratory Pune, followed by Post-doctoral study with Prof. Yujiro Hayashi at Tokyo University of Science, Japan. His main research interests are; asymmetric organocatalysis and its synthetic applications, development of new synthetic methodology through green processes and total synthesis of biologically active natural/non-natural products. He visited Prof. D. B. Ramachary research group as "IASc-INSA-NASI-fellow" during June-July 2011.