Chapter-3

Urea as an Adductor
Urea was discovered in 1773 by Rouelle as a component of urine (Rouelle, 1773) and it was first synthesized in the laboratory in 1828 by F. Wöhler (Wöhler, 1828). This initial synthesis from ammonia and hydrogen cyanate is of historical importance in that it was the first time an organic compound had been synthesized using an inorganic reagent; this result was contrary to the doctrine of vitalism which was prevalent at that time, and hence the demise of vitalism was initiated.

Urea is quite versatile and has continued to demand attention ever since its discovery. This small molecule is biologically important, and has commercial and industrial utility. However, for over the past 70 years a large amount of chemical research involving urea has been undertaken due to the capacity of urea to form inclusion compounds with a large variety of organic materials. A brief overview of various interesting aspects of urea is as follows:

### 3.1 Urea as an organic compound

![Urea molecular structure](image)

**General properties** (Budavari, 1996)

**Molecular formula** \((\text{NH}_2\text{CO})\)

**Synonyms** Carbamide, carbonyldiamide.

**IUPAC name** Diaminomethanal

**Molecular weight** 60.06

**Chemical composition** C 20.00\%, H 6.71\%, N 46.65\%, O 26.64\%

**Occurrence** Occurs as tetragonal prisms, colorless, odorless, develops odor of ammonia on improper storage.

**Melting point** 134.7°C melts with decomposition.

**Taste** Cooling, saline taste.

**Density** 1.32 g/cm³
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**Solubility**

Urea is known to exhibit following solubility profile in various solvents:

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>1000</td>
</tr>
<tr>
<td>95% alcohol</td>
<td>100</td>
</tr>
<tr>
<td>Boiling 95% alcohol</td>
<td>1000</td>
</tr>
<tr>
<td>Absolute alcohol</td>
<td>50</td>
</tr>
<tr>
<td>Methanol</td>
<td>167</td>
</tr>
<tr>
<td>Glycerol</td>
<td>500</td>
</tr>
<tr>
<td>Chloroform</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Petroleum ether</td>
<td>&lt; 0.1</td>
</tr>
</tbody>
</table>

**Densities of aqueous solutions**

<table>
<thead>
<tr>
<th>Strength (w/v)</th>
<th>Density (g/cm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1.027</td>
</tr>
<tr>
<td>20</td>
<td>1.054</td>
</tr>
<tr>
<td>50</td>
<td>1.145</td>
</tr>
</tbody>
</table>

**pH of aqueous solution (10%)**

7.2

**Decomposition Products on heating**

Biuret, ammonia and cyanuric acid.

**3.2 Urea as a physiological substance**

Urea occurs in nature as the major nitrogen-containing end product of protein metabolism by mammals, which excrete urea in the urine. It is synthesized in the liver by urea cycle, wherein one of the nitrogen comes from ammonia and the other is transferred from amino acid aspartame, while the carbon comes from carbon dioxide (Brusilow and Horwich, 2001). It is then secreted into the blood stream (normal blood urea level: 2.5 -7.5 mmol/l blood) and taken up by the kidneys for excretion in the urine. The adult human body discharges almost 50 g (1.8 oz) of urea daily. In addition small amount of urea is excreted in sweat along with sodium chloride (Nelson and Cox, 2005).
Urea is used in many commercial protein supplements in veterinary practice and is sometimes used in mixing feed on the farm. Urea is included in beef cattle diets to economically replace a portion of the protein content (Clanton, 1978). If properly used, urea is an *inexpensive protein source*. It is used most frequently and efficiently in high grain diets because starch in the grain is rapidly digested once it enters the rumen. Bacteria must have sufficient amounts of carbohydrates available in the rumen to make protein. Energy from roughages is digested too slowly for efficient use of urea. Thus, higher levels of urea can be used when cattle are fed grain versus forage-based diets. (Woods, 1997)

### 3.3 Urea as a commercial chemical

Commercial uses of urea include:

- As a raw material for the manufacture of plastics specifically, *urea-formaldehyde* resin
- As a raw material for the manufacture of *various glues* (urea-formaldehyde or urea-melamine-formaldehyde). The latter is waterproof and is used for marine plywood
- As a component of *fertilizer and animal feed*, providing a relatively cheap source of fixed nitrogen to promote growth
- As an alternative to rock salt in the *deicing of roadways and runways*. It does not promote metal corrosion to the extent that salt does
- In textile laboratories used both in dyeing and printing as an important auxiliary
- As an additive ingredient in *cigarettes*, designed to enhance flavor
- Sometimes used as a *browning agent* in factory-produced pretzels
- As an ingredient in some *hair conditioners, facial cleansers, bath oils and lotions*
- It is also used as a reactant in some *ready-to-use cold compresses* for first-aid use, due to the endothermic reaction it creates when mixed with water
- Active ingredient for diesel engine *exhausts treatment*
- Used, along with salts, as a *cloud seeding agent* to expedite the condensation of water in clouds, producing precipitation
- As a clean burning fuel for motor vehicles and stationary engines
Urea as an Adductor

- As a flame-proofing agent
- As ingredient of many tooth whitening products
- Used as protein denaturant in laboratory
- Frequently used in textile laboratories, both in dyeing and printing, as an important auxiliary for providing solubility to the bath and retaining some moisture which is required for the dyeing or printing process
- Used in fertilizing the ocean, which is suggested to reduce atmospheric CO$_2$ concentrations by encouraging algal blooming

Medical and diagnostic uses

- Urea is used in topical dermatological products to promote rehydration of the skin
- Preparations covered by an occlusive dressing, used for nonsurgical debridement of nails
- Blood urea nitrogen (BUN) test is a measure of the amount of nitrogen in the blood that comes from urea, indicates a moderate-to-severe degree of renal failure
- C$^{14}$-labeled urea used in the urea breath test (used to detect the presence of Helicobacter pylori in the stomach and duodenum of humans (The test detects the characteristic enzyme urease, produced by the bacteria, by a reaction that produces ammonia from urea)

Regulatory status of urea

Urea as a formulation aid is included in Generally Recognised as Safe list by FDA (CFR, 1984)

As per International Program on Chemical Safety (INCHEM):

Urea is an important endogenous product of protein and amino acid catabolism and consequently 20-35 g of urea is excreted daily in human urine. The blood concentration of urea is also relatively high, 3.3-6.7 mmol/L. It can be expected that the human organism is well adapted to urea within the physiological range of concentrations and even beyond. This is supported by clinical evidence from high dose administration orally and intravenously for therapeutic purposes. This may partly explain why urea has not been rigorously studied with toxicological tests. Nevertheless, urea appears to cause little
or no toxicity to most mammalian species (ruminants are more sensitive because of microbial ammonia production) and humans at reasonable dose levels. Hence, urea should be of low current concern to human health. The estimated human exposure (EHE) level for urea can only be given very crudely, and it can probably vary widely depending on the food consumed. *As a tentative value 3 g/day (about 40 mg/kg body weight/day) is proposed.* (INCHEM, 1997)

### 3.4 Urea as a crystal

Urea is a white crystalline material melting at 134.7 °C and X-ray diffraction patterns of urea reveal a tetragonal structure with extensive hydrogen bonding, wherein each carbonyl oxygen is involved in a hydrogen bond with both anti hydrogen of each adjacent molecule (*Figure 3.1*).

At room temperature and at zero pressure, urea lattice consists of ribbons of molecules linked in a head-to-tail fashion along the tetragonal c-axis (Zavodnik *et al.*, 1999). Each ribbon is surrounded by four identical orthogonally oriented ribbons pointing in the opposite sense along the c-axis. The urea molecule is planar and retains its full molecular point symmetry. Each carbonyl oxygen atom accepts four N-H.........O hydrogen bonds, an unusual feature for such a bond type (Smith, 1952). This dense (and energetically quite favorable) hydrogen bond network is probably established at the cost of efficient molecular packing: the structure is quite open, the ribbons forming tunnels with square cross-section 3.94 Å X 3.94 Å. The strongest interaction involves the double H-bond in the head-to-tail arrangement of urea dimers, while the single H-bond linkage between anti-parallel ribbons yields about half as much (Zavodnik *et al.*, 1999). The hydrogen bonds are thus all of similar strength, as reflected also by their nearly identical length.
Fig. 3.1 Crystal structure of tetragonal urea at room temperature (Zavodnik et al., 1999)
3.5 Urea as an adductor

In 1940, Bengen stumbled upon the fact that \( n \)-octyl alcohol forms an inclusion compound with urea. He was investigating the behavior of milk proteins in the presence of urea (Bengen, 1940). He found that any attempt to separate the fat resulted in the formation of troublesome foams, so he added a few drops of \( n \)-octanol as an anti-foaming agent. After distillation, the residue was found to contain crystals of urea-\( n \)-octanol complex. Thus was discovered the first of the long series of urea channel compounds. In subsequent years, Bengen demonstrated that similar crystalline adducts could be formed with a variety of linear organic compound (Bengen, 1951, Bengen and Schlenk, 1949). By the beginning of the following decade, Smith had thoroughly determined the crystal structure of the urea hexadecane inclusion compounds (Smith, 1952) and this structure still stands as the defining host structure of most urea inclusion compounds.

In the presence of straight-chain hydrocarbons urea generally forms a \textit{hexagonal helical structure surrounding a canal like void space}. A helical canal is the one in which one part of the wall have the characteristics of a helix, that is unidirectional coupling of rotation about, and translation along the canal axis (Bishop and Dance, 1989). Other example of helical inclusion compounds in solution is starch-iodine complex, in which a starch molecule has formed a helix around a straight chain of iodine molecules (Saenger, 1984). This complex is additionally stabilized by chemical bonding. The term \textit{canal}, \textit{cannel}, \textit{tube}, \textit{tunnel} have been used by various authors to describe host cavities extended in one dimension without restriction to cross-sectional shape (Bishop and Dance, 1989). Weber and Josel proposed the terms \textit{helical tubuland} for the host structure and \textit{helical tubulate} for the host-guest complex (Weber and Josel, 1983).

The urea host structure has the hexagonal space group \( p6_{1}22 \), in which \( 6_{1} \) screw axis passes along the canal. The urea molecules occur in columns, and radiate from \( 3_{1} \) screw axes, with O atoms close to the axis. Additional symmetry elements are \( 2_{1} \) screw axes parallel to and midway between adjacent \( 3_{1} \) axes, and lateral two-fold axes pierce the canals and \( 6_{1} \) axes at intervals of \( c/12 \) (Bishop and Dance, 1989).
3.5.1 Fundamental structure of urea inclusion compounds

The urea inclusion compounds generally crystallize in long, hexagonal prisms or occasionally as hexagonal plates (for example with cetyl alcohol). The crystalline structure of urea-linear hydrocarbon inclusion compounds has been determined by X-ray diffraction studies (Schlenk, 1949a; Smith, 1952). The unit cell is hexagonal and the structure has six urea molecules per unit cell (Fig. 3.2).

The sequence of urea molecules around the canal axis constitutes a triple helix. The overall structure of the crystal is that of parallel tubes in which the hydrocarbon molecules are held together in a loose network of hydrogen bond between the nitrogen and oxygen atoms. The urea molecule is coplanar with the walls of the hexagonal prism, and the prisms are packed into a distinctive honeycomb lattice. The lattice is maintained by the maximum possible number of hydrogen bonds: the two donors by each NH$_2$, and four acceptor by each oxygen atom (Fig. 3.3). Each oxygen atom is linked by hydrogen bonds to four nitrogen atoms and each nitrogen atom is so bonded to two oxygen atoms.

All hydrogen bonds virtually lie within the walls of the hexagonal prisms and can be divided into two types. The shorter bonds designated as $N_1$—H—-$O_2$ and $N_1$—H—-$O_4$ are close to 2.93 Å long and the longer bonds $N_1$—H—-$O_3$ and $N_1$—H—-$O_5$ are close to 3.04 Å long. Although the oxygen atoms of the urea molecules are superimposed along vertical edge at a distance of 3.7 Å, the urea molecules are rotated with respect to each other by an angle of 120°, forming a spiral (Bhatnagar, 1968). Therefore the host structure is remarkable in that all host molecules and inter-host hydrogen bonds project onto a hexagonal array with minimal cross-sectional area, and with unusually large proportion of the projection area available to the guest species (Bishop and Dance, 1989).

The structure of the lattice of hexagonal urea may be envisaged by looking at the base of a bunch of perfectly aligned, hexagonally shaped pencils. The wood of these pencils stands for helices of hydrogen bonded urea molecules, wrapped around the sticks of lead, which represent guest molecules (Fig. 3.4). *Hexagonal urea with its long, straight tunnels or canals, is not stable itself, but can exist only due to stabilizing effect of the guest molecules it has taken in. The situation is much like the support a climbing vine receives from the trunk of the tree it entwines* (Hoor, 1996).
Fig. 3.2 Cross-section of the urea-n-hydrocarbon inclusion compound (Smith, 1952).

Figure 3.3 Arrangement of hydrogen bonding in urea-n-hydrocarbon complexes (Frank, 1974)
Fig. 3.4 Channel structure of urea adducts- a two-dimensional enclosure in which complexing crystals wrap around a mandrel of another substance (Marshner, 1955).

Thus, the typical urea inclusion compound exists in a hexagonal crystal lattice, similar to the tetragonal lattice of pure urea in that there is extensive hydrogen bonding but dissimilar in that each anti-hydrogen is hydrogen bonded to different carbonyl oxygen. The hydrogen bonds between neighboring molecules in tetragonal urea form lead to a rather loose structure. Therefore, maximum interaction between the urea molecules is less than the usual ones, whereas in the clathrate of urea with a hydrocarbon, the maximum interaction is close to the normal one due to an additional interaction with the chain of the n-paraffin (Bhatnagar, 1968) (Table 3.1).

**Table 3.1 Interatomic distances (Å) in different forms of urea (atoms numbering with reference to Figure 3.3) (Bhatnagar, 1968).**

<table>
<thead>
<tr>
<th>Urea Clathrates</th>
<th>Tetragonal Urea</th>
</tr>
</thead>
<tbody>
<tr>
<td>C—O</td>
<td>1.28</td>
</tr>
<tr>
<td>C—N</td>
<td>1.33</td>
</tr>
<tr>
<td>N₁—N₁</td>
<td>2.30</td>
</tr>
<tr>
<td>N₁—H ..........O₂</td>
<td>2.93</td>
</tr>
<tr>
<td>N₁—H ..........O₃</td>
<td>3.04</td>
</tr>
</tbody>
</table>

Several representations of the channels formed by the hexagonal urea inclusion compound can be constructed, showing that the hydrogen bonded network forms helical ribbons which are interwoven to form a honeycomb of linear parallel channels in which the guest molecules reside (Figure 3.5).
Figure 3.5 Various representations of urea channels; a) Stick representation of urea host channels; b) channels viewed from above, showing van der Waals radii; c) channel viewed side, showing helical ribbon structure

Urea host channels have minimum van der Waals diameters of 5.5-5.8 Å (George and Harris, 1995) (Fig. 3.6)

Fig. 3.6 Minimum diameter of the urea host channels as a function of position along the channel axis (George and Harris, 1995).

The diameter of urea channel has been compared with the cross section of n-octane, benzene, 3-methylpentane and 2, 2, 4-trimethylpentane (Fig. 3.7). It is obvious from the figure that whilst 3-methylpentane can be accommodated in the channel, 2, 2, 4-trimethylpentane cannot be accommodated. This determining factor as to whether or not a molecule can act as a guest molecule is thus its ability to fit into the space available in the urea channel (Schlenk, 1949).
3.5.2 Formation of urea inclusion compounds

There has been rather little work done on the mechanism of the formation of urea inclusion compounds, but a recent study on a series of urea-ketone inclusion compounds indicates a template mechanism of growth of urea inclusion compound crystals. Fig. 3.8 presents representative step growth mechanism of formation of urea inclusion compounds in the presence of a suitable guest moiety, 2-decanone in the instant example. The mechanism is thought to include the following: a) at some point some of the ketone molecules in the urea/ketone solution are lined up next to one another and parallel to the channel axis of the urea; b) one of the ketone molecules becomes displaced relative to the other, c) this displacement results in around the protruding ketone molecule; d) the outside of this urea channel becomes a binding site for another ketone molecule; e) this channel formation is propagated either laterally or along the channel axis to form the inclusion compound. This mechanism is supported by recent FT-IR spectroscopic studies.
Fig. 3.8 Step growth mechanism proposed for urea/ketone inclusion compounds. (Hollingsworth et al., 1996).

Fig. 3.9 Space-filling drawing of a hexagonal channel in the urea n-hexadecane clathrate, determined by X-ray diffraction (Smith, 1952).

of the urea-water/butanol system and the urea/water/valeric acid system in which it was concluded that the urea inclusion compound structure is present in solution. As a result of the combination of the size of the urea channels and the smooth and rigid nature of the
insides of the channels, it is usually found that the guests in urea channels are held fairly loosely and can undergo a range of rotational and translational motion (Hollingsworth et al, 1996).

Some degree of substitution of the carbon chain is allowed: e.g. 1-bromohexane forms an inclusion compound whilst 2-bromooctane does not. On the other hand 2, 2-difluoroctane does form an inclusion compound, probably because of the smaller size of the fluorine atoms. In the case of oxygen derivatives of n-alkanes, neither the hydroxyl group in 2-octanol, nor the carbonyl group in 2-heptanone prevents inclusion compound formation (Zimmerschield et al, 1950; Redlich et al, 1950). (Fig. 3.9).

The effect of substitution is clearly seen with a series of C-14 compounds where 1-cyclopentynonane and 2-, 3-, and 4-methyltridecane form inclusion compounds, but 2, 4-dimethyldodecane, 3-ethyldodecane, and 1—cyclohexyloctane do not form inclusion compounds (Sergienko, et al, 1975). Competitive inclusion has also been studied between tetradecane and its isomers in binary mixtures. The more highly branched compounds form an insignificant amount (0.5-2%) of inclusion compound even when present at > 75% content in the binary mixture. The less highly branched hydrocarbons give about 1% inclusion compound at < 25% content and 8.5 - 10% inclusion compound at < 90% content in the binary mixture (Ovezov et al, 1977).

Among long chain esters of sufficient length, derivatives of lightly branched alkanes can form inclusion compounds e.g. esters in which either the acid or alcohol portion of the molecule bears a methyl group (Linstead and Whalley, 1950). However, if both the acid and the alcohol portions bear methyl substituents, no inclusion compound formation can be observed. Larger groups such as ethyl and phenyl groups also prevent inclusion compound formation (Truter, 1951; Aylward and Wood, 1956).

Urea forms inclusion compounds not only with hydrocarbons and their alcohols, esters and ether derivatives, but also with aldehydes, ketones, carboxylic acids, dicarboxylic acids, amines nitriles, thioalcohols and thioethers, provided that their main chain consists of six or more carbon atoms. Thus, inclusion compounds of urea with methyl octadecanoates, octadecadienoates and octadecatrienoates, with methyl stearate, stearic acid and with the three types of ethylenic C_{18} acids can be prepared. The degree of
unsaturation or the isomerism of the double bonds does not seem to affect the ability of the guest molecules to form inclusion compounds (Schlenk and Holman, 1950). Urea also forms inclusion compounds with a number of butane and butadiene derivatives, which on γ-irradiation can form stereo-regular polymers (White, 1960).

Aromatic compounds would be expected from their size and shape to be capable of forming inclusion compounds provided that they are not highly substituted, but benzene and its smaller homologues never form such inclusion compounds. If however the benzene carries a long chain substituent, e.g. octadecylbenzene, then an inclusion compound will be formed (Findlay, 1962).

There are two main criteria which determine whether or not a particular urea inclusion compound will be formed, namely the length of the carbon backbone of the guest, and the degree of branching or substitution in the guest carbon skeleton (Fetterly, 1964). In terms of the length of the carbon backbone, the aforementioned guests must have a carbon skeleton consisting of six or more atoms in order to successfully form an inclusion compound with urea. There is a twofold reason for the lack of inclusion compound formation with smaller molecules. The first part concerns the volatility of the smaller molecules; the smaller a molecule within a given family, the greater its vapor pressure, and the easier the escape from the urea channels. The guests are necessary to "prop open" the urea channels, and once the guests are gone the hexagonal urea lattice collapses to give the tetragonal structure. The second part arises due to the fact that between the guest molecules in the urea channels there are regions of low electron density (i.e. void), which do not contribute to the "propping open" of the urea channels (even though the guest molecules are usually packed within van der Waals contact of one another), so the smaller the guest molecule, the greater the proportion of these regions of low electron density, and consequently, the more unstable the urea host lattice (Swern, 1955).

In terms of the degree of branching or substitution in a guest molecule, little or no branching or substitution is usually a requirement for urea inclusion compound formation with smaller guest molecules of a given family. This is a direct consequence of the diameter of the channels of the urea host lattice, and to determine if a proposed guest will form an inclusion compound with urea, it is necessary to compare the maximum lateral
guest dimensions with the dimensions of the host channels. With respect to larger molecules of a given family increasing the length of the carbon backbone increases the enthalpy of complexation, so a degree of branching or substitution is tolerable. Minimum carbon backbone required for some organic compounds to form an adduct with urea has been summarized in the Table 3.2 (Hollingswoth and Harris, 1996).

**Table 3.2 Minimum carbon backbone with substituents allowing urea inclusion compound formation (Hollingswoth and Harris, 1996).**

<table>
<thead>
<tr>
<th>Terminally substituted</th>
<th>Minimum number of unbranched heavy atoms</th>
<th>Nonterminally substituted</th>
<th>Minimum number of unbranched heavy atoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>6</td>
<td>2-methyl</td>
<td>10-13</td>
</tr>
<tr>
<td>COOH</td>
<td>4</td>
<td>2-ethyl</td>
<td>24</td>
</tr>
<tr>
<td>1-bromo</td>
<td>5</td>
<td>2-chloro</td>
<td>6</td>
</tr>
<tr>
<td>1-phenyl</td>
<td>18</td>
<td>2-bromo</td>
<td>8</td>
</tr>
<tr>
<td>α-alkene</td>
<td>7-8</td>
<td>2-hydroxy</td>
<td>6</td>
</tr>
<tr>
<td>1-cyano</td>
<td>7</td>
<td>β-alkene (cis)</td>
<td>8</td>
</tr>
<tr>
<td>α,ω-dicyano</td>
<td>8</td>
<td>2,2-difluoro</td>
<td>6</td>
</tr>
<tr>
<td>β-naphthyl ester</td>
<td>17</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Decomposition of urea inclusion depends upon the nature of the guest molecule. The inclusion compounds of volatile compounds tend to decompose slowly, even at room temperature, whereas that of hexadecane, for example, is stable at room temperature and only begins to decompose just near its melting point.

**3.5.3 Crystal morphology of urea inclusion compounds**

For alkane/urea inclusion compounds, spontaneous crystal growth using conventional solution crystallization procedures generates long hexagonal needle morphology (with tunnel axis parallel to the needle axis). However, by incorporation of selective growth inhibitor (5-octadecyloxyisophthalic acid) that reduces the rate of crystal growth along tunnel direction, crystals of alkane/urea inclusion compounds can be induced to grow as hexagonal flat plates, rather than the long needle crystals (Fig. 3.10). Similarly, by altering the concentration of crystal growth inhibitor, crystal with any desired morphology can be grown between two extremes of long needle crystals and flat plate crystals (Leo and Harris, 1999; Kelly *et al*, 2001).
Fig. 3.10 Optical micrographs of crystals of hexadecane/urea inclusion compounds grown (a) under conventional conditions (b) and (c) with 3% and 5% growth inhibitor respectively (Harris, 2007).

3.5.4 Structural properties of urea inclusion compounds

3.5.4.1 One-dimensional property: the incommensurate structural nature

An important fundamental property of solid inclusion compounds is the degree of structural registry between the host and guest substructures (Rennie and Harris, 1990 and 1992). In general, the guest molecules in conventional urea inclusion compounds are arranged in a periodic manner (repeat distance $g$) along host tunnels, with an incommensurate relationship between $g$ and the repeat distance ($h$) of urea molecules along the tunnel (Fig. 3.11). In classical terms, the inclusion compound is incommensurate if there are no sufficiently small integers $p$ and $q$ for which $pg \approx qh$, and commensurate if sufficiently small integers $p$ and $q$ can be found to satisfy the equality. One consequence, with important physico-chemical implications of an incommensurate structural relationship between the host and guest components is that different guest molecules within a given tunnel sample a range of different environment, with respect to
Fig. 3.11 Schematic two-dimensional representation of a urea inclusion compound viewed perpendicular to the tunnel axis, indicating showing the periodicity (denoted h) of the host substructure along the tunnel axis and the periodicity (denoted g) of the guest substructure along the tunnel axis.

Fig. 3.12 The hexadecane-urea inclusion compounds at ambient temperature, showing nine complete tunnels with van der Waals radii, viewed along the tunnel axis. The guest molecules have been inserted into the tunnels; illustrating orientational disorder (Harris, 1994).
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the host structure. In the commensurate case, a significant energetic 'lock-in' between the host and guest substructure will occur for a specific position of the guest substructures relative to the host substructure (Smaalen and Harris, 1996; Lefort et al, 1996).

3.5.4.2 Three dimensional ordering of guest molecules

This aspect of structural studies involves ordering of guest molecules in three dimensions within urea host structure pertaining to positional relationship between guest molecules in adjacent tunnels (Fig. 3.12). Importantly, it is found that the nature of the inter-tunnel ordering depends critically on the functional groups present on the guest molecule, with different families of guest molecule exhibiting different characteristic modes of inter-tunnel ordering (Fukao et al, 1986; Harris and Hollingsworth, 1990). The disorder of the guest molecules has reportedly made it impossible to actually solve the basic guest structure for any conventional urea inclusion compound at ambient temperature.

3.5.4.3 Low temperature phase transition

Another structural aspect, which has been extensively investigated, is the low temperature phase transition of urea inclusion compounds. At sufficiently low temperature, most conventional urea inclusion compounds undergo a phase transition which is associated, inter alia, with a change in symmetry of the basic host structure (hexagonal in the higher temperature usually becoming orthorhombic in the low-temperature phase) and a change in dynamic properties of guest molecules (Fig. 3.13). These phase transitions have been investigated extensively for alkane-urea and α,ω-dibromoalkane-urea inclusion compounds, both with regard to structural and dynamic aspects (Chatani et al, 1977; Casal et al, 1984); in qualitative aspects, the behavior of the alkane-urea and α,ω-dibromoalkane-urea inclusion compounds with respect to these transitions is very similar. The guest molecules are usually dynamic at ambient temperature, and the average host structure has a high symmetry. At sufficiently low temperature, the extent of the dynamics of the guest molecules diminishes, and the guest molecules adopt a well defined orientation with respect to the host; concomitantly, the host structure distorts to a lower symmetry that reflects the ordered or disordered distribution of the guest molecules (Fukao, 1990).
Fig. 3.13 Low temperature phase transition for urea inclusion compounds showing hexagonal structure of dodecane \((C_{12})-U\) at 293 K and at lower temperature (Yeo and Harris, 1997).

Fig. 3.14 Both enantiomers of urea molecules as helical ribbons in an inclusion compound (Atwood et al, 1984).
3.5.4.4 Host-guest chiral recognition

Urea is a chiral planar molecule which is building block of the well known chiral inclusion compounds of space group P6$_1$22 (or P6$_5$22). Guest molecules are included in channels which run through the crystal parallel to the 6$_1$ axis (Yellin et al, 1984). This chirality of the urea tunnel structure is generated spontaneously during crystal growth of the inclusion compound, and represents an example of chirality being introduced into a crystal by spontaneous assembly of achiral molecule into a chiral packing arrangement (Fig. 3.14). Clearly, chiral host structure can exert an important influence on the structural and chemical properties of chiral guest molecules. As R-guest-host and S-guest-host inclusion compounds have a diastereoisomerism relationship, they should generally differ in energy, and a given crystal of a chiral host should therefore have a preference for incorporating one particular enantiomer of a chiral guest.

3.5.4.5 Co-inclusion phenomena

Using binary guest systems, inclusion compounds can be doped with a certain partition of guest during spontaneous crystal growth. Thus, if two guest molecules G$_1$ and G$_2$ are present in the crystallization solution in the equal amount, crystals having different portion of G$_1$ and G$_2$ are obtained depending on the relative affinity of the host to the guest. For a given host structures their affinity for including chemically similar guest molecule is higher if the length of guest molecule increases (Fig. 3.15).

*Fig. 3.15 Schematic two-dimensional representation of a urea inclusion compound viewed perpendicular to the tunnel axis, indicating incorporation of two guest moieties G$_1$ and G$_2$ (Lee et al, 2001).*
Similarly competitive co-inclusion of two different types of guest molecule X(S)_{nj}X and X(S)_{nj}X (X, an appropriate end-group; S, appropriate spacer group; and nj \neq nj) within the same host tunnel has been investigated as a system for estimating intermolecular interaction energies (Harris et al, 1999; Lee et al, 2001).

3.5.5 General applications of urea inclusion compounds

It is clear that urea inclusion compounds exhibit a wide range of interesting and important fundamental physico-chemical phenomena. Since the urea inclusion compounds display a selectivity which is essentially governed by the size of available channels, much work has been carried out to exploit this selectivity in separating the components of mixtures on an industrial scale.

3.5.4.1 Urea adduction in petroleum industry

The formation of urea complexes with long chain organic compounds was found to be a powerful technique for isolation of alpha olefins and normal olefins from petroleum streams. An example of such a process is the removal of high melting-point paraffins, which tend to solidify at low temperature from various oils. The straight chain hydrocarbons are removed from the petroleum fraction by mixing the oil with urea and allowing the formation of the urea channel compounds. The inclusion compound is filtered or allowed to settle, and the supernatant is decanted. Both batch and fluidized-bed methods have been developed for these processes. Followings are the commercial applications of urea adduction in petroleum industry (Oswald, 1991; Gupta et al, 1998).

- Sonneborn's Petrolia Refinery, Pennsylvania; (Hoppe, 1964; C. S. Croman, 1959). In operation since 1950, designed to improve the cloud point and pour point of medicinal white oils.

- The Deutsche Erdol AG Plant at Heide; (Hoppe, 1964). The plant, with a 50 tons/day capacity, went on stream in 1954 and was used for dewaxing gas oils and spindle oils.

- Standard Oil Company (Indiana); (Rogers et al 1957). The company has operated, since 1956, a large urea dewaxing plant with a capacity of 100 tons. The process is adapted to light lubricating stocks used for low-cold-test oils.

- Moscow Oil Refinery (USSSR); (Marechal and Radzitzky, 1960).

- Process of Shell Oil Co., Wilmington, USA; (Hoppe, 1964). 

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- Process of Shell Petroleum Co. Ltd: (Hoppe, 1964)
- Christex Process: (Hoppe, 1964). It is a semi commercial plant built in 1953, with capacity of 10 Cubic Mtr./day for production of n-paraffins for kerosene and gas oils.
- Murex Process used by The Nippon Mining Company of Japan to extract n-paraffins in the carbon range C9 to C30. The plant has been running since the end of 1967, having a capacity of 40000 T/Yr.
- Gulf Research and Dev. Co. Process: (Carlson, et al, 1969). The above patent describes a urea process which can extract normal hydrocarbons in the carbon 20 range of C6 to C54, preferably C9 to C23 from the feed stocks containing 15 to 45% by weight of n-alkane.

3.5.4.2 Urea adduction in chromatography

Urea inclusion compounds have been studied as stationary phases, to obtain information on the behavior and properties of these compounds under gas chromatographic conditions, to draw conclusions concerning their stability and selectivity and finally to use them as stationary phases for analytical purposes. Similarly, interactions occurring in gas-solid chromatographic systems involving a common adsorbent or support coated with host molecules have also been studied using a wide-pore silica as a strongly absorbing substance and an inert chromatographic support. A separation process using urea in partition chromatography was successfully employed as an analytical technique for the determination of the major α-olefin and n-paraffin components of coal tar pitch (Karr, 1955; Karr and Comberiati, 1965). Recently direct separation and quantitative determination of (n-, iso-) alkanes in neat asphalt using urea adduction and high-temperature gas chromatography (HTGC) has also been reported (Netzel and Rovani, 2007).

3.5.4.3 Urea adduction in purification of fatty acids

The first description of the urea-fatty acid complexes by Bengen F in 1940 revolutionized fat chemistry for about 20 years. With this approach, oleic (Swern et al. 1952), linoleic and linolenic acids (Swern et al., 1953) were isolated and purified (80-95%) from natural sources. Owing to its low cost, low toxicity, and simplicity, urea fractionation has been most frequently used for the purification of fatty acids from fish oil (Abu-Nasr, et al, 1954; Ratnayake et al 1988) and from several vegetal oils e.g. blackcurrant oil, borage...
oil, linseed oil, rapeseed oil. Hayes D.G. presented extensive review of the main applications of urea fractionation (Hayes, 2002).

3.5.4.4 Urea adduction in non-linear optics

The potential to exploit inclusion phenomena in the field of non-linear optics has received considerable attention in recent years. The material studied was the urea inclusion compounds containing 1, 10-dibromodecane guest molecules, and its successful application as dichroic filter has been demonstrated. However, the commercial applications of these compounds in X-ray polarimetry is still to be exploited (Collins et al, 2002).

3.5.4.5 Urea adduction in textiles.

It is desirable to produce polymeric fibers with diameters ranging from nanometers to a few microns and thus with an inherent high surface-to-volume ratio. These fibers are finding potential applications in drug delivery, tissue engineering, membranes, nanocomposites, etc. An independent method for preparing highly structured materials is the self-assembled formation of inclusion complexes of polymeric guests inside a host matrix (Chenite and Brisse, 1991). For instance, poly(ethylene oxide) (PEO) has been complexed with urea, where the polymers are packed in one-dimensional channels constructed from an essentially infinite three-dimensional network of hydrogen-bonded urea molecules (Vasanthan et al, 1996). The polymer chains are thus highly extended at the molecular scale. However, their molecular orientation because it strongly influences most mechanical, optical, and electrical properties of polymers (Liu and Pellerin, 2006).

3.5.4.6 Urea adduction in improvement of handling characteristics

A novel solution to the handling of viscous, adhesive materials and potent or dangerous compounds is the formation of a urea inclusion compound with appropriate substances in these categories. Liquid non-ionic polyoxyethylene surfactants have been complexed with urea to form a solid powder which is easily handled (Varadaraj and Brons, 1998). Straight chain alkyl ethers, esters and fatty acid derivatives of polyoxyethylene surfactants form inclusion compounds, whereas sorbitan alkylate and alkyl aryl ethers of polyoxyethylene series do not due to large size of the sorbitan moiety and of benzene ring. Uniqema applied a non-ionic high ethoxylated alcohols (a waxy solid and hence
difficult to handle) for urea clathrate manufacturing and introduced the surfactant as free flowing solid (marketed as Atplus® UCL 1007, where UCL stands for urea clathrate).

3.6 Conclusion

The fact that urea inclusion compounds display a wide range of interesting and important fundamental physicochemical properties is well established (Harris, 2007). Application of wide range of experimental and computational techniques has been essential in the endeavor to understand these fundamental properties. At present there are no pharmaceutical applications based upon urea inclusion compounds in contrast to those of cyclodextrins, wherein large number of pharmaceutical products based upon complexation with cyclodextrin have already been marketed. Thus, given the vast amount of fundamental information that has now been accumulated for these solid inclusion compounds, there is considerable scope to develop and advance potential applications of urea as an adductor for the improvement of numerous pharmaceutical characteristics of drugs.