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Reviews

Molecular recognition of caffeine in solution and solid state

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I would like to dedicate this article to Prof. Ajit K. Mahapatra whose constant inspiration and unflinching encouragement impel me to construct this work.

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ABSTRACT

The molecular recognition of caffeine in both solution and solid state is important to understand different enzymatic reactions *i.e.*, enzyme–substrate interactions, immunological reactions *in vivo*, selective host–guest complexation and catalytic reactions in bio-mimetic chemistry. The weak intermolecular forces in recognition system direct the molecules toward self-linking in supramolecular engineering in the chemistry of life and material science. In this contribution, it has been illustrated the immense variety of receptors that have been designed for caffeine recognition in both solid and solution phase. The binding studies for the recognition of caffeine are reported by different research groups including our group. It is important to understand the goal of developing artificial molecular receptors, capable of binding very efficiently and very selectively with caffeine which is described elaborately in this context. The modern bioorganic chemistry concerns the design of synthetic molecules that mimic various aspects of enzyme chemistry and to understand their essential roles in biological systems. The stimulating effect of caffeine is not only exploited in nutrient technology but also in cosmetics and pharmaceuticals, which accounts for the economic importance of this particular additive. Although caffeine was first time isolated by Ferdinand Runge from coffee beans almost 200 years ago, it still has some surprise in hoard.

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1. Introduction

Caffeine is probably one of the most widely used psychoactive drug in the world and it is cheap and readily available. Among the methylxanthine derivatives, caffeine is the most frequently consumed alkaloidal compound. Besides the traditional sources of caffeine, *viz*, coffee, black tea and green tea, caffeinated beverages with increased levels of the alkaloid are recently gathering larger shares among soft drinks and in various analgesics. The xanthine derivatives have several common pharmacological actions such as CNS-stimulation, diuretic, anti-bronchospastic and anti-cough. Caffeine, a neuromodulator can enhance learning and memory and may have neuroprotective properties. A protective role of caffeine has been hypothesized or studied for a number of neurodegenerative diseases, including Parkinson's diseases, Alzheimer's disease, ischemic disease, Huntington disease and fetal methylmercury poisoning. Caffeine competitively inhibits different adenosine receptors and their associated G protein to make a person feel alert. A mild stimulant of the central nervous system, caffeine also stimulates cardiac muscle, relaxes smooth muscle, increases gastric secretions, and produces diuresis [1,2].

Besides these therapeutic effects, xanthines which include caffeine as well are also of other importance such as in the determination of freshness of fish [3]. The design of biosensor receptors is particularly important to monitor the freshness of fish by molecular recognition which is crucial in the use and marketing of fish and this is determined by the concentration of xanthine. Caffeine in combination with an analgesic [4a] (analgesic adjuvancy), such as aspirin, is widely employed in the treatment of different types of headache. Now a days obesity is a growing problem causing significant morbidity and mortality. A number of investigations have been used with green tea and caffeine to induce human weight loss. Caffeine's use as an ergogenic aid has been proven to increase physical endurance. The use of caffeine for short-term endurance appears to have no affect on the athlete [4b].

Though caffeine is a potent collection of biologically active compounds, sometimes caffeine is regarded to be harmless for adults in general; there are severe concerns about its unfavorable influences on young children and pregnant women, including the risk of fetal death [5]. The stimulating effect of caffeine is not only exploited in nutrient technology but also in cosmetics and pharmaceuticals, which accounts for the economic importance of this particular additive [6–8].

Caffeine overdose can result in a state of central nervous system over-stimulation called caffeine intoxication [9,10]. High doses can result in restlessness, nervousness, insomnia, fidgeting, anxiety, excitement, insomnia, flushing of the face, increased urination, gastrointestinal disturbance, muscle twitching, a rambling flow of thought and speech, irritability, irregular or rapid heartbeat, and psychomotor agitation. Extreme overdose can result in death [11,12]. An exception to this would be taking a drug such as fluvoxamine or levofloxacin, which blocks the liver enzyme responsible for the metabolism of caffeine, thus increasing the central effects and blood concentrations of caffeine fivefold [13,14].

In general, the more caffeine consumed, the more severe withdrawal symptoms [15–17] are likely to be, but as little as one standard cup of coffee a day cannot produce addiction to caffeine. The latest research demonstrates, however, that when people do not get their usual dose they can suffer a range of withdrawal symptoms, including headache, fatigue, and difficulty in concentrating. They may even feel like they have drowsiness, dysphoric mood including depression, irritability, and flu-like symptoms of nausea, vomiting and muscle pain or stiffness [18]. A systematic method has been developed for reducing caffeine consumption gradually over time by substituting decaffeinated or non-caffeinated products. Using such a method allows people to reduce or eliminate withdrawal symptoms.

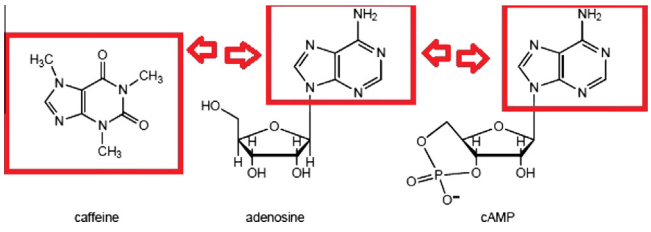
So lots of questions arises how caffeine reacts inside the cell. When caffeine arrives at a cell in the body, it first encounters the plasma membrane. The properties of this membrane determine whether and how the cell will react to caffeine. Will it cross the membrane boundary and enter the cell? What determines whether it crosses the membrane? If it does not, how can caffeine's interactions with membrane components lead to changes in cell function?

Hence, the molecular recognition of caffeine in both solution and solid state is important to understand their fundamental roles in biological systems [19,20]. Recognition of such biomolecules with abiotic synthetic receptors has great significance to understand the enzyme reactions [21–23] (enzyme–substrate interactions), immunological reactions *in vivo*, [24,25] selective host–guest complexation and catalytic reactions in bio-mimetic chemistry.

1.1. Enzyme–substrate interactions

An enzyme is specific to the substrate it binds to. It is dependent on structure and placement of the substrate. If the sequence is complementary then it ensures the binding of the two components. In the case of a single substrate, the substrate bonds with the enzyme active site, and an enzyme–substrate complex is formed. The substrate is transformed into one or more products, which are then released from the active site. The active site is now free to accept another substrate molecule.

Pharmaceutical drugs work the same way Enzymes work [26]. They bind to a specific binding site that either inhibits or activates a specific biological action. The reason behind the relationship between Caffeine and alertness and wakefulness is the big structural similarity between the caffeine molecule, adenosine and cyclic adenosine phosphate. The structures similarity allows caffeine molecules to bind to the same binding site of receptors or enzymes that reacts with adenosine derivatives. Adenosine has a very important role in the regulation of brain activity. The human brain builds up adenosine molecules during the day. When the level of built up adenosine increases in the human brain, adenosine starts binding to its binding sites (receptors) in the human brain which activates mechanisms that lead to drowsiness and sleep. Since caffeine has the same structural molecule it binds to the same receptors that adenosine binds to, preventing adenosine to bind to that specific receptor in the human brain and delaying the sleeping and drowsiness process.



1.2. Immunological reactions

Immunological reactions [27] in humans can and do occur against DNA fragments as evidenced by the autoimmune disease SLE (Systemic lupus erythematosus). In this disease, antibodies are produced against DNA fragments and nucleoprotein released from dying cells. This results in a Type III Immune Mediated Hypersensitivity Reaction. In fact, there are a small number of potentially

self-reactive cells with access to their respective autoantigens such as human thyroglobulin, myelin basic protein and DNA normally present in the body. The only thing holding them in check normally is properly functioning homeostatic mechanisms that have obviously gone astray in conditions such as SLE and Rheumatoid arthritis. Immune complex glomerulonephritis is another condition associated with the production of antibodies against DNA and DNA–protein, etc. In patients with SLE, immune complex deposits containing antibodies to single stranded and double stranded DNA have been detected in the kidney tissue.

While these Type III reactions do not cause the classic 'IgE allergic' response, they can and do cause insidious disease when these antigen–antibody reactions form insoluble complexes at fixed sites within the body that may give rise to acute inflammatory reactions, eg rheumatoid arthritis. The production and release of inflammatory mediators and proteolytic enzymes, etc can damage tissue and further intensify inflammatory responses. Type III complex mediated hypersensitivity reactions can affect the skin producing edema and erythema, or the lungs e.g. farmer's lung, pigeons fanciers disease & pulmonary aspergillosis.

Some people have an adverse reaction on exposure to certain foods that can make them unwell. This can be a recurring reaction, happening each time that person ingests the food. Symptoms depend on the mechanism of reaction, but range from vomiting and diarrhoea, skin reactions such as eczema and urticaria, to dramatic angio-oedema, severe respiratory distress and anaphylaxis. One way to classify adverse reactions to foods is as either:

- Immunological reactions – both IgE (acute, often rapid, onset) and non-IgE-mediated (delayed and non-acute reactions).
- Nonimmunological reactions.

Traditional allergists believe that food hypersensitivities are primarily IgE-mediated and treat with avoidance diet and/or drug therapy. Diagnosis is by history, elimination diets, skin tests, or food challenge. Non IgE-mediated food intolerance is classified as non-immune adverse reactions to food of a pharmacologic (caffeine, histamine, tyramine, serotonin, dopamine, etc.); metabolic (lactose intolerance); or idiosyncratic nature, e.g., food dyes, preservatives (sulfites), flavor enhancers (MSG). The AAOA indicates that provocation–neutralization techniques were developed primarily for these delayed, less obvious, non-IgE-mediated food hypersensitivities and not for confirmation of immediate food allergy obvious by history. Test substances have also included chemicals such as formaldehyde and alcohol, histamine, tobacco, newsprint and inhalant allergens.

The impact of caffeine on immune function has been focused in recent studies. In this regard, a number of in vitro and *in vivo* studies have demonstrated that caffeine modulates both innate and adaptive immune responses. For instance studies indicate that caffeine and its major metabolite paraxanthine suppress neutrophil and monocyte chemotaxis, and also suppress production of the pro-inflammatory cytokine tumour necrosis factor (TNF)-alpha from human blood. Caffeine has also been reported to suppress human lymphocyte function as indicated by reduced T-cell proliferation and impaired production of Th1 (interleukin [IL]-2 and interferon [IFN]-gamma), Th2 (IL-4, IL-5) and Th3 (IL-10) cytokines. Studies also indicate that caffeine suppresses antibody production. The evidence suggests that at least some of the immunomodulatory actions of caffeine are mediated via inhibition of cyclic adenosine monophosphate (cAMP)–phosphodiesterase (PDE), and consequential increase in intracellular cAMP concentrations. Overall, these studies indicate that caffeine, like other members of the methylxanthine family, is largely anti-inflammatory in nature, and based on the pharmacokinetics of caffeine, we suggest that many of its immunomodulatory effects occur at concentrations that are relevant to normal human consumption. Finally, the potential of caffeine-induced immunomodulation to significantly impact upon health and well-being are discussed.

1.3. Catalytic reactions in biological systems [28]

The enzyme Xanthine oxidase generates reactive oxygen species, which catalyze the oxidation of hypoxanthine to xanthine and can further catalyze the oxidation of xanthine to uric acid. These enzymes play an important role in the catabolism of purines in some species, including humans. Most of the protein in the liver exists in a form with xanthine dehydrogenase activity, but it can be converted to xanthine oxidase by reversible sulfhydryl oxidation or by irreversible proteolytic modification. The active site of XO is composed of a molybdopterin unit with the molybdenum atom also coordinated by terminal oxygen (oxo), sulfur atoms and a terminal hydroxide. In the reaction with xanthine to form uric acid, an oxygen atom is transferred from molybdenum to xanthine, whereby several intermediates are assumed to be involved. The reformation of the active molybdenum center occurs by the addition of water. Like other known molybdenum-containing oxidoreductases, the oxygen atom introduced to the substrate by XO originates from water rather than from dioxygen (O_2).

Caffeine acts as an anti catalyst to an enzyme called cyclic phosphodiesterase (CAMP–PDE); whose job is to block the production of cAMP (cyclic adenosine monoposphate). CAMP is produced by the binding of a hormone called epinephrine. As caffeine inhibits CAMP–PDE from doing its job, cAMP generated by epinephrine is increased and staysactive in the cell for a longer period. This cAMP produced then diffuses through the cell and activates an enzyme called kinase which in turn produces adenosine triphosphate (ATP). ATP is an enzyme essential for the contraction and relaxation of heart muscles. The result of increased cAMP levels (due to caffeine) is increased levels of ATP ultimately leading to an increase in the responsiveness of heart muscles causing an increase in heart rate.

The weak intermolecular forces in molecular recognition system direct the molecules toward self-linking in supramolecular engineering in the chemistry of life and material science. Supramolecular chemists have devised several tailor-made chemo-receptors [29] that allow expected designed interaction in solution. The application of molecular imprinting polymers (MIPs) [30–32] also offers new possibilities. Recently, several research groups accomplished the synthesis of artificial receptors for xanthine derivatives. The design of artificial receptors, their synthesis and the binding studies for the recognition of caffeine has been reported by us and also other research groups.

2. Molecular recognition of caffeine

The designed receptors are based on the choice of different fluorophores as spacers which can accommodate the bicyclic xanthine guests in between the binding phenolic hydroxyl or carboxyl groups. Among all the xanthine alkaloids, caffeine being the strongest base, its binding constants is maximum as all the nitrogens are methylated. Xanthine alkaloids, such as caffeine, are a class of alkylated oxopurines. Natural compounds like catechin [33], theaflavin [34], cyclodextrin [35,36], potassium chlorogenate [37], etc. are capable of binding caffeine or theobromine through hydrophobic interactions. Caffeine also shows heterogeneous association with different dicarboxylic acids [38–41], hydroxy acids [42] and simple heterogeneous stacks with methyl gallate [43,44] in their solid state.

2.1. Modes and binding sites [45,46]

Caffeine has features which are reminiscent of peptides [47], particularly those associated with imino acids such as proline [*viz*, the two –CO-N (Me)-groups]. So caffeine competes effectively with proteins for phenolic substrates and it is possible to regenerate proteins, in a biologically active state, from insoluble protein polyphenol complexes by treatment with caffeine. It is also possible to remove tannin [48] from the reaction mixture of both the presence and absence of protein shown diagrammatically bellow.

Caffeine + Tannin = Caffeine-Tannin
Caffeine + Protein-Tannin = Protein + Caffeine-Tannin

A further feature of interest in these crystalline phenol–caffeine complexes is the relative orientation of the planner caffeine and phenolic partner in the layer lattice. In this aspect, the term 'polarization bonding' [49] has been used to describe both charge transfer bonding and generally weaker interactions between the polar groups of one component and a polarisable second component. So it is very interesting to note that in the various phenol–caffeine complexes the phenolic groups and the associated nuclei are generally stacked above the 6-membered ring of the caffeine molecule. Such form of association of the two components (e.g. caffeoyl ester and caffeine) develops complementary polar characteristics [50] of the type shown below (Figs. 1 and 2).

Caffeine possesses a number of features which optimize its effectiveness as a small molecule for complexation with polyphenolic substrates. The phenolic group is a good proton donor but a poor proton acceptor in hydrogen bonding systems. It is assumed that in the complexation of caffeine with polyphenols, hydrogen bonding systems. It is assumed that in the complexation of caffeine with polyphenols, hydrogen bonding between the polyphenol (proton donor) and the caffeine (proton acceptor) may ultimately make specific contribution to the stability of the complex. The hydrophobic contributions are probably the most important single factor influencing caffeine–polyphenol interactions in aqueous media. In phenol–caffeine complexation, the phenolic groups and the associated aromatic nuclei are generally stacked above the six membered ring of caffeine because their associations are developed by complementary interacting dipoles within the molecules. So the caffeine–polyphenols are reversibly complexed with one another via (i) hydrogen bondings (ii) hydrophobic interactions and (iii) ionic interactions. The relative quantitative importance of these three types of interactions, responsible for caffeine–polyphenol complexation with variable stoichiometry is described.

Hormann and Viani, using NMR spectroscopy, concluded that in aqueous media the caffeine potassium chlorogenate complex was best described [51] as a hydrophobically bound π molecular complex and percipiently they suggested that in solution the

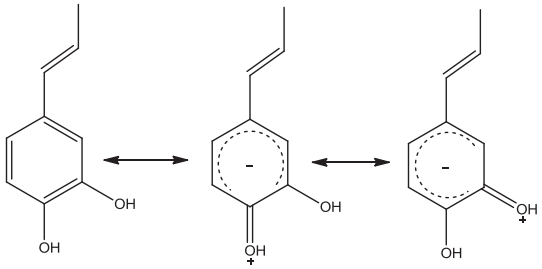


Fig. 1. Resonance structure of polyphenolic compound [49].

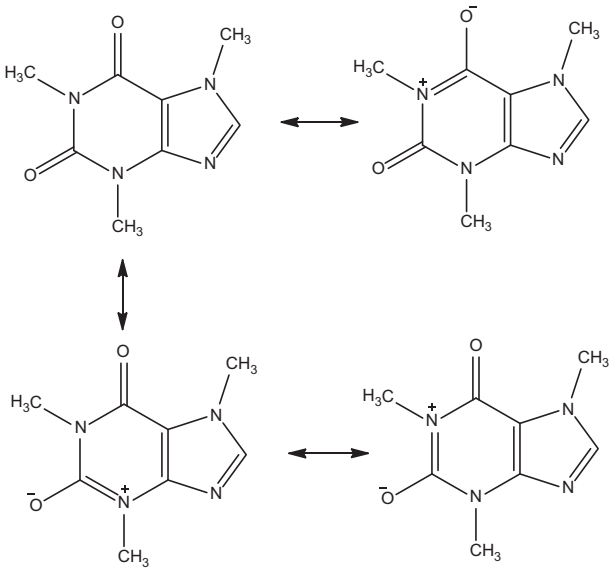


Fig. 2. Complementary polar characteristics of caffeine [50].

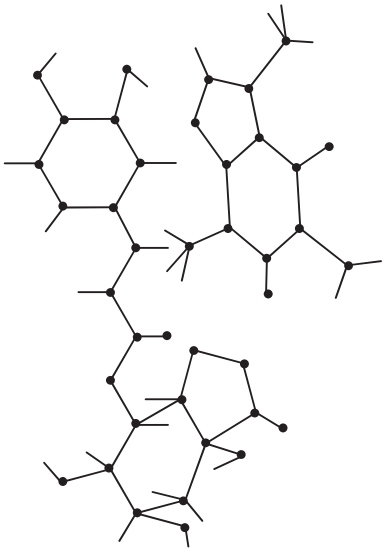


Fig. 3. Hydrophobically bound π molecular complex [51].

time-averaged conformation of the complex resembled that shown in Fig. 3. The crystal structure of the caffeine—potassium chlorogenate 1:1 molecular complex derived from coffee beans has been illustrated. The relationship of this structure to the general question of the mechanisms of polyphenol association and precipitation is commented upon.

It is proposed that the plane of the caffeine molecule is parallel to the plane of the aromatic ring of the caffeoyl ester group and the five and six membered rings of the nitrogen heterocycles are equally involved in the complex formation.

3. Complexation of caffeine-tweezers with polyhydroxyaromatic acids in solution

Caffeine forms complexes of variable stoichiometry with polyphenols. In aqueous medium, polyphenols readily associate with several alkaloids leading to complexation through hydrogen bonding and hydrophobic interactions. Review of the literature reveals

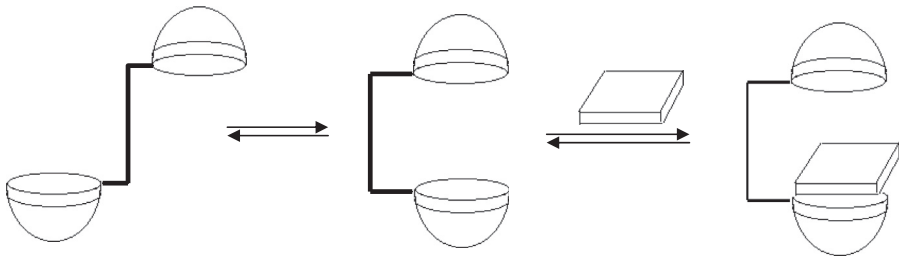


Fig. 4. Caffeine molecular twzeer [52].

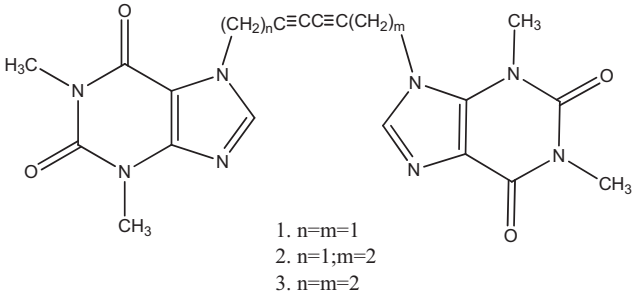


Fig. 5. The structure of diyne unit.

that Whitlock Jr. et al. have synthesized several bi-functional derivatives of caffeine molecular tweezers [52a] (Fig. 4) by maintaining 2–3 characteristic features in the formation of 'sandwitch' type complex of aromatic molecules in aqueous solution.

The rigid diyne unit (Fig. 5) prevents self-association [52b] of the two caffeine moieties by maintaining the caffeine–caffeine distance of approximate 7 Å in the *syn* conformation. The other structural feature, a rigid *syn* conformation is not met. The important study from the diyne unit established that the rigid spacer could not prevent self association of the attached chromophores, in water, thereby increasing the complexation efficiency 100 fold over a flexible analogue. However this diyne unit does not fix the caffeine moiety in a syn arrangement, nor does it orient them in a parallel planes.

Association constants were determined by phase participation of the tweezers ($\sim 10^{-4}$ M) with varying concentrations of 2,6-dihydroxybenzoate and 1,3-dihydroxy-2-naphthoate giving the binding constant values of 21830 M^{-1} and 10410 M^{-1} respectively.

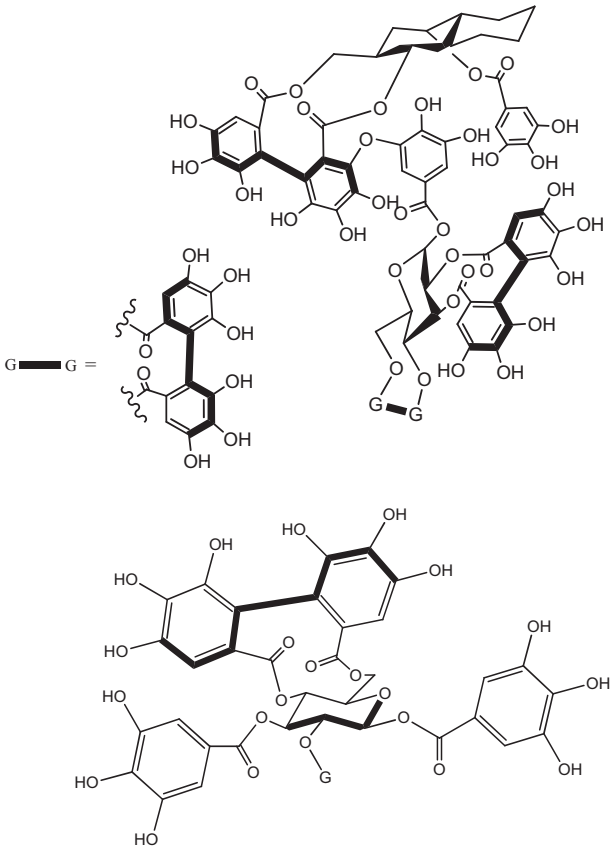


Fig. 6. Natural polyphenol Sanguin and Tellimagrandin-2 [56,57].

4. Caffeine recognition in solution

4.1. In nature

The association of natural polyphenols with proteins and structurally related compound caffeine influences the taste [53], nutritional value [54] and the microbial decomposition of plant materials in the formation of soils [55]. In aqueous medium polyphenols readily associate with variable stoichiometry and it reduces undesirable physiological actions of caffeine. So in the aqueous media, natural polyphenols [56,57] (Fig. 6) readily associate with caffeine and related heterocycles such as theobromine and theophylline. Association constants (K_a = 138 M^{-1}) for the formation of 1:1 complexes between caffeine and polyphenols were studied in solution by ^{1}H NMR spectroscopy and microcalorimetry.

Complexation studies of caffeine in aqueous solution have been performed with a number of known polyphenols and cyclodextrins. In recent years a great research effort has been made concerning the development of xanthine alkaloids having a consistent antibronchospastic, CNS stimulator and analgesic adjuvant activity [58,59]. Lilley and Haslam emphasized the importance of association of natural polyphenols with proteins and structurally related compound such as caffeine which have significantly influences factors like taste and nutritional value. The complexation of caffeine with polyphenols has been studied by Haslam et al. In aqueous medium, a range of phenols and natural polyphenols readily associate with caffeine and related other xanthine alkaloids (see Figs. 7–10).

The most important task to design artificial receptors [60–62] for recognition of this type of bigger binuclear substrate is to place the hydrogen bonding groups (donors and acceptors) in an appropriate cavity where the particular guest can make maximum number of hydrogen bonds with the host leading to a stronger complexation.

Like other xanthines and monomeric units of nucleic acids (bases, nucleosides and nucleotides) it is known to self-associate in aqueous solutions, but the nature of this association is a matter of dispute. It has been suggested that the association process [63,64] is such that aggregates containing several species occur,

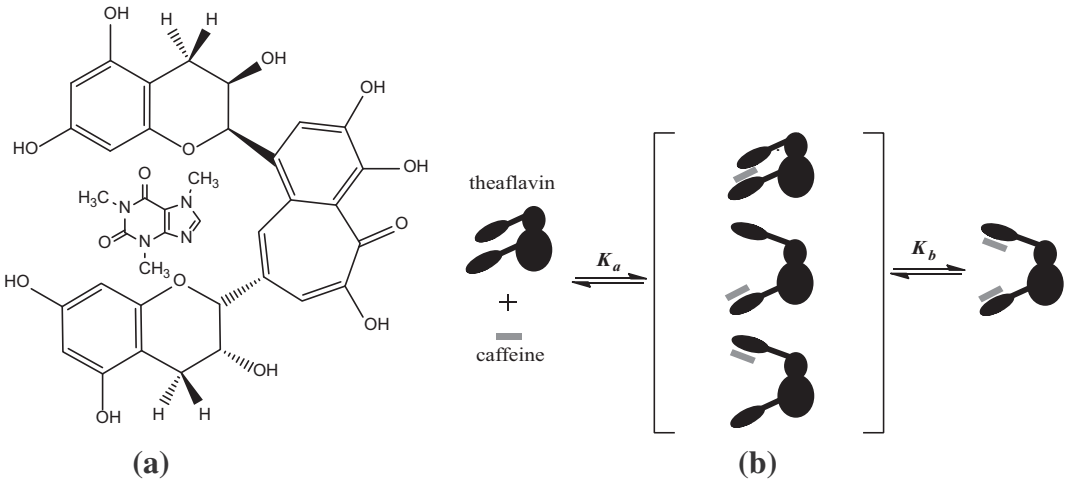


Fig. 7. (a) Theaflavin–caffeine complex (b) Proposed model by Williamson's group for the binding interaction between caffeine and theaflavin [67,68].

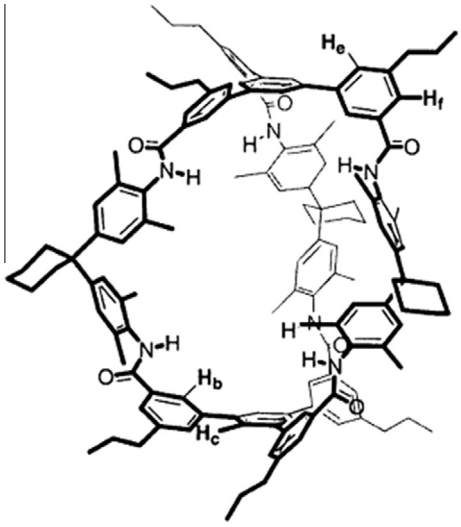


Fig. 8. Macrobicyclophane co-receptor for binding caffeine, developed by Ballester et al. [76].

while other results can be interpreted using relatively simple models. Lilley and group [65] investigated the association of caffeine in water and in aqueous sucrose solutions at 25 °C. The association constant (K_a = 58.3 M^{-1}) of caffeine with sucrose had been determined by solubility, distribution, enthalpy of dilution and NMR chemical shift measurements. All the results were consistent with a model (the isodesmic model) in which the caffeine associates to form dimers, trimers, etc. and for which, the equilibrium constant, for each step, in any solvent mixture studied, was the same. Values were presented for thermodynamic quantities which represent the solution properties.

The theaflavin family of polyphenols contribute to the taste and color of tea, and there complexation with caffeine is responsible for the formation of tea creaming. The self-association [43,66] (K_a = 2301 M^{-1}) of theaflavin and caffeine was studied using NMR methods and it is shown that caffeine forms stacked complex with theaflavin [67,68] while theaflavin forms stable dimmers.

The theaflavin monomer consists of a planar benzotropolone ring system, with the two flavan rings approximately orthogonal to this plane, and stacked against each other. In the dimer, two benzotropolone rings align with an antiparallel geometry. Two molecules of caffeine bind to one molecule of theaflavin in a strictly sequential manner, with first and second association constants of 11.9 and 16.5 l mol^{-1}, respectively. Tea contains many other polyphenols of similar structure which could play a similar role to theaflavin [34]. The above study was carried out in 10% dimethyl sulfoxide, in which binding constants are weaker than in water [69]. A comparison with previous studies [70] suggests that the binding constants will be roughly 30% stronger in water. This would imply that in tea caffeine is extensively self-associated and that theaflavin is almost entirely dimeric. However the weak binding of single caffeine molecules to dimeric theaflavin indicates that the concentration of both caffeine and theaflavin present in

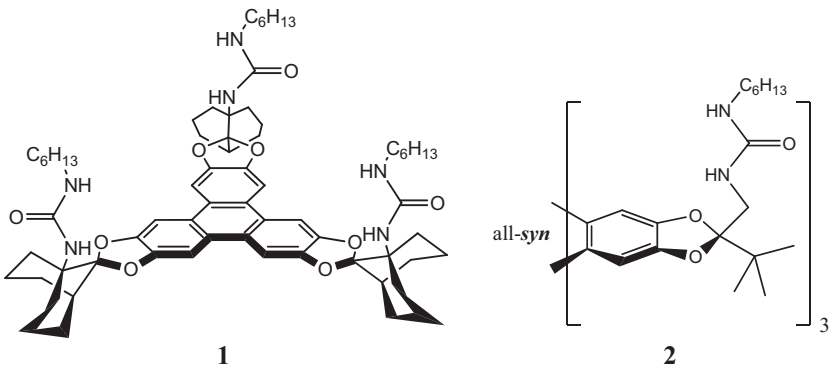


Fig. 9. Funtionalised triphenylene ketals receptor developed by Waldvogel's group.

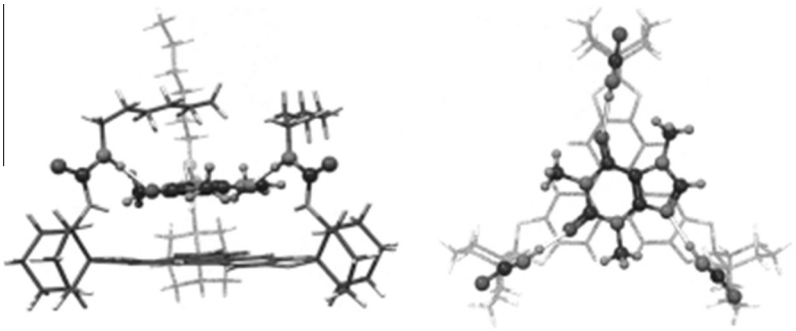


Fig. 10. X-ray crystal structure of the host–guest complex of 1 with caffeine. Caffeine and anchoring groups are emphasized as ball and stick method by Waldvogel et al. [77].

heterogeneous complexes will be low compared to their total concentration. If this is the case then it is likely that the thearubigins and/or other polyphenolic molecules (including the gallated theaflavins) present in black tea play an important role in the formation of tea cream. As the temperature is reduced, the binding constants become stronger, favoring supramolecular assembly. Such assemblies are typically insoluble. This observation therefore provides an explanation of the turbidity which forms as tea cools, known as tea creaming. The formation of tea creams reduces the concentration of soluble caffeine and polyphenols in tea, therefore changing the taste and mouth feel of the tea. The formation of tea cream, and the change in organoleptic properties associated with tea creaming, are predicted to be reduced if the concentration of either caffeine or polyphenols in tea is reduced.

4.2. Development of receptors

In the field of supramolecular chemistry various macropolycyclic architectures [71–75] have been constructed with an intense interest. A new co-receptor macrobicyclophane for binding caffeine has been developed by Ballester et al. [76]. The co-receptor binding sites are based on the hydrogen bonding abilities (K_a = 7050 ± 56 M^{-1}) of secondary amides. ^{1}H NMR titrations demonstrate molecular recognition of caffeine by formation of a 2:1 complex in $CDCl_3$.

The experimental studies reveal close intermolecular contact between the methyl groups of the caffeine and the aromatic and amide protons of the guest. The result also shows the good agreement with endocavity binding of the caffeine, in a geometry which places it parallel to the central benzene ring of the spacer and within stacking distance. This structure is also consistent with the large upfield changes in chemical shifts observed for the signals due to the caffeine methyl groups. The models of the free and bound forms of the guest suggest that there is no significant change in the conformation of the host on complexation.

Using molecular recognition and reactions with signaling ability, different novel sensors have been developed. In this context Waldvogel's group [77] proposed first artificial receptor for caffeine based on a scaffold of rigid functionalized triketals of hexahydroxy triphenylene [78] which perform as novel receptors for the selective recognition of caffeine including other alkylated oxopurines. They studied the host–guest interaction of receptor and caffeine in dichloromethane solution. NMR titration of the experiment confirms 1:1 stoichiometry of both components and show a complex formation constant of 35,600 M^{-1}.

Waldvogel's group also modified their triphenylene ketal [79] based receptor by which electrospray tandem mass spectrometry has been easily explored. Binding affinities of different xanthine alkaloids including caffeine are probed in the gas phase with collision induced dissociation. The relative stabilities of the substrate–receptor complexes are rapidly determined and the findings are correlated with the corresponding results in solution.

Using mass spectrometric analysis the above receptor provided a tool for the fast screening of various substrates. These results were mostly reliable and consistent even without applying the NMR spectroscopy. The reasonable results allowed qualitative conclusions concerning the stability of different substrates in above receptor (Fig. 11).

Molecular recognition using non-covalent interactions with abiotic receptors have some potential applications [80–85], such as sensors, carriers, and other molecular devices. Goswami et al. [86] designed and synthesized new polyphenolic synthetic receptors for caffeine. The binding results of caffeine are also studied by NMR and UV method.

They first designed the macrocyclic receptor (Fig. 12) for caffeine. But it was frustrating to see that the following fails to bind caffeine probably as the cavity was small such binuclear guest and the amide protons of the compound were also less basic. The guest caffeine is a basic compound (xanthine base) and therefore it needs acidic substrates for its stronger complexation (see Figs. 13–15).

The recognition strategy of substrate-induced association has been introduced by developing the different biomimetic semirigid receptors for the binding of caffeine and other xanthines as well. The binding studies reveal the space requirements of most favorable binding site of caffeine with the receptors. This follows the

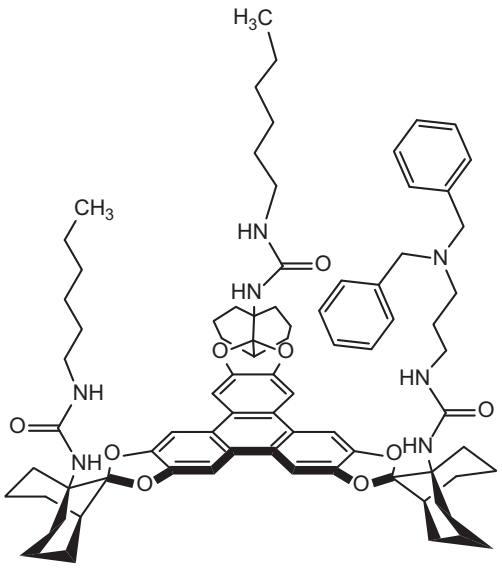


Fig. 11. Modified receptor for MS investigations developed by Waldvogel's group.

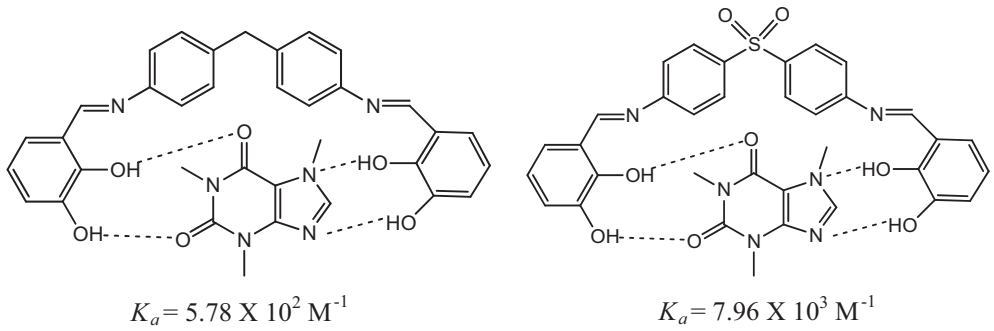


Fig. 12. Synthetic polyphenolic receptor–caffeine complexes.

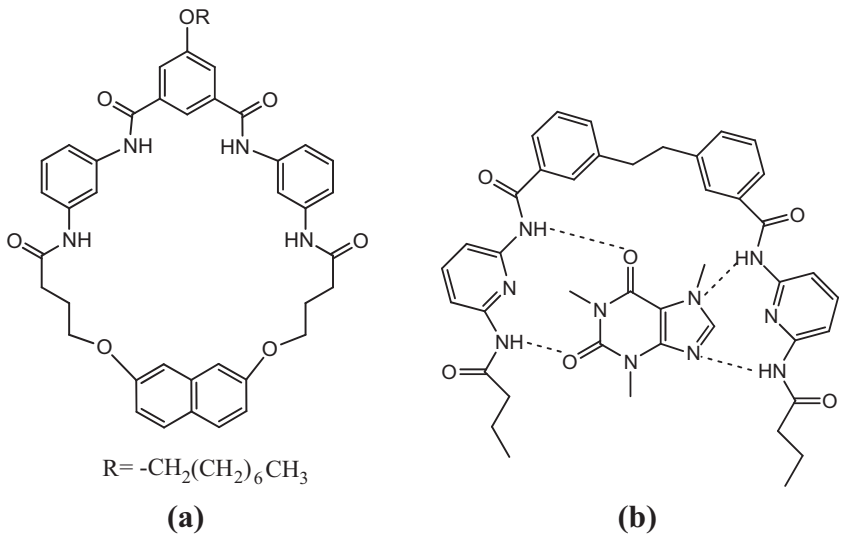


Fig. 13. The receptors made by Goswami and Mahapatra (a) first macrocyclic receptor for caffeine (b) receptor with large cavity to bind caffeine strongly.

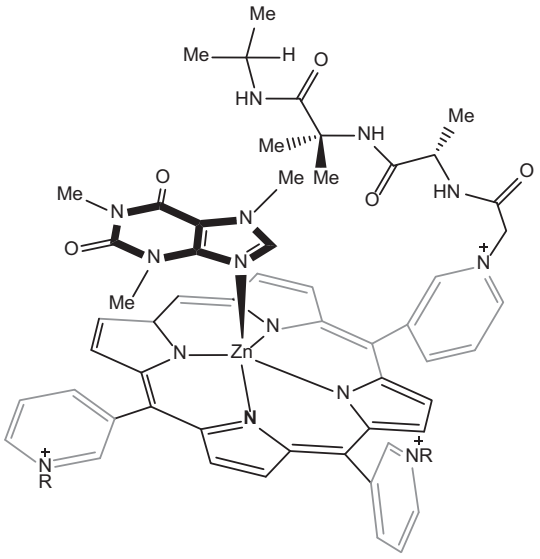


Fig. 14. Tetracationic peptide–porphyrine Zn co-ordinates receptor for caffeine.

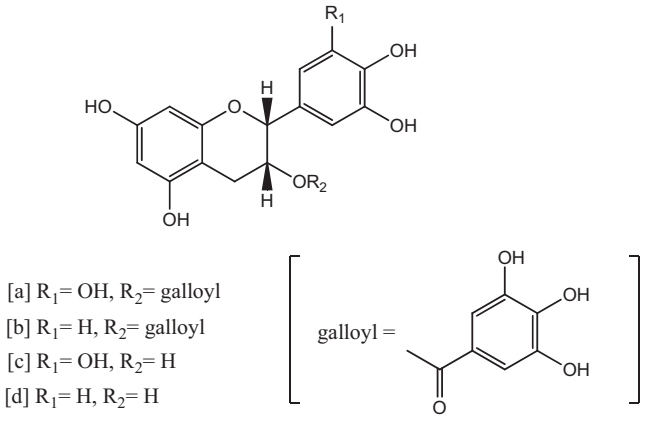


Fig. 15. Structure of the four major catechins in green tea.

creation of a bigger synthetic cavity in the functionalized receptors for caffeine.

Recognition of caffeine in aqueous solution has been achieved for the first time by using water soluble, tetracationic peptide–porphyrine Zn co-ordinates receptor molecules [87–93]. The binding mechanism has been studied by UV–vis, NMR and microcalorimetry. The association constant for caffeine with receptor shows very high (K_a = 6000 M^{-1}) with respect to low polar aprotic solvents (see Figs. 16–18).

The above work shows that the synthetic receptors can be achieved only very simple porphyrin–peptide conjugates which are developed by using one or two amino acids and, at the stage of the study, with relatively small differences in side-chain nature. The results show for the first time molecular recognition of caffeine

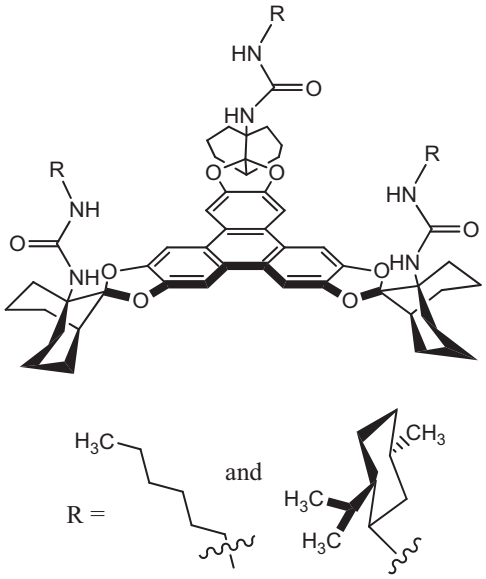


Fig. 16. Receptors for caffeine developed by Waldvogel's group [120].

in aqueous solution and provide a detailed view of the binding process coming from different experimental techniques. The data show that even porphyrin Zn-complex, which bears simple alkyl chains, binds caffeine. However, the use of amino acid or peptide chains allows the introduction of additional interactions. In particular, if the chains on the pyridyl rings are longer than ten interactions with the porphyrin surface and, therefore, influence on the recognition site become possible. The balance of the various contributions to binding is very subtle and involves competition for the hydrophobic surface and additional stabilizing stacking interactions.

Much more complex porphyrin–peptide conjugates, bearing chains as long as 20 amino acids and which mimic heme–protein have been reported [94]. The affinity of these water-soluble receptors may be tailored by proper choice of peptide moieties.

(+)-Catechin and (−)-epicatechin as well as their gallic acid conjugates are ubiquitous constituents of vascular plants. The two isomers are mostly associated with cacao and tea constituents. Catechins and their derivatives are thought to contribute to the beneficial effects ascribed to tea. Tea catechins and polyphenols are effective scavengers of reactive oxygen species in vitro and may also function indirectly as antioxidants through their effects on transcription factors and enzyme activities including various physiologically amended effects such as anti-carcenigenic [95,96] anti-metastatic [97] anti-oxidative [98,99], anti-hypertensive [100], anti-hypercholesterolemic [101] anti-bacterial [102], anti-dental carries and intestinal flora amelioration activities. The fact that catechins are rapidly and extensively metabolized emphasizes the importance of demonstrating their antioxidant activity *in vivo*. To explain the binding energy of a catechin–caffeine complex in water through molecular recognition, the Hayashi group [33] estimated stoichiometric ratios, binding constants and free energy of binding in water for the complexation between the four major tea catechins and caffeine by titration experiments with ^{1}H NMR. An investigation of the ^{1}H NMR chemical shift changes in the catechin–caffeine complex solution giving association constant (K_a) values of 89 M^{-1}.

The group concluded that both gallate-type and non gallate-type catechins can bind with caffeine in water though the gallate-type catechins had greater than the nongallate-type affinity for caffeine owing to the galloyl group.

Due to the ease of application and measurement, spectrometric applications have attracted considerably the attention of many researchers in the field of chemical sensoring. Fluorimetric methods convince by their extreme sensitivity and the ease of designing the appropriate system [103,104]. Several sensoring principles

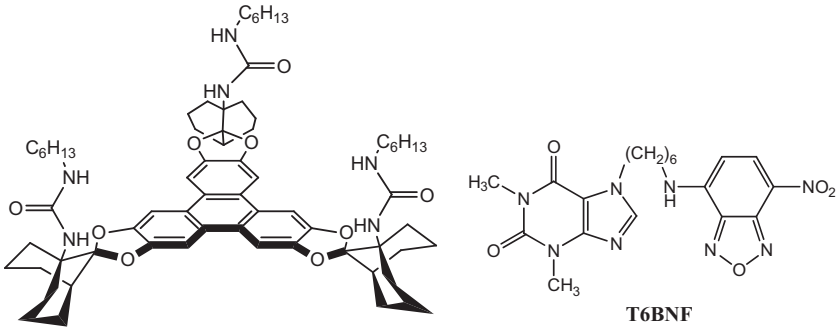


Fig. 17. Receptors for competitive indicator displacement assays by Waldvogel's group.

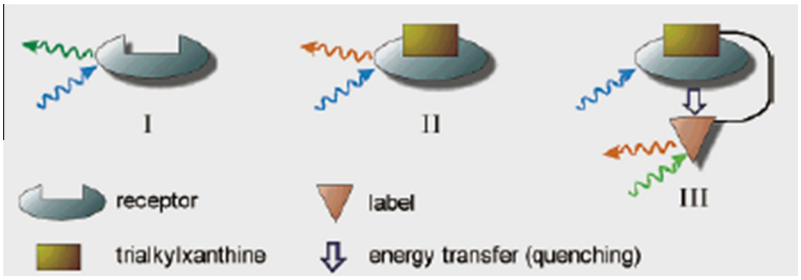


Fig. 18. Effects on fluorescence upon binding of receptor **1** (**I**) to caffeine (**II**) and a competitive guest with a quenching label (**III**). In **III** no emission from the receptor is observed [121].

require significant changes of the electronic structure and thus are limited to ionic analytes. In the molecular recognition of neutral molecules execute a huge variety of developments [105–110]. Fluorescent chemosensors that rely exclusively on hydrogen bonding are reported as well [111–119].

The Waldvogel's receptor based on triphenylene ketals influences their fluorescence properties while interact with oxopurines and specially used for sensing caffeine. This gives a rapid and easy insight into the binding behavior of synthetic caffeine receptors and their guests. This was the first approach proposed by Siering et al. [120].

In this contribution the stronger host–guest interactions has been established by the fluorometric detection of caffeine and caffeine derivatives bearing extended alkyl substituents with a supramolecular receptor. In addition, the group set up an unexpected, methanol induced self-aggregation, which could be utilized for the formation of controlled, surface-disposed layers.

Waldvogel's next report describes a competitive "indicator-displacement assays" approach to describe a realistic assay for caffeine by supramolecular sensing to charged analytes. The method also explains a simple analytical protocol by which quantitation of caffeine can be measured in beverages. Caffeine is found in many soft drinks and in various analgesics. Due to its adverse effect on minors and pregnant women, it is a desirable method for the determination of caffeine content in the beverages [121].

The small RNAs selectively bind and recognize small heterocyclic molecule theophylline and caffeine in its 13-mer binding pockets where caffeine and theophylline forms one and two H-bond respectively. In this way Mecozzi and Anderson [122] first demonstrated that a 33 nt RNA aptamer that binds to the bronchodilator theophylline with a *K*a of $\sim 3.3 \times 10^6\ M^{-1}$ was selected as a simple model system due to its small size and planar ligand. This aptamer (PDB code 1EHT) is able to discriminate against caffeine, with a 10^4-fold difference in binding affinity [123,124].

Molecular dynamics simulations 4 ns in length with explicit water solvent were performed on the 13-mer-theophylline complex as well as on the 13-mer-caffeine complex and the result predicted structural stability of the RNA and binding of those alkaloids. Thermodynamic integration calculations predicted binding energies, ΔG_{bind}, of theophylline and caffeine to the 13-mer as −5.8 kcal/mol (K_a = 16,800 M^{-1}) and −5.0 kcal/mol (K_a = 4400 M^{-1}), respectively. The predicted binding energies and selectivity were confirmed experimentally by in vitro binding assays of the 13-mer RNA with both theophylline and caffeine. This work suggests the new possibility for therapeutic intervention using very short RNAs.

Molecular recognition has been implemented in molecular imprinting technology. The concept of binding of a molecule to a "receptor" with high selectivity over its close structural analogues has been translated elegantly into the technology of molecular imprinting, which allows specific recognition sites to be formed in synthetic polymers through the use of various templates. Due to the specific nature of the interactions between rebinding template and the chemical functionalities within the pores or cavities of the cross linked polymer matrix, it is expected that molecularly imprinted solid phase extraction has the ability to discriminate between closely related compounds. Molecular imprinting technology allows specific recognition sites to be formed in synthetic polymers through the use of various templates [30–32].

The imprinted polymers find a wide range of applications in the field of separation science, analysis, sensor design, catalysis and so on. Molecular imprinting of synthetic polymers with a target molecule can be done if the target presents as a template or imprint molecule during the polymerization. Organic–inorganic hybrid materials have been found to be highly advantageous as they exhibit flexibility, low density, long shelf-life with excellent optical and mechanical properties [125–127].

In non-covalent molecular imprinting (the most common approach) the template interacts with a functional monomer via hydrogen bonding, electrostatic or hydrophobic interactions. This pre-polymerization complex is then incorporated into a polymer network by a cross linker. Molecularly imprinted polymers (MIP) that exhibit high selectivity and affinity to the predetermined molecule are a rapidly growing research focus. The special binding sites are formed by the self-assembly of a template molecule with specific functional groups and the monomer, followed by a cross-linking co-polymerization.

Lin et al. successfully synthesized transparent and monolithic, caffeine imprinted poly{(methacrylamide)-co-(vinyl trimethoxysilane)} and poly{(methacrylic acid)-co-(vinyl trimethoxysilane)}–silica hybrid MIP by a random free radical polymerization followed by sol–gel process. The methacrylamide [methacrylamide (MAAM)–vinyl trimethoxysilane (VTMOS)–hexamethyldisilazane (HMDS)] derived end capped MIP is showed higher selectivity as well as imprint factor than that of methacrylic acid-based polymers. The linear copolymers of functional monomers such as MAA/MAAM with VTMOS which obtained via free radical mechanism (Fig. 19) have the desired functionalities can undergo hydrolysis and condensation with TEOS under suitable conditions. A solution containing caffeine, 3% dilute hydrochloric acid was mixed with the copolymer solution in order to self arrange the template inside the cross-linked matrix. The copolymer–caffeine–TEOS mixture was stirred at room temperature for 15–30 min to initiate the hydrolysis of TEOS and resulted in a homogeneous solution. The formation of covalent bonds between the polymer and TEOS during the sol–gel reaction prevents the thermodynamically induced

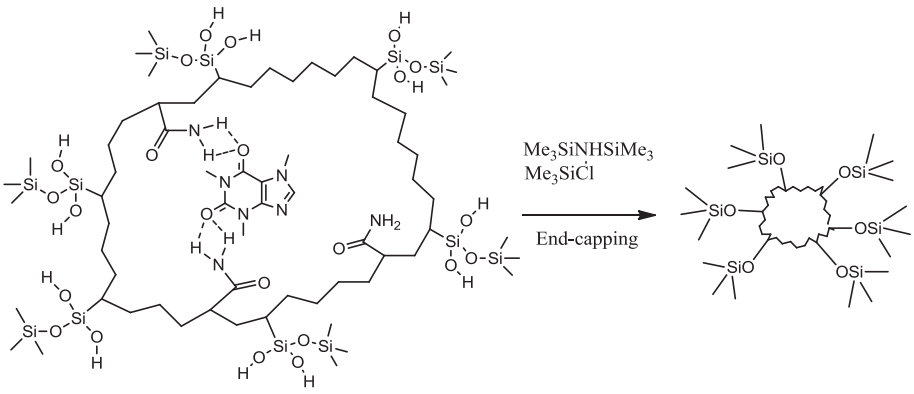


Fig. 19. Organic–inorganic hybrid MIP.

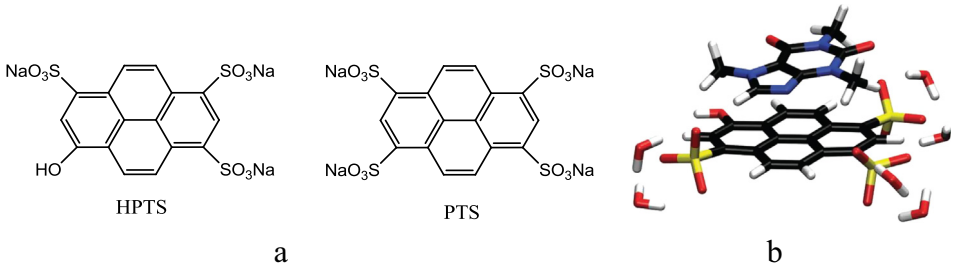


Fig. 20. (a) Structure of HPTS and PTS (b) energy minimized structure of caffeine–HPTS complex [136].

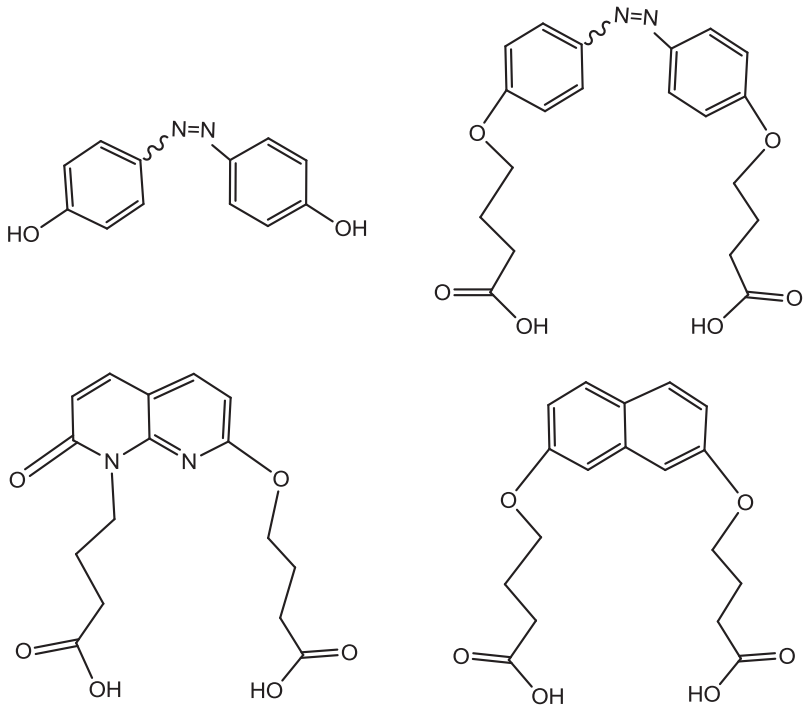


Fig. 21. Different fluorescent receptors for caffeine recognition.

organic–inorganic phase separation as well as maintains a regular organization of the template molecule in the polymer matrix (see Fig. 20).

The effective utilization of organic–inorganic hybrid MIP is the stationary phase of column chromatography (HPLC) and chemical sensor applications. The main disadvantages of the molecularly imprinted polymers (MIP) are ionic and non-specific adsorptions, which can be prevented to a considerable extent by the end capping of surface silanol groups [128–131]. The non-specific adsorption due to the surface silanol moieties prevented effectively by end capping with trimethylsilyl groups.

A molecularly imprinted polymer (MIP) was formed using an inorganic polymer by a sol–gel process. The monomers which were used to synthesize the inorganic polymer were tetraethoxysilane (TEOS), triethoxymethylsilane (MTES), and triethoxyphenylsilane (PTES). Caffeine was chosen as a template for the molecular imprinting, and theophylline was chosen as the analogous counterpart compound. The discriminating ability of the synthesized MIP to these two-compounds was estimated in this study. The MIP showed the highest discriminating ability when the ratio of TEOS:MTES:PTES in the synthesis of the inorganic polymer was 1:1:3, the α value was highest when the reaction temperature of the sol–gel reaction was 50 °C, and the pH of the reaction system was ~6.5 [132–135].

In conclusion, the result showed that the balance between the hydrophobic character and the amount of hydroxyl groups in the MIP is important to achieve the highest discriminating ability.

Severin's group [136] first proposed the commercially available fluorescence dye 8-hydroxypyrene-1,3,6-trisulfonate (HPTS) which can be used as a selective molecular probe for the detection of caffeine in aqueous solution as the dye is soluble and stable in water even in the presence of oxygen. The dye displays a high quantum yield and a long excitation wavelength. In aqueous solution, HPTS aggregates with viologen derivatives and with organometallic p-complexes to result in a pronounced quenching of the fluorescence. Using these characteristics the group investigates HPTS as a potential probe for the detection of caffeine in water.

Our group [137] designed some artificial fluoro receptors (Fig. 21) based on the structural features of caffeine, a difficult recognition targets as its nitrogen's are fully methylated causing N-CH_3 moiety a poor recognition site for binding.

The most important task to design artificial receptors for recognition of this type of bigger substrate is to place the hydrogen bonding groups (donors and acceptors) in an appropriate big cavity where the particular binuclear guest can make maximum number of hydrogen bonds with the host leading to stronger complexation.

The simple hydrogen-bonding acidic fluoro-receptors formed stronger complexes with methyl xanthine, caffeine. Therefore a

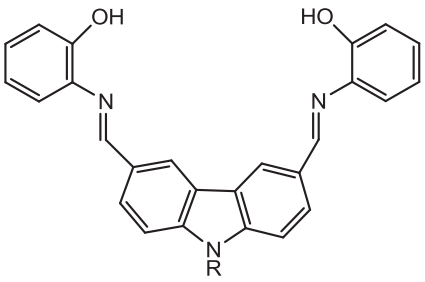


Fig. 22. The carbazole based imino-phenol flurescent probe for caffeine detection.

mixture of caffeine and non-natural acidic receptor will be more associated than isolated solutions of each species. During the course of the investigations, it was found that the binding of caffeine with acidic receptors is stronger than that of other xanthine alkaloids. The more basic nature of the caffeine among the other xanthines studied suggests stronger association constants with the acidic receptors. In fact caffeine guest leads to an increasing signal and produces a reliable and fast identification method of the caffeine content in beverages. Our results imply that the removal of caffeine from foods or drinks containing appreciable quantities of caffeine will be significantly determined by sensing caffeine.

Our group also [138] presents the promising fluorescent probe: carbazole based imino-phenol for caffeine detection. The receptor exhibits a highly sensitive and selective fluorescence enhancement toward the caffeine over other xanthines in aqueous buffer (pH 7.2). The host–guest interaction has been accomplished in aqueous solutions by using the 'turn-ON' fluorescence sensing of caffeine while binding with the receptor. The design of a water-soluble carbazole fluorosensor for caffeine possessing two imino-phenol moieties have an affinity toward the ring oxygen and most basic imidazole 'N' of the caffeine. We chose carbazole as the signal transduction unit because of its chemical stability, large Stokes shift and high fluorescence quantum yield [139].

The detection of caffeine with this new fluorescent probe (Fig. 22) of high sensitivity and selectivity has been developed (Fig. 23). The group established imaging of caffeine in living cells in aqueous media first time (Fig. 24). The receptor was successfully expressed in cells, which demonstrates its potential usefulness as a molecular probe in biological systems.

In conclusion, the fluorimetric detection of caffeine by use of artificial supramolecular receptor is possible. This system represents a powerful chemosensor method for the detection of

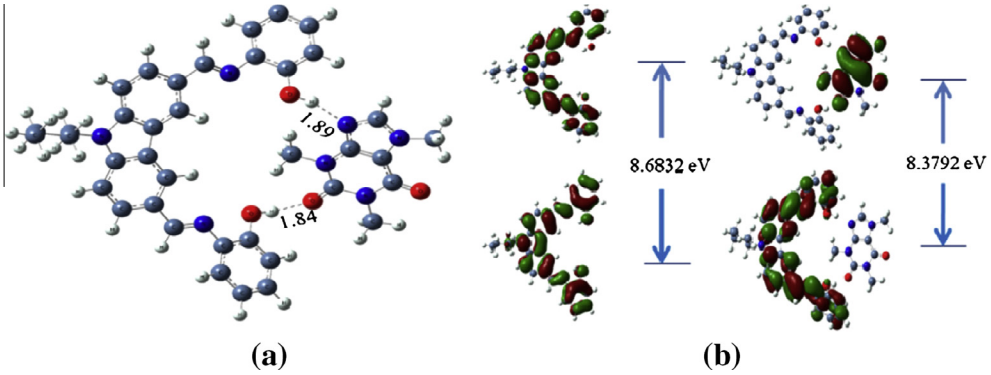


Fig. 23. (a) Energy-minimized structure of the Probe 1–Caffeine complex (b) HOMO and LUMO of Probe 1 and Probe1–Caffeine Complex observed by Mahapatra et al. [138].

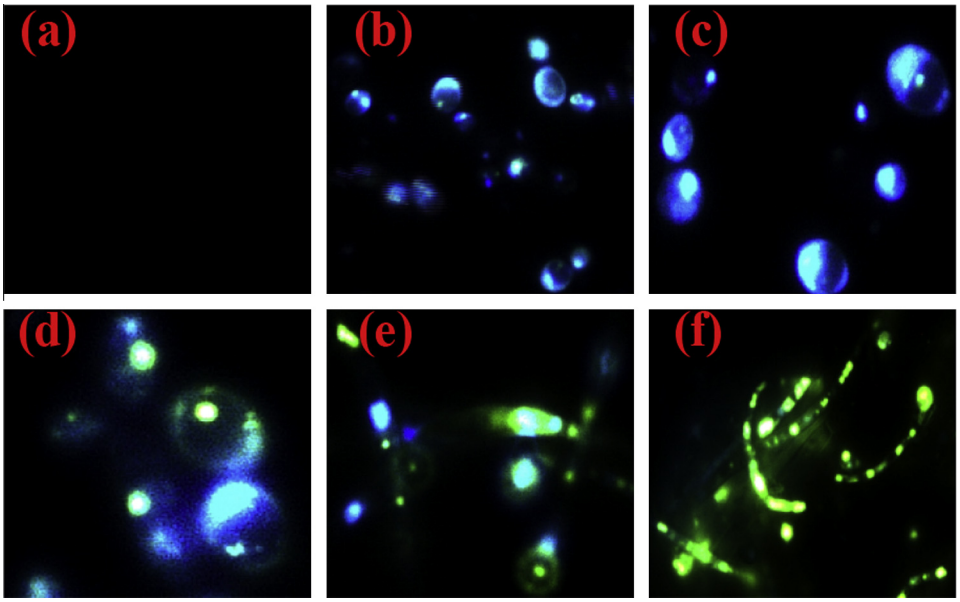


Fig. 24. Fluorescence and brightfield images of living cells (a) images of Candida albicans cells + probe 1 (10 lM) (b) images of cells + probe 1 + caffeine (5.0 lM), and fluorescence images (c–f) of Candida albicans cells incubated with 10 lM, 20 lM, 30 lM, 40 lM of probe 1 for 25 min, respectively.

medicinally and technically highly-relevant analytes. A consistent picture of binding of the receptors with caffeine is highlighted.

5. Solid state recognition of caffeine

5.1. Caffeine co-crystalisation

Caffeine, a pharmaceutically important alkaloidal drug [5,140,141], whose solid-state phase behavior is of interest to the manufacturing industry. The compound readily forms a hydrate, whose crystal structure has been determined by single crystal X-ray diffraction. The hydrate may transform ambient conditions to an anhydrous β-phase, which in turn converts to a second anhydrous α-phase at higher temperature. It appears that no fully or ordered crystal-phase has ever been isolated for pure caffeine; these two phases still defy a complete structural determination, because only powders and disordered crystals are obtained. Caffeine is a model pharmaceutical compound that is known to be unstable to humidity with the formation of a crystalline non-stoichiometric hydrate [142]. It is commonly employed as a formulation additive to analgesic remedies (analgesic adjuvant) [19] due to its weak basic character; the weakly basic imidazole nitrogen of caffeine results in a pK_a of 3.6 [143]. Due to its weak basicity, caffeine may be particularly suited for co-crystallization in its neutral form with aromatic carboxylic acids and polyphenols.

Our ongoing interest in the field of molecular recognition to study the hydrogen bonding interactions of caffeine with the substrates of acidic moiety inspired us to investigate the supramolecular behavior and to locate improves properties of caffeine in hydrogen bonding environment in the solid state. Interestingly, it is known that polyphenols form complexes with caffeine, especially in black tea and coffee. Such complexation is not only an interesting chemical phenomenon, but also may show interesting unique biological activities. We thus intended to know the detailed structure of the complex of polyphenols and carboxylic acids with caffeine in the crystal state. Thus a plenty of discussion on the solid state recognition of caffeine has directed us to construct the following objectives.

(i) To study crystal engineering concept to the template directed solid state synthesis of molecular targets and development of other functional materials
(ii) To investigate the role of non-conventional interactions in the formation of supramolecular structure e.g. C–H···O, π-stacking, ion dipole interaction
(iii) To check supramolecular crystal lattice in the presence of solvent
(iv) To establish hydrogen bonding selectivity with different types of acidic and basic centers
(v) To investigate the new pharmaceutical properties through co-crystallization of model pharmaceutical compound caffeine with acidic substrates.

5.2. Importance of co-crystal

Co-crystallization of pharmaceutically active molecules represents a viable means of enhancing physical properties. Co-crystals have emerged as an important tool in the design and construction of solid state materials with tailor-made properties [144–148]. Co-crystals, one of the synthetic targets in crystal engineering, are long known class of compounds [149–151]. The pharmaceutical co-crystals are a subset of a broader group of multi-component crystals that comes from supramolecular context.

They are related to one another in that at least two components of the crystal interact by hydrogen bonding and other non-covalent interaction rather than by ion pairing. Most recently, in the field of pharmaceuticals, co-crystallization has been shown to be an effective means of altering a drug's physical properties, such as solubility and melting point [152–154]. Several of these are pharmaceutically acceptable co-crystals, including 1:1 complexes of caffeine with antibiotic sulfa drugs [155–157]. There have been a number of studies investigating the complex between caffeine and dicarboxylic acid which disclose robust supramolecular network characteristic for caffeine–carboxylic acids assemblies [158,38,40,41]. Further, we noticed that the carbonyl group of caffeine, in a molecular complex of caffeine with methyl 3,4,5-trihydroxybenzoate (methyl gallate) [35], served as a hydrogen bond acceptor in an O–H···O bond with the benzoate component. Several caffeine co-crystals were reported and systematic crystal engineering study of polyphenolic and aromatic hydroxy dicarboxylic acid is important to develop model pharmaceutical co-crystals of caffeine and this has been attractive.

6. Molecular recognition of caffeine with polyphenols and carboxylic acids

Caffeine possesses a number of features which optimize its effectiveness as a small molecule for complexation with polyphenolic substrates. The phenolic group is a good proton donor but a poor proton acceptor in hydrogen bonding systems. It is assumed that in the complexation of caffeine with polyphenols, hydrogen bonding between the polyphenol (proton donor) and the caffeine (proton acceptor) may ultimately make specific contribution to the stability of the complex. Some important complexation studies on caffeine in solid state performed with a number of known polyphenols and cyclodextrins receptor has been reported. Caffeine is difficult recognition target as its nitrogen is fully methylated causing N-CH_3 moiety a bad recognition site for receptor.

The complexation of caffeine with simple polyphenols has been studied by Baxter et al. [43] in solid state by using X-ray crystallographic analysis of the complexes of caffeine with methyl gallate (Fig. 25) and 3-nitrobenzoic acid [159,39]. Although caffeine is at least 95% present in dimeric form which breaks in presence of strong hydrogen bonding acidic substrate such as, polyphenol and other acidic substrate.

Some other caffeine and polyphenol complexes were reported by several scientists using potassium chlorogenate by Gorter (Fig. 26), 5-chlorosalicylic acid by Shefter and pyrogallol by Arnone. Interestingly they are investigated that these crystalline, intermolecular complexes are characterized by a layer lattice structure in which the caffeine and the aromatic substrate are stacked in alternating layers, which are approximately parallel, with an interplaner separation of 3.3–3.4 Å.

The crystal structure of the caffeine complex with potassium chlorogenate [160,37], first isolated from coffee beans by Gorter shows similar features as noted above in the case of methylgallate and pyrogallol. However, an additional critical stabilizing factor is the coordination of seven oxygen atom in an irregular polyhedral arrangement around the central potassium cation (Fig. 26).

The critical survey of various reports and reviews on the interaction of caffeine with polyphenols thus reveals the importance of xanthine alkaloids having consistent antibronchospastic, CNS-stimulation and trachycardial activity. Some significant progress has been made in complexation study of caffeine with natural polyphenols by Haslam group.

The hydrophobic contribution is nevertheless probably the most important single factor influencing caffeine–polyphenol interaction in aqueous medium. Distinctive features of all the crystalline phenol–caffeine complexes are examined by X-ray studies which show the relative orientation of the planar caffeine and

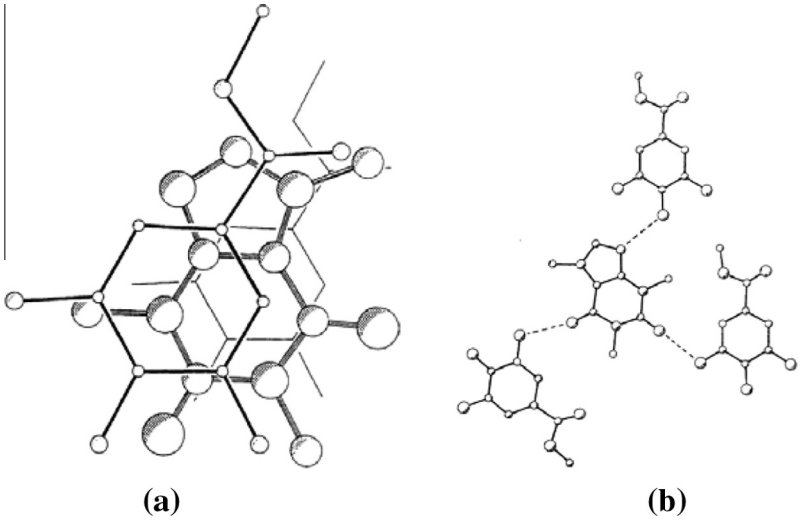


Fig. 25. (a) Caffeine–methyl gallate complex: Layer lattice structure (b) caffeine–methyl gallate complex: In plane hydrogen bonding. [159,39].

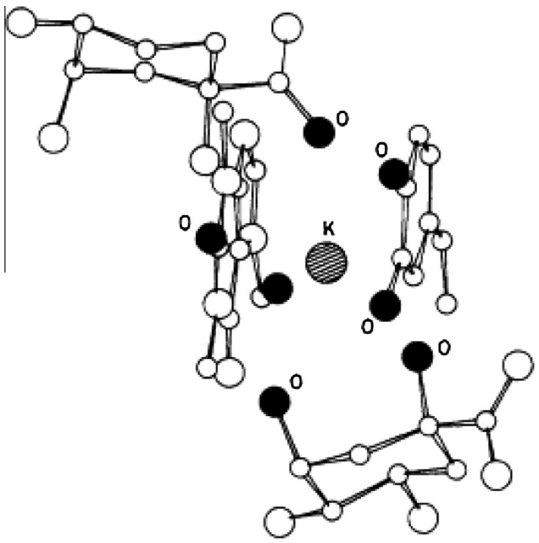


Fig. 26. Potassium chlorogenate complex with caffeine, isolated from coffee beans by Gorter [160].

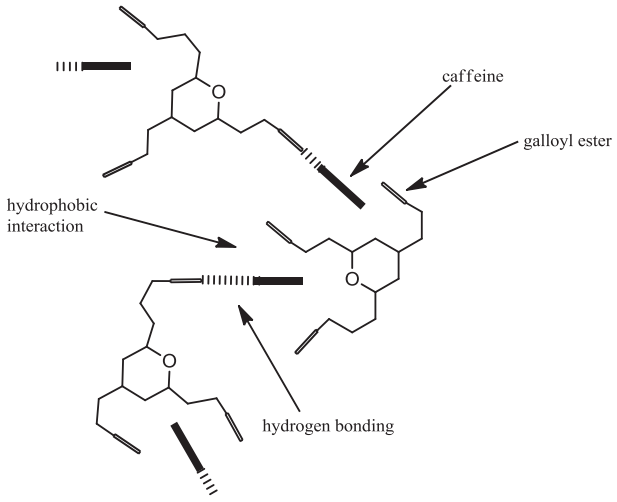


Fig. 27. Different types of interactions with caffeine–polyphenol complexation.

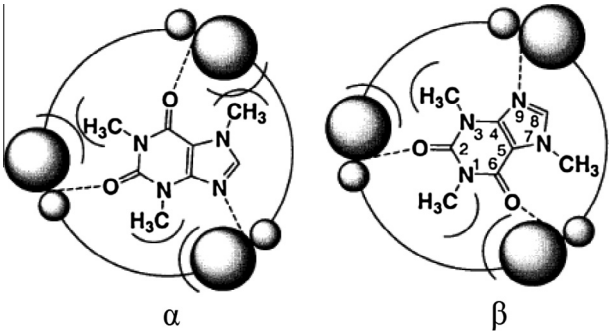


Fig. 28. Enantiofacial isomers α- and β-forms of caffeine, first proposed by Waldvogel [161].

the phenolic partner in the layer lattice. On the basis of these observations it is possible to suggest that the polarization bonding forms in solution. In the following model (Fig. 27), caffeine molecules cross-link by hydrophobic stacking and/or hydrogen bonding with separate polyphenol molecules.

A comprehensive study was therefore undertaken by Astill et al. [44] to determine the contributions of product and preparation variables on the total soluble solids, caffeine and polyphenol contents of tea extracts. The results of this study show that the variety, growing environment, man featuring conditions and grade (particle size) of the tea leaves each influencing the tea leaf and final infusion composition. Additionally, the composition of the tea infusion was shown to be influenced by whether the tea was contained in a teabag and, if so, the size and material of construction of the bag. Finally, the preparation method, including the amounts of tea and water used, infusion time, and amount of agitation, was shown to be a major determinant of the component concentrations of tea beverages as consumed.

The novel concept for the enantiofacial differentiation of caffeine molecules by supramolecular interactions were first proposed by Waldvogel [161]. He suggested two enantiofacial isomers α- and β-forms of caffeine (Fig. 28). These two forms of caffeine can efficiently crystallize in the solid state with suitable receptors using steric demands of the alkyl groups.

From the spectroscopic studies in solution and investigations of the caffeine complexes in the solid state, the group concludes the triphenylene ketals based chirally modified receptors are capable of enantiofacial differentiation of single molecules of caffeine.

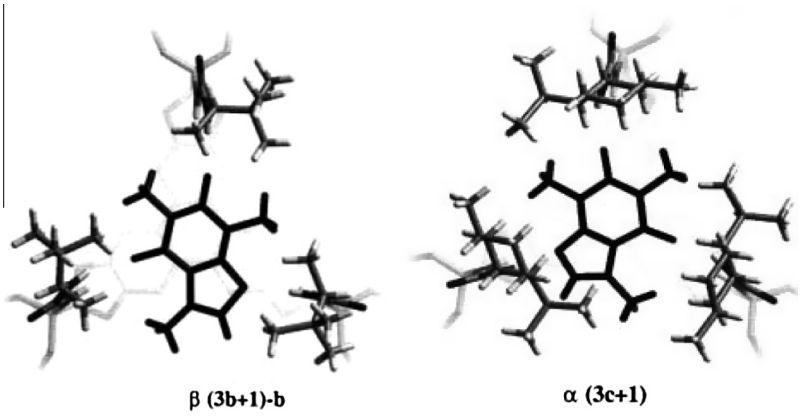


Fig. 29. Molecular structure of the caffeine complexes [161].

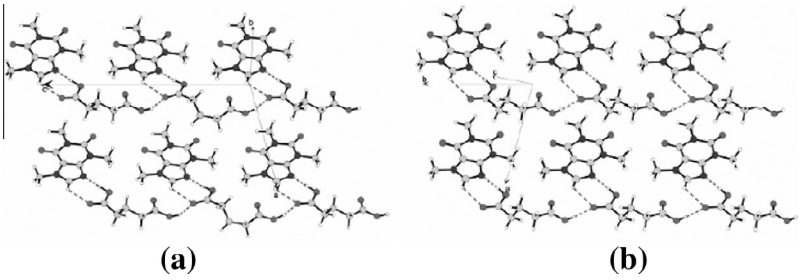


Fig. 30. Caffeine–glutaric acid co-crystal polymorph (a) monoclinic and (b) triclinic identified by Jones's group [41,162].

The repulsive interactions of two different isomers can be achieved by steric modifications of the cavity of the receptor.

From the crystal analysis a consistent picture of enentiofacial differentiation has been achieved both in solution as well as in the solid state. Thus for the combination of 3b with 1, the crystal structure shows that exclusively the b form is present (Fig. 29), while 3c behaves as a cage where caffeine is placed into the menthyl substituted receptor. When caffeine is placed into the menthyl substituted receptor 3c it behaves as though it were in a cage. Thus, both diastereomeric forms were found in the crystalline phase. For occupation of the disfavored β form, one arm of the receptor has to turn through about 40°. The caffeine molecule and the arm of the receptor are disordered in this particular complex which is a result of the partial formation of the α complex at this specific position (see Fig. 30).

The new technique of co-crystallization i.e. solvent drop grinding methodology with a minimal addition of a solvent of appropriate polarity is successfully used for preparation of caffeine–glutaric acid polymorph control of co-crystallization in a green chemistry fashion. Jones's group [41,162] identified two polymorphs of caffeine–glutaric acid co-crystal at ambient temperature of a chloroform solution. Single crystal Xray diffraction analysis identified the cocrystals are the rods as monoclinic and the blocks as triclinic (Fig. 21). Both polymorphs possess 1:1 caffeine: glutaric acid stoichiometry and exhibit identical secondary architecture, such that a two-dimensional sheet results from an array of hydrogen bond-containing ribbons.

Caffeine is known to exist as two anhydrous crystal forms (α- and β-) and one crystalline nonstoichiometric hydrate [163,164]. The nonstoichiometric crystalline hydrate of caffeine has been reported to contain 0.8 mol of water per mole of caffeine [165]. Gavezzotti's group [166] first isolated anhydrous and hydrated caffeine single crystals (Fig. 22). In this contribution the molecular recognition energies between two caffeine molecules and also between caffeine and water have been calculated. The results reveal the largely predominant mode to be the stacking of parallel caffeine molecules, an intermediately favorable caffeine–water interaction, and many other equivalent energy minima for lateral interactions of much less stabilization power (see Fig. 31).

When caffeine crystallizes in the presence of water, the caffeine–water complex is probably already present before crystals are formed. The solvent is then retained as a surrogate for

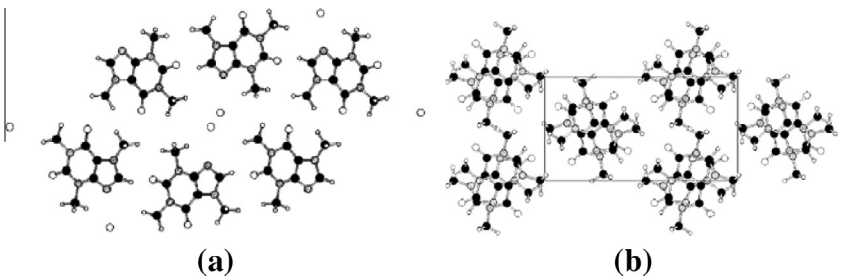


Fig. 31. (a) The crystal structure of caffeine monohydrate (b) the crystal structure of anhydrous caffeine proposed by Gavezzotti group [166].

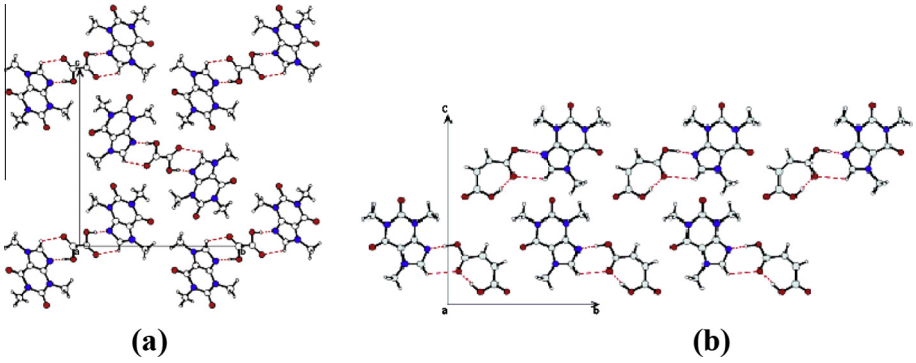


Fig. 32. Crystal packing of (a) caffeine with oxalic acid and (b) caffeine with glutaric acid reported by Jones group [38].

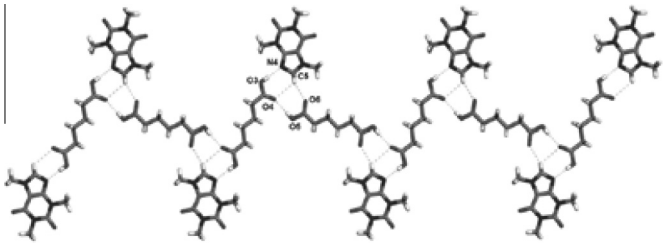


Fig. 33. A view of caffeine–adipic acid trimers along the crystallographic plane.

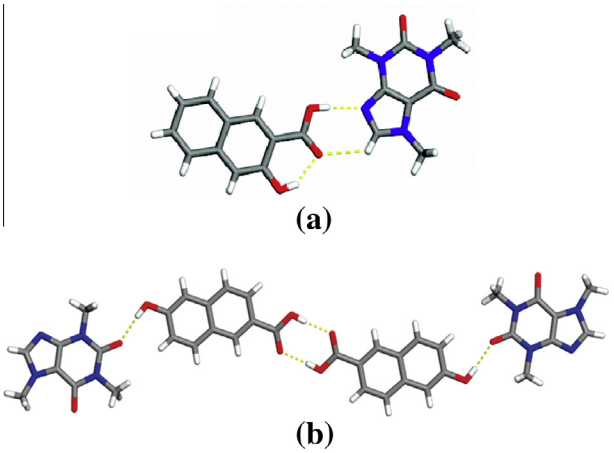


Fig. 34. (a) A perspective view of the neutral 1:1 caffeine:3-hydroxy-2-napthoic acid assembly (b) a perspective view of the 1:1 caffeine:6-hydroxy-2-naphthoic acid, established by Zhang's group [168].

solute–solute hydrogen bonding and for weak and scarcely selective lateral interactions. By the same reasoning, when caffeine monohydrate loses water, it cannot simply recrystallize by closing the voids. If there is enough energy to break the water–caffeine bond, there is also enough energy to break the weak intercolumn interactions. Once the leading recognition mode, stacking, has been satisfied, there is uncertainty among a number of energetically almost-equivalent, lateral interactions among the six recognition sites, thats why caffeine cannot easily crystallize in the absence of water is that.

Jones group [38] reported a series of co-crystals of the model pharmaceutical compound caffeine with dicarboxylic acids. The crystal structures for a total of five co-crystals containing caffeine with oxalic, malonic, maleic and glutaric acids had been isolated and a systematic crystal engineering study was performed by his group (Fig. 32). Cocrystals were formed in 2:1 and 1:1 caffeine/acid stoichiometries by the methods of solution precipitation and solid-state grinding. The relative humidity (RH) stability profile of these cocrystals differed from pure crystalline caffeine, in that no cocrystal hydrates have been found; rather, the cocrystals that were unstable with respect to RH generally exhibited dissociation into crystalline starting components. By this means it clearly demonstrates the approximate stability to that of caffeine, whereby they were unstable at high RH but stable at lower RH. In the context of the goal of pharmaceutical cocrystallization is to engineer pharmaceutical cocrystals with specific improved properties which measure the resultant change of a targeted physical property (see Fig. 33).

The crystals from caffeine/acid materials significantly differentiated between salts (ionic complexes) and cocrystals (neutral complexes). For each of the crystal structures obtained, acidic protons were located on the acid in the X-ray difference maps, which confirmed in each case that salt formation (ionization) had not occurred. It is also noted that ambient temperature FT-IR spectra of each powder sample exhibited a broad peak ranging from ca. 2200 to 2800 cm^{-1}, interpreted as the O–H stretching modes of un-ionized, strongly hydrogen-bonded carboxylic acids. The lack of a band associated with a symmetric carboxylate stretch, which typically would be observed from ca. 1300 to 1420 cm^{-1}, is further indication of the nonionic character of these complexes. A stoichiometry of 2:1 caffeine/acid is observed for the cocrystal of **caff–oxalic acid** and **caff–malonic acid** from the solved crystal structures, and for the cocrystal of **caff–maleic acid** from ^{1}H NMR. The trimeric caffeine–acid–caffeine motif is also demonstrated in above structures.

A hidden co-crystal of caffeine and adipic acid was first identified by Zhang's group [167] using the novel co-crystal screening technique. Here caffeine and adipic acid built a three component caffeine–acid–caffeine adduct through a "zipper" like solid state assembly (Fig. 24). Caffeine and adipic acid build a three-component caffeine–acid–caffeine adduct linked with a strong O–H...N hydrogen bond and a weak C–H...O hydrogen bond type interaction. This trimeric adduct is assembled with another molecule of adipic acid, which links the caffeine–acid–caffeine trimer into a molecular tape via O–H...O and C–H...O hydrogen bonds. The existence of cocrystals without extensive crystallization trials can be determined rapidly by hidden co-crystal screening method.

To improve the physical properties of caffeine (e.g., physical stability against hydration), as well as model compounds for studying preparation methods (e.g., solvent-free grinding) and structural effects associated with pharmaceutical co-crystals in general, now a days different co-crystals of caffeine with carboxylic acids have been studied through crystal engineering. Bucar et al. [168] synthesized and analyzed a group of caffeine-containing co-crystals of hydroxyl-2-napthoic acids *via* single crystal X-ray diffraction and

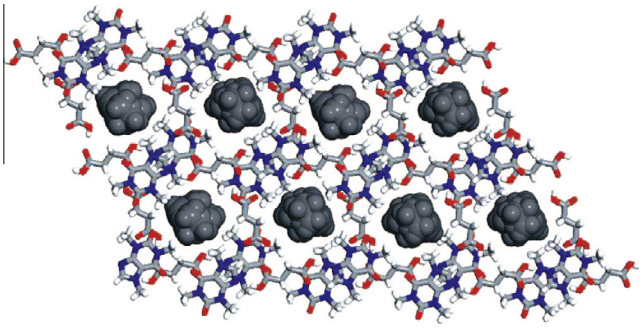
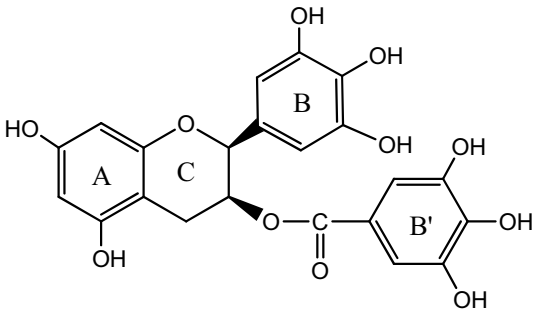
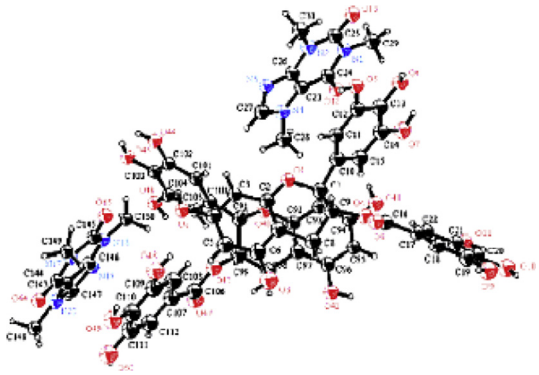


Fig. 35. Fragment of two-component host framework caffeine along with disordered guest molecules succinic acid, proposed by Friscic et al. [169].



(-)-Gallocatechin gallate (GCg)

(a)



(b)

Fig. 36. (a) Chemical structure of Gallocatechin gallate (GCg) (b) ORTEP drawing of GCg–Caffeine complex, prepared by Ishizu's group [170].

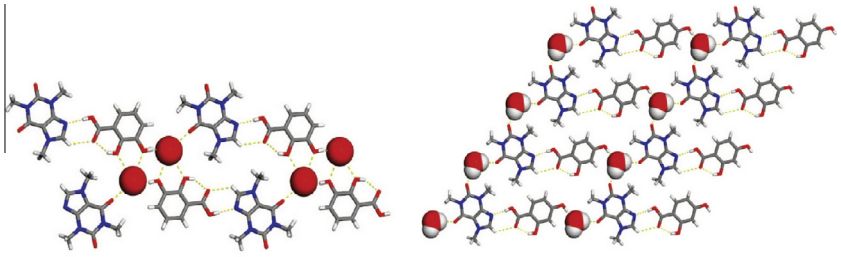
IR analysis. The known imidazole–acid synthon, structural analyses of these solids have revealed an unusual case in which a carboxylic acid dimer forms in the presence of a rationally introduced heterosynthon. The imidazolecarboxylic acid heterosynthon was observed in co-crystals involving 1-hydroxy-2-naphthoic and 3-hydroxy-2-naphthoic acid (Fig. 34a and c). In case of 6-hydroxy-2-naphthoic acid, the co-crystal exhibits a hydrogen-bonded carboxylic acid dimer in the presence of a hydroxyl–caffeine heterosynthon.

Friscic et al. [169] proposed two alternative inclusion host lattices which has been obtained from the cocrystallisation of caffeine and succinic acid. They described two host frameworks based on the same heteromolecular building block **caffeine–succinic acid** having different topologies. The **caffeine–succinic acid** building block is a flat molecular assembly where previous report says for multicomponent host lattices that achieved molecular inclusion using bowl-shaped constituents. The group suggests that the inclusion capability of the new hosts is most likely caused by the dumbbell shape of the assembly that hinders the formation of a close-packed structure in the absence of a guest. The heteromolecular building blocks of **caffeine–succinic acid** are based on the assembly of common, dumbbell-shaped frameworks (Fig. 35). A grinding-based screening procedure revealed that host formation is dependent on the molecular recognition properties of the guest but independent of the state of aggregation, allowing the inclusion of compounds that are solids, liquids, or gases under ambient conditions.

Altering the relative ratio of components in a co-crystal, host frameworks switch from one to another. To manipulate the stoichiometric composition of a co-crystal, the heteromolecular host frameworks described herein also exhibit properties attractive for molecular storage: the versatility to absorb molecules that are solids, liquids, or gases at ambient conditions and the flexibility of the inclusion channel.

In aqueous solution a merohedrally twinned crystal of the complex of (−)-gallocatechin gallate and caffeine was prepared by Ishizu's group [170] and also X-ray crystallographic analysis was performed. The driving force for the formation of the complex was thought to be mainly the π–π interaction B′ ring [33] of GCg and caffeine, the B ring of GCg and caffeine (Fig. 36a and b).

The Zhang's group [171,172] described nine cocrystals involving caffeine and structural isomers of (di)hydroxybenzoic acids. The cocrystals are studied using a new technique which is based on thermodynamically driven solution-mediated phase transformation (**SMPT**). This method enabled the rapid discovery of nine new solid phases involving caffeine. These caffeine phases were identified using single-crystal X-ray diffraction and FT-IR spectroscopy as cocrystals based on 2-, 3-, 4 hydroxybenzoic- and 2,3-, 2,4-, 2,5-, 3,4-, and 3,5-dihydroxybenzoic acids (Fig. 37). This novel work provide further groundwork for designing and modulating



(a) **(b)**

Fig. 37. (a) polymeric ribbon containing caffeine, **2,3-DBA** and water cross-linked via O–H(water)···N(imidazole), O–H(carboxy)···N(imidazole), and O–H(water)···O(hydroxy) hydrogenbonds, (b) 2D network involving caffeine, **24DBA** and water sustained by O–H(water)···O(carbonyl) and O–H–(hydroxy)···O(water) hydrogen bonds, Zhang's group [171,172].

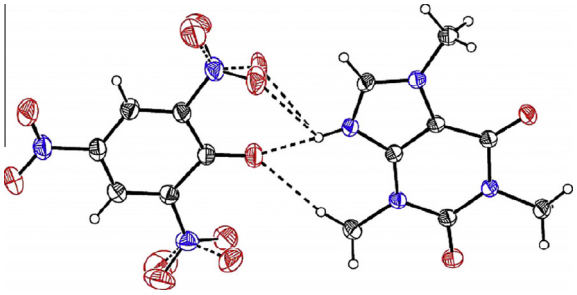


Fig. 38. Single-crystal molecular structure of CAFP, Kandavelu's group [173].

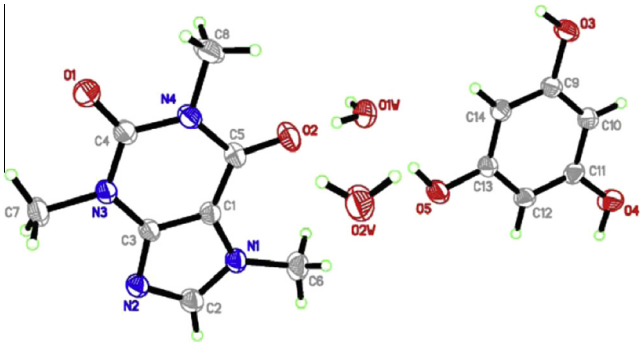


Fig. 40. ORTEP diagram of co-crystal A [174].

the structures of pharmaceutically relevant solids as caffeine is the combination of combinations of amide, urea, and imidazole groups which are prevalent in pharmaceuticles agents. The ease of the highly efficient screening method to discover cocrystals is also expected to further benefit the area of solid-state chemistry of multicomponent solids.

Caffeine possesses a total of three sites that can act as hydrogen-bond acceptors. One group is based on an N-atom of an imidazole while the remaining two groups are based on O-atoms of carbonyl groups of a urea and an amide moiety. Author selected CCFs acts as multiple hydrogen bond donors to increase the diversity of synthons in caffeine based cocrystals. A CCF with multiple hydrogen-bond donor and acceptor groups can be expected to interact with more than one PA and, hence, afford assemblies with high PA:CCF ratios. The group selected a carboxylic acid with single and multiple donor groups along the periphery as a CCF because imidazole–carboxylic acid interaction is the most prevalent heterosynthon in caffeine-based cocrystals. Since hydroxy groups are known to participate extensively in hydrogen bonds with carbonyl groups, mono- and dihydroxybenzoic acids were selected as CCFs. The crystal structure data suggested that the urea and amide carbonyl groups of caffeine could interact with the pendent hydroxy groups of the CCFs.

The first charge transfer organic molecular salt complex between caffeine and picric acid (Fig. 29) was synthesized by Kandavelu's group [173]. Good-optical-quality single crystals of caffeiniumpicrate (CAFP), were successfully grown by the slow evaporation solution growth technique at room temperature. The molecular structure of CAFP was established by different technical methods e.g., UV–vis, FT-IR, NMR spectral techniques, etc. The UV–vis spectrum exhibits the clear π–π^* band of picrate ion in this new organic charge transfer molecular complex salt. From the powder XRD pattern the various planes of reflections have been identified. From TG/DTA analyses the decomposition temperature and percentage weight loss of the material has been obtained (see Fig. 38).

The other four co-crystals [174] are of respectively caffeine with phloroglucinol (Cocrystal A), isophthalic acid (Cocrystal B), 4-hydroxy benzoic acid (Cocrystal C) and 5-hydroxy isopthalic acid (Cocrystal D). In these solids, caffeine forms molecular complexes in which the carboxyl group interacts with the N atom of the imidazole ring via an O–H···N hydrogen bond. The desired supramolecular interaction was the acid–base heterodimer synthon [175] (Fig. 39) through strong O–H···N and weaker C–H···O hydrogen bonding [35,176–179]. Caffeine forms co-crystals [180–183] with carboxylic acid components which are held together by one of the two heterosynthons: (i) an $R_2^2(7)$ heterosynthon and (ii) an $R_3^3(11)$ network based on $R_2^2(7)$ and $R_2^2(6)$.

The crystal structure analysis reveals that an asymmetric unit of each co-crystal **A, B, C** and **D** contain a minimum one molecule of caffeine and one molecule of acidic substrate. Co-crystals of **A** and **D** form hydrated crystals with two and one molecule(s) of water respectively in their asymmetric units.

Authors have chosen weak acidic groups like carboxyl or hydroxyl group to see the binding with caffeine where they wanted to prove the strong acid–base interaction in the co-crystals i.e. between carboxyl and imidazole moieties without any proton transfer which actually happens. All the four complexes are neutral as determined from X-ray structure analysis. The carbon–oxygen bond distances were consistent with the formation of a non proton transferred co-crystal in each case but not the formation of ionic co-crystal through carboxylate ion. Salts and co-crystals are multicomponent crystals that can be distinguished by the location of the proton between an acid and a base. The Fourier difference map suggest that the acidic proton was located 0.876–0.975 Å from the O atom of the carboxylic acid.

Co-crystal **A** is a crystal of (Fig. 40) caffeine and phloroglucinol which form a co-crystal hydrate with two molecules of water. The components of the co-crystal hydrate are held together by hydrogen bonding and crystallizes in the monoclinic *P*21/c space group where unit cell contain four molecules ($Z = 4$).

Co-crystal **B** is developed by crystallizing caffeine and isophthalic acid. The numbering scheme of co-crystal **B** is shown in Fig. 41. The caffeine and isophthalic acid forms two binary component assemblies involving an intermolecular O–H···O and O–H···N hydrogen bonds. The acid –base pairs interact parallaly *via* weak van der Waals forces to form stacks. The stacks are sustained by C16–H16B···O1 hydrogen bonds [180,181].

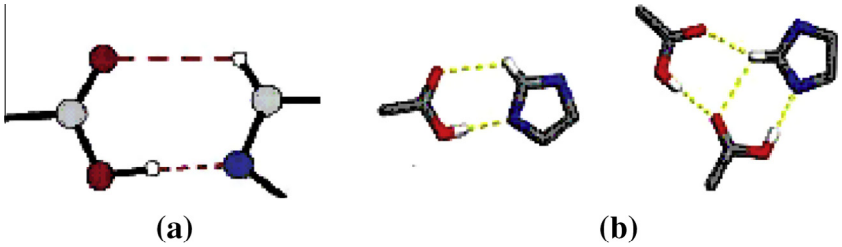


Fig. 39. (a) Heteromeric synthon 31b showing strong O–H···N and weaker C–H···O hydrogen bond interactions. (b) the most common acid-imidazole heterosynthons present in caffeine–carboxylic acid co-crystals.

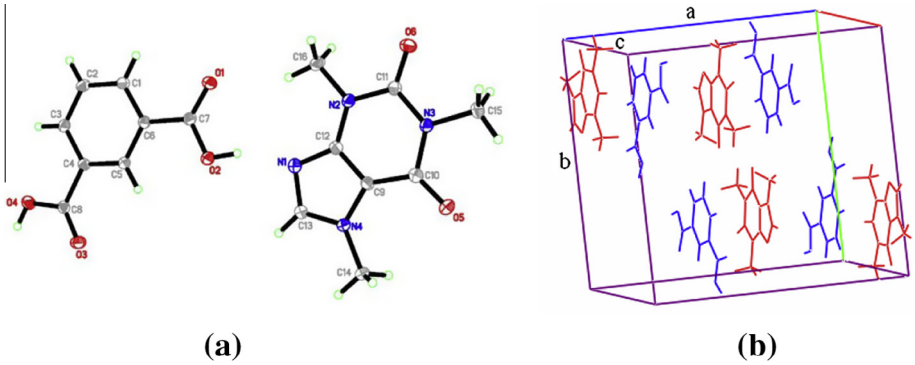


Fig. 41. (a) ORTEP diagram of co-crystal **B** (b) Co-crystal **B** showing (a) the crystal packing structure: red for caffeine and blue for isophthalic acid.

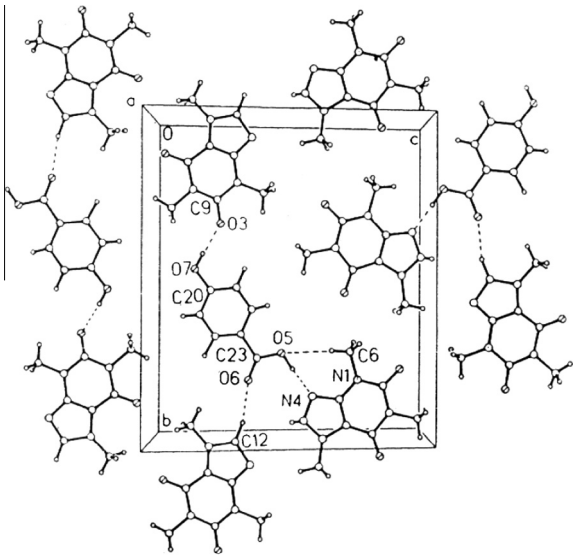


Fig. 42. Hydrogen bonding network of caffeine and 4-hydroxybenzoic acid 2:1 complex [182].

Caffeine and 4-Hydroxybenzoic acid crystallizes to form co-crystal **C.** In 4-hydroxy benzoic acid, both the acidic functionalities are of considerable acidic character to make a stronger association with caffeine. The complexation was also evidenced by ^{1}H NMR spectrum of the co-crystal of the complex (Fig. 42) in $CDCl_3$ which shows 2:1 proton ratio of 4-hydroxy benzoic acid and caffeine respectively. Here we report, the unprecedented C–H···O hydrogen bonding [182] mediated molecular complexation of caffeine and 4-hydroxybenzoic acid.

Co-crystal **D** is made of Caffeine and 5-hydroxy isophthalic acid which is associated with one water molecule. Co-crystal hydrate **D** crystallizes in the triclinic $P\bar{1}$ space group where the unit cell contains two molecules ($Z = 2$). Interestingly the complex was organized in a 3D stair [183–185] like (Fig. 43) supramolecular network in the solid state.

From the above study the group established that an asymmetric unit of each co-crystal A, B, C and D contain a minimum one molecule of caffeine and one molecule of acidic substrate. Co-crystals of A and C form hydrated crystals with two and one molecule(s) of water respectively in their asymmetric units. Weak acidic groups like carboxyl or hydroxyl group have been chosen to see the binding with caffeine where we wanted to prove the strong acid–base interaction in the co-crystals i.e. between carboxyl and imidazole moieties without any proton transfer which actually happens. All four complexes are neutral as determined from X-ray structure analysis. The carbon–oxygen bond distances were consistent with the formation of a co-crystal in each case but not the formation of ionic co-crystal through carboxylate ion. Salts and co-crystals are multi-component crystals that can be distinguished by the location of the proton between an acid and a base. The group has also performed the IR spectral analysis of the complexes which agreed with the simple hydrogen bond formation and that no proton transferred complexes were formed. Additionally, analyses of the carbonyl stretching band in the infrared spectra, which are all above 1600 cm^{-1}, confirmed un-ionized carboxylic acids and thus co-crystal formation for these new phases occur. A typical ionized carboxylic acid salt band would be expected to occur 1300–1420 cm^{-1}, is further indication of the nonionic character of these complexes.

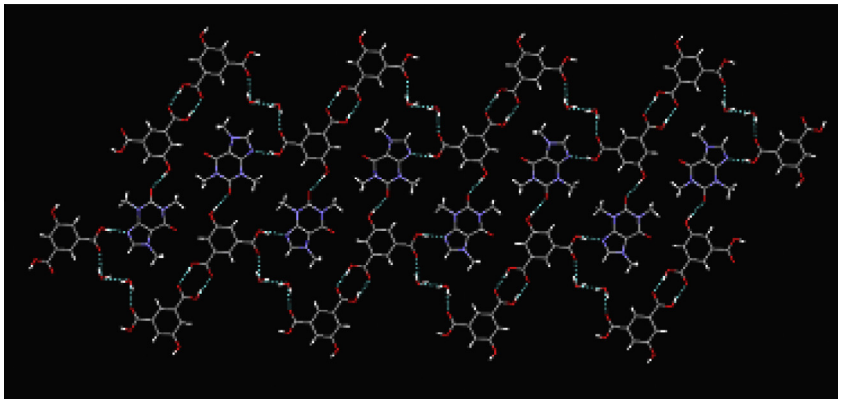


Fig. 43. Co-crystal C showing the crystal packing structure: green for caffeine, blue for 5-hydroxyisophthalic acid and red for water molecule.

7. Conclusion

Caffeine's widespread use and popularity have caused many people to view the substance as an addictive drug. Thus making caffeine is the most inexpensive and readily available drug known to man. Then on the other hand there are people who view caffeine as a helpful stimulant that increases the individual's concentration and awareness as well as many other physical traits. The important thing to remember is that caffeine's affects based on the person, the amount ingested the frequency of consumption, and individual metabolism.

The present review illustrates the immense variety of receptors that have been designed for molecular recognition caffeine in both solid and solution phase. Emphasis was put on the understanding of the goal of developing artificial molecular receptors, capable of binding very efficiently and very selectively with caffeine. The modern bioorganic chemistry concerns the design of synthetic molecules that mimic various aspects of enzyme chemistry and to understand their essential roles in biological systems.

All the systems described above in solution phase are to investigate the significant selectivity and high affinity for the target molecule in organic solvent and aqueous media as well, for promising applications in caffeine detection. The fluorimetric detection of caffeine by use of artificial supramolecular receptors represents a powerful chemosensor method for the detection of medicinally and technically highly-relevant analytes. Moreover the removal of caffeine from foods or drinks containing appreciable quantities of caffeine will be significantly determined by sensing caffeine.

The hydrogen bonds are used extensively as a tool to design the structure of molecular crystals, because of their strength as well as directional nature relative to other intermolecular non-covalent interaction. The understanding of the nature of non-covalent intermolecular forces responsible for molecular recognition and selectivity has become a major focus of mention in biological chemistry. One facet of this problem concerns plant polyphenols. Polyphenols of proanthocyanidins, ester of gallic acid, hydroxybenzoic acid and hexahydroxydiphenic acid are a distinctive group of higher plant secondary metabolites.

The goal of pharmaceutical co-crystallization is to develop pharmaceutical co-crystals with specific improved properties. The aim of the co-crystallization study through designed pharmaceutical co-crystals measures the different physical properties. In this contribution, several model pharmaceutical co-crystals of caffeine with aromatic hydroxyl compounds, dicarboxylic acid and hydroxy carboxylic acids are structurally described. It was the aim of the study to design a series of pharmaceutical co-crystals with diverse structural functionality to be involved into the self-assembly processes.

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