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A Brief Review on Urea and Biotin Recognition

Tanushree Sen*
Assistant Professor, Department of Chemistry, Jagannath Kishore College, Purulia, West Bengal, India

***Abstract*: Recognition of both urea and biotin is important due to their biological significances. Urea is toxic, pollutant and causes serious biological disorders; on the other hand, biotin (referred to as vitamin H in human) is an essential cofactor for several enzymes that have diverse metabolic functions. Recognition of these substrates by different artificial receptors is an interesting (and challenging) problem. Progress made along this direction has also been discussed.**

***Keywords*: Supramolecular chemistry, host-guest interaction, urea recognition, biotin recognition, fluorescent chemosensor.**

1. Introduction

The design and synthesis of artificial receptors to study the host-guest interaction with biologically important molecules are important in the area of molecular recognition. It is worth mentioning that the recognition and detection of bioactive substrates such as urea, biotin, carbohydrates, carboxylic acids, and amino acids have gained considerable success. Among the molecules biotin (referred to as vitamin H in human) is an essential cofactor for several enzymes that have various metabolic functions. It consists a pentanoic acid side chain and a cis-fused bicyclic moiety with sulfur atom in the ring. Crystallographic studies have established the relative stereochemistry at the asymmetric carbon. The crystal structure of biotin shows that the carboxyl group of one biotin molecule is intermolecularly hydrogen bonded to the urea linkage of the other biotin molecule. The valeryl chain is severely twisted from the maximally extended all trans-conformation. To bind and sense this interesting biological substrate of defined stereochemistry, considerable efforts were directed at a limited number of designed receptors.

2. Urea Recognition

Recognition of individual molecules is one of the most fundamental processes both in chemistry and biology. Preparation of synthetic molecules to mimic the biological processes is important in the area of molecular recognition.[1,2] Considerable efforts have been made in designing molecules which may become good receptors for specific tasks. It is worth mentioning that recognition and detection of bioactive substrates like urea,[3] biotin,[4] carbohydrates,[5] carboxylic acids,[6] amino acids[7] etc. have gained considerable success.

Among these substrates of biological significance, urea is important because it is toxic, pollutant and causes serious biological disorders.[8,9] Urea is the end-product of nitrogen metabolism and a well-known protein denaturant that can cause damage in concentrations even in micromolar range. Thus, the need to develop structurally simple synthetic receptors capable of detecting urea in low concentrations is important in clinical and analytical chemistry. Urea contains several hydrogen bond donors and acceptors (Figure 1) for which it shows various inclusion properties.[10] Ordinary crystalline urea is tetragonal, but it forms an inclusion compound with a guest, crystallizing in a hexagonal lattice[11] containing the guest molecule in long channels. Progress in designing and synthesizing new receptors capable of recognizing urea has contributed significantly in supramolecular chemistry. The different approaches for successful complexation and detection of urea in solvents of varying polarity are briefly summarized below.

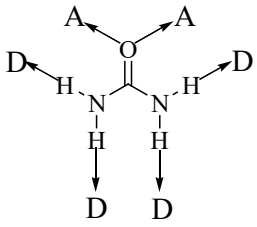


Fig. 1. Hydrogen bond donors and acceptors in urea

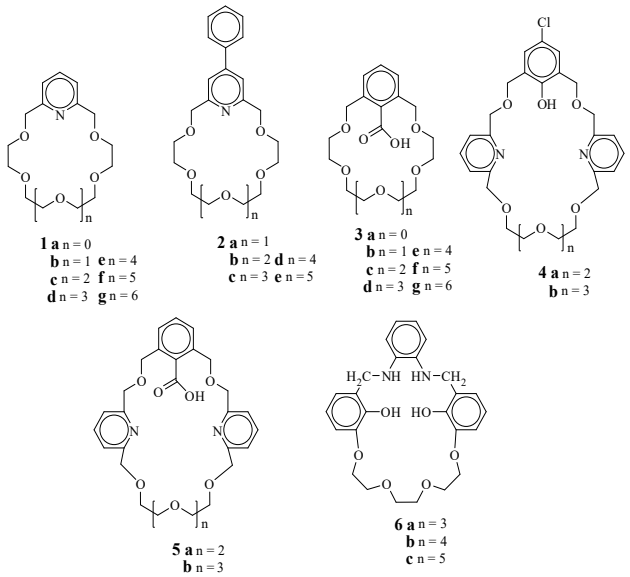


Fig. 2. Crown ether-based synthetic receptors for urea

Crown ether is a simple molecule which tends to bind urea. Pedersen explored this possibility and showed that urea

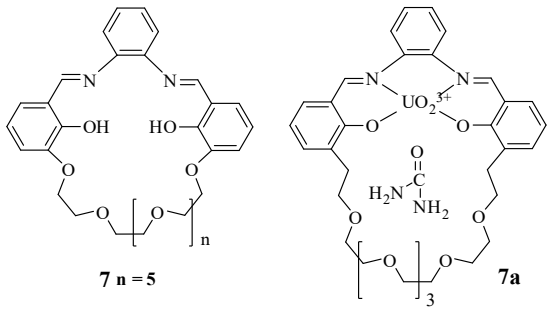
*Corresponding author: tanu_sen20@yahoo.co.in

interacts with simple crown ethers such as benzo-18-crown-6.[3] However, the nature of the interaction between host and guest was not studied further.

In relation to this, measurement of the acidities of macrocycles containing intraannular acidic groups provide a method to evaluate the complexation of such crown ethers with neutral molecules in polar media. In this context, Reinhoudt *et al.* synthesized six types of crown ethers 1-6 possessing intraannular pyridinium, phenolic, and/or carboxylic groups (Figure 2).[12] Complexation with urea was assessed by accurate potentiometric titrations, liquid-liquid or solid-liquid extraction experiments, and X-ray crystallography.[12]

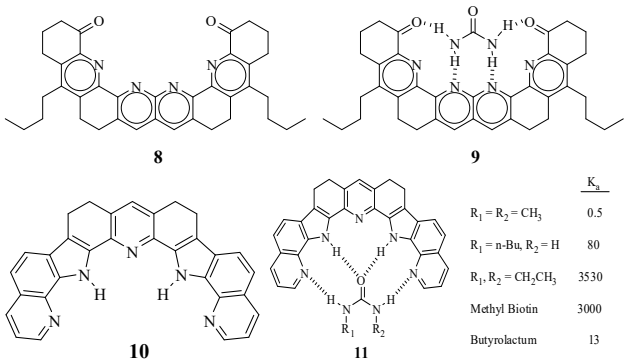
They also reported X-ray crystal structures of the 1:5 complexes of 18-crown-6 and aza-18-crown-6 with urea.[13] In these complexes urea was bound in a perching fashion, and the association constants of these complexes were very low (urea-18-crown-6, log $Ks < 0.1$, H_2O, 25 ^{O}C).

Van Staveren solved the crystal structure of the ternary complex of a Schiff base macrocycle **7** which showed that the electrophilic uranyl cation and urea both complex cooperatively in the cavity of the macrocycle.[14]



7 n = 5 **7a**

Bell *et al.* reported the synthesis of naphthyridine fused polyaza heterocycle 8 which exhibited unusual ability to dissolve urea in relatively nonpolar solvents.[15] With the assistance of CPK molecular model and NMR study they suggested the binding structure 9.

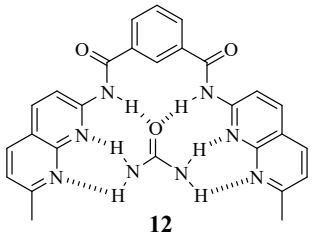


8 **9** **10** **11**

Fig. 3. Cavity shaped molecular receptors for urea and substituted ureas

Thummel *et al.* synthesized a cavity shaped molecule 10, which not only solubilized urea in chloroform but also formed complexes with a variety of substituted ureas (Figure 3). The NMR titration results indicated the binding model depicted in structure 11.[16]

In a simple way, Goswami *et al.* showed that two naphthyridines under isophthaloyl spacer (12) effectively solubilized urea in chloroform with a moderate binding constant value.[17]



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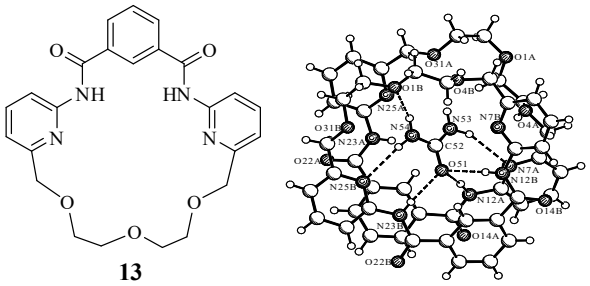
Ghosh *et el.* designed and synthesized a pyridine amide-based macrocyclic receptor 13 which exhibited strong inclusion of carbonyl guest such as acetone. The bonded acetone was slowly displaced from the cavity by urea resulting in a sandwich type complex (Figure 4).[18]



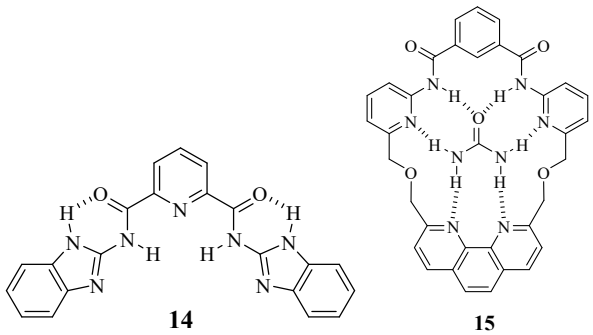
13

Fig. 4. Complex of urea into cavity of receptor 13

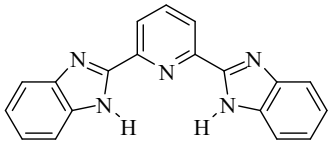
Gale *et al.* introduced a 2,6-dicarboxamidopyridine cleft with appended benzimidazole groups 14 functions as a receptor for neutral guests in solvent mixtures of d_6-DMSO and d_3-CH_3NO_2.[19]

In addition to these approaches, fluorometric detection of urea by a fluorescent receptor has recently been a current interest to the supramolecular chemistry community. Few recent examples of this class are available in the literature. Goswami *et al.* has shown that macrocyclic receptor 15 can sense urea in the cavity and reports the complexation characteristics through the change in emission of the receptor. The cavity showed weak interaction with thiourea.[20]

A 2,6-bis(2-benzimidazole) pyridine receptor 16 developed by Iyer *et al*. showed urea binding with concommitant change in fluorescence.[21]

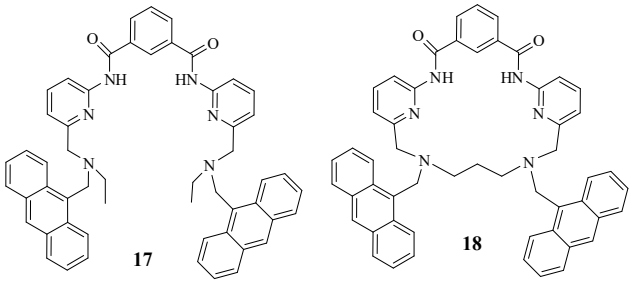


14 **15**



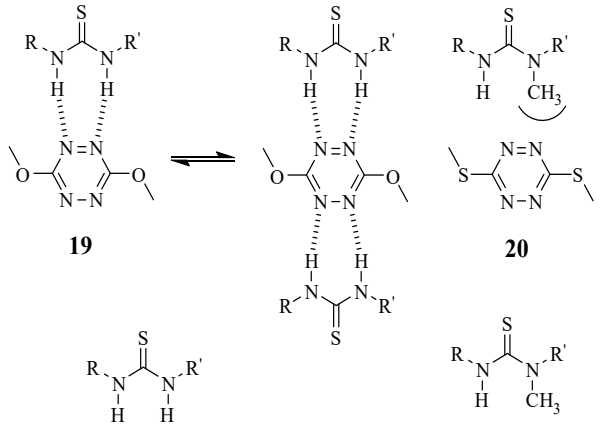
16

Anthracene-based open and macrocyclic PET sensors 17 and 18 have recently been reported by Ghosh *et el.* for fluorimetric detection of urea in both polar and less polar solvents.[22] The macrocyclic analogue 18 was found to be more effective than the open receptor 17 in sensing urea in organic solvent.



17 **18**

In a study Rotello and coworkers have shown that tetrazines 19 and 20 (Figure 5) can be used as the binders of thiourea but not in the oxidized state. They demonstrated that redox-modulated binding between tetrazines and thiourea stabilizes the tetrazine radical anion. The hydrogen-bound complex serves as an "on/off" switch where both tetrazines exhibit no appreciable binding in the oxidized state and substantial binding upon reduction of the tetrazine core.[23]

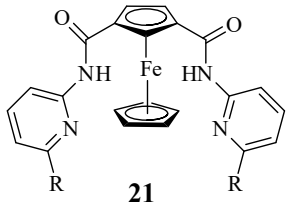


(a) R = CH_2CH_3
R' = $(CH_2)_7CH_3$
(b) R = CH_2CH_3
R' = CH_2CH_3

R = CH_2CH_3
R' = $(CH_2)_5CH_3$

Fig. 3. Representative tetrazine complexes displaying both 1:1 and 1:2 possible binding modes

It is mentionable that potentiometric sensors, based on gel-immobilized enzymes, and calorimetric sensors decompose urea into CO_3^{2-} and NH_4^+ ions in the former case and CO_2 and NH_3 in the later.[24] Studies concerning the binding of cyclic ureas are also focused on organic receptors that bind through hydrogen bonds.

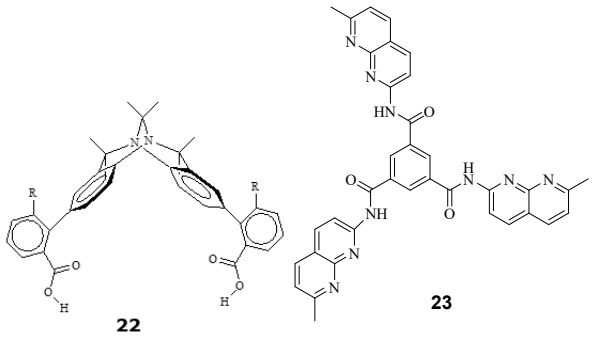


21

In relation to this, Tucker *et al*. based on Hamilton's strategy have reported a ferrocene-based receptor 21 that binds ethylene urea, trimethylene urea through complementary hydrogen bonds.

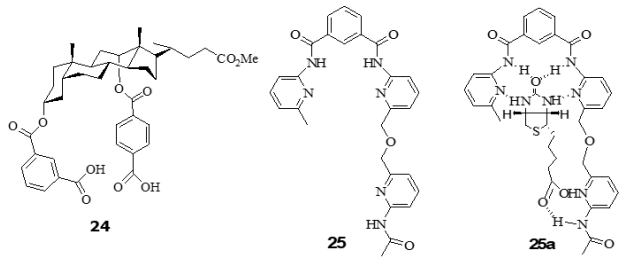
3. Biotin Recognition

Like urea biotin is also an important substrate of biological significance. Biotin (referred to as vitamin H in human) is an essential cofactor for several enzymes that have diverse metabolic functions.[25] Structurally it consists of a pentanoic acid side chain and a *cis*-fused bicyclic moiety with sulfur atom in the ring. Crystallographic studies have confirmed the relative stereochemistry at the asymmetric carbon.[26-27] Crystal structure of biotin shows that the carboxyl group of one biotin molecule is intermolecularly hydrogen bonded to the urea linkage of the other biotin molecule.[28]



22 **23**

The valeryl chain is severely twisted from the maximally extended all *trans*-conformation. To bind and sense this biological substrate of defined stereochemistry, considerable efforts were directed at a limited number of designed receptors. In this aspect, the use of Troger's base receptor 22 as reported by Wilcox and co-workers, was noteworthy.[29]



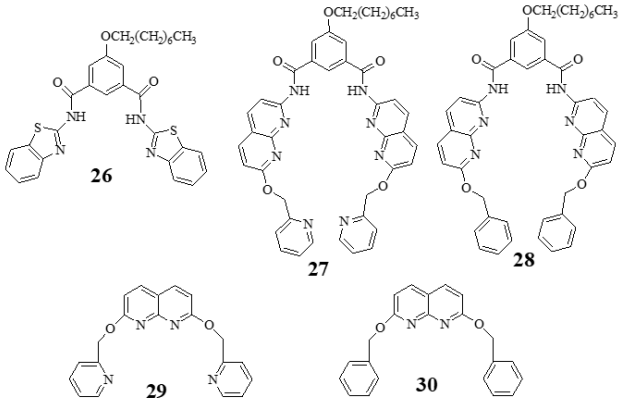
24 **25** **25a**

A naphthyridine-based tripodal receptor 23 has been reported by Claramunt *et al*. for the recognition of biotin methyl ester

through several interaction points by showing a great binding constant.[30]

Maitra *et al.* have designed and synthesized a bile acid-based molecular tweezer 24 containing a pair of carboxyl groups, for the complexation of biotin methyl ester.[31] A poly-aza heterocycle-based receptor 10 has also been designed and synthesized for the recognition of methyl biotin with a moderate binding constant value.[16] This concept was further explored by Chou *et al*. with an idea of multiple hydrogen bonds tuning guest/host excited-state proton transfer reaction in order to recognize biotin methyl ester and other urea derivatives.[32]

Pyridine amide-based simple receptor 25 is also known to bind biotin itself involving both the carboxylic acid and the cyclic urea part of the bicyclic unit of biotin.[4] Ultrasound and biochemical detection of biotin and biotinylated polypeptides has also been reported.[33]



Ghosh *et al.* have designed and synthesized charge neutral benzthiazole-based receptor 26 and naphthyridine-based receptors 27-30 as fluorescent chemosensors for the detection and sensing of biologically important substrates biotin, urea and their derivatives.[34,35] The binding constant values as determined are moderate and appreciable. The intrinsic fluorescence of benzthiazole and naphthyridine motifs in the receptors effectively senses the complexation of biotin and urea in $CHCl_3$ containing 1% CH_3CN by exhibiting a significant increase in emission during titration. The significant change in emission of 26 in the presence of biotin methyl ester and urea clearly distinguishes them from thiourea and substituted N, N'-dimethylurea.

4. Conclusion

Both urea and biotin are important due to their biological significances. Recognition of these substrates by different artificial receptors is an interesting (and challenging) problem. In this context, design and synthesis of various molecular receptors and their sensing capability is of very much importance in the field of molecular recognition. From this review article, it can be concluded that especially the receptors based on heterocyclic moiety such as pyridine, naphthyridine, benzimidazole or thioimidazole can act as fluorimetric chemosensors in this recognition process. Progress made along this direction has been discussed in this article and will be helpful for future researchers to move along this direction.

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