1. INTRODUCTION

The main constituent part of present day Organic Chemistry - Synthesis - is perhaps having the longest history. The ideas of functionalisation and stereochemistry, for example, have their origins in the second half of the nineteenth century, the concepts of bonding and reaction mechanism, as we know them today, clearly belong to the present century, but synthesis, the cardinal part of organic chemistry has a history spreading over many centuries. Though its origins are much earlier, the development of organic synthesis in a systematic and a streamlined manner belongs to the nineteenth century. In more recent times, the growth of organic synthesis is almost on par with the growth of Organic Chemistry as a whole. With the increase in understanding of structural and theoretical chemistry and the development of refined experimental methods, the chemist has been able to start with more and more ambitious synthetic goals. These led in turn to the discovery of new reactions and extrapolation of already set reactions. The fundamental ideas which lie behind this strategy, like a covalent bond is formed in the vast majority of synthetically useful processes, by the
interaction of electrophilic and nucleophilic atom, are not at all complicated.

The biological importance of proteins or peptides need not be overemphasised. Peptides provide much scope for development of pharmaceuticals, either by mimicking the action of the normal peptide or by blocking the action of the normal peptide, thus acting as an antagonist. The cyclic decapeptide gramicidin S is a powerful antibiotic produced by certain bacteria and phalloin is a highly poisonous heptapeptide. Among the hormones, oxytocin which is produced in the human pituitary gland in the brain causes ejection of milk and uterine contraction, gastrin which stimulates release of HCl in the stomach and angiotensin II causing an increase in blood pressure are small peptides. Apart from these, many act as neurotransmitters, growth factors, ion carriers, toxins and nucleopeptides.

The starting materials for peptide synthesis will, of course, be \( \alpha \)-amino acids. At first sight one might imagine that compounds which are based on such a simple structural unit can fulfil a diversity of functions. However, the formulation of peptides as polyamides of \( \alpha \)-amino acids is substantiated by a large body of evidence. In principle, peptide bond is formed by the nucleophilic attack of the N-
atom of the second component on the carbonyl C-atom of the first. The union of the two amino acids to form peptide is much restricted by a number of reasons. The main reason is that the amino acids themselves join together only at elevated temperatures. Such drastic conditions, of course, are not recommended and do not allow rational peptide synthesis. For this reason, it is appropriate to start from correspondingly 'activated' amino acid derivatives. A general approach to the synthesis of a peptide is shown in Scheme 1.1. The reactivity of the carboxylate group of one amino acid is boosted by an activating group X. To prevent reaction with its own amino group to give a polymer, an amino protecting group is first attached. The amino protected carboxylate activated amino acid may then be reacted with the other amino acid to give a dipeptide.

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\begin{align*}
R & \quad R' \\
(A) - \text{NH} - \text{CH}_2 - \text{CO} \overset{X}{\text{X}} & \quad \overset{Y}{\text{Y}} - \text{NH} - \text{CH}_2 - \text{CO} \overset{P}{\text{P}} \\
(\text{A)} & \quad \text{NH} - \text{CH}_2 - \text{CO} - \text{NH} - \text{CH}_2 - \text{CO} \overset{\text{P}}{\text{P}} \\
\end{align*}
\]

A - Amino protecting group  
P - Carboxyl protecting group  
X - Carboxyl activating group

Scheme 1.1
Thus, the real problem in peptide synthesis lies in the protection as well as in the activation of functional group. The activation involves the replacement of the hydroxylic group of carboxyl function with electron withdrawing substituent to enhance the polarisation of the carboxyl group and hence its reactivity. Activation of functional group is usually done by converting the acids to azides, mixed anhydrides, acid halides and active esters. In these methods, high reactivity of carboxyl moiety towards nucleophilic attack is achieved. At the same time, the rigorous conditions such as the use of base, temperature etc. make the synthesis much more troublesome. To activate carboxyl group with a mild precursor is a real task, nowadays. With this aim, a number of activating groups have been reported recently.

The drawbacks of the classical activating groups, led to the design of a number of coupling agents. These include DCC, HOBT (1-hydroxybenzotriazole), HOAt (1-hydroxy 7-azo benzotriazole), BOPA (N,N'-bis(2-oxo-3-oxazolidinyl) phosphorodiamide azide) etc. The important criteria for a good coupling agent are (i) it should be inert towards the amine component (ii) it should not generate a reactive intermediate containing a nucleophilic centre (iii) it would
not cause overactivation which would lead to side reactions or by-products and (iv) it should work under mild and neutral conditions. All the reagents mentioned above are not entirely free from shortcomings and therefore the search for better activating groups is in progress.

Photochemical activation procedures have been widely exploited in the synthesis of peptides. A photoremovable protecting group contains a chromophore which is sensitive to light, but relatively stable to most of the wide variety of chemical reagents commonly encountered in the ground state manifold. Here the wavelength of the light used is absorbed only by the protecting group and will not affect other parts of the molecule. In the activation approach, the functional group is derivatized with a light sensitive chromophore, which can serve as a latent activator of the functional group. On irradiation with light of suitable wavelength, the functional group is converted to an active form and the chromophore is removed. This active species permits the synthesis under mild and neutral conditions. The important photochemical activating groups include nitroindolines, 2-thionothiazolidines and 5-azido-1,3,4 oxadiazoles.

For the last two decades there has been tremendous
advances in the chemical synthesis of peptides. Peptide synthesis has proven indispensable for the structural elucidation of many recently isolated natural products having peptide structure. Investigation of the structure-activity relationship of biologically active peptide also demands the synthesis of many analogues of a given peptide. The development achieved in the chemical synthesis of peptide would not have been possible without the contribution of R.B. Merrifield in 1963. In his method (Solid phase peptide synthesis) a peptide chain could be assembled in a stepwise manner with the growing chain covalently anchored to an insoluble matrix and at all the stages of the synthesis, the peptide would be completely insoluble and would be in a suitable physical form to permit washing and rapid filtration at the end of each step. The intermediate peptide in the synthesis would thus be purified by a very simple procedure rather than the usual tedious crystallisation methods. Thus, the preparation of a long polypeptide or protein could be achieved by saving time, effort, and materials to a very large extent. After synthesis, the peptide can be released from the solid support by suitable reagents. In solid phase peptide strategy, the original support used by Merrifield - 2% divinylbenzene crosslinked polystyrene is still widely used.
The polymer, functions as a carrier and at the same time act as a protecting group of the N-protected C-terminal amino acid. Many of the coupling reagents used in solution phase have been used in SPPS also.

The importance of thiol as mild carboxyl activating group has attracted attention nowadays. Thiol function can be used both in the conventional process and photochemical mode of activation, where the excited state behaviour of thiol group is utilised. Though, thiol functions are suitable as mild carboxyl activating group, only scant reports are appeared in the literature.

Thus, the proposed thesis deals with the study of two hitherto unreported heterocyclic thiol compounds, 2-mercaptobenzothiazole and 2-mercaptobenzoxazole as carboxyl activating groups. Syntheses of amides, esters and peptides were carried out using these derivatized heterocyclic systems.

The entire thesis is divided into 7 chapters. In chapter 2 an introductory survey of the different activation methods is given. A background on the photochemical method is also included in this chapter. In chapter 3 the activation of different carboxyl groups using 2-
mercaptobenzothiazole is discussed. Aminolysis, alcoholysis and selective aminolysis are discussed along with a mechanistic pathway for these reactions. Chapter 4 deals with the activation reactions of 2-mercaptobenzoxazole. Reactions using amines, alcohols and amino alcohols are discussed in this chapter.

Chapter 5 describes the kinetic studies carried out with 3-acyl benzothiazoline-2-thione and 3-acyl benzoxazole-2-thiones. Attempts were done to compare the rate of reactivities of 3-acyl benzothiazoline-2-thione and 3-acyl benzoxazoline-2-thione with amines. However, no attempt has been made for a quantitative evaluation of the kinetic parameters involved in these reactions.

The application of the two carboxyl activating groups - 2-mercaptobenzoxazole and 2-mercaptobenzothiazole is the subject matter of chapter 6. Peptide syntheses were carried out by making use of both solution and solid phase peptide synthesis strategies. Chapter 7 sums up the results of the investigation carried out, the conclusions that are arrived at and the scope of the present investigation in different perspectives.
ACTIVATION OF CARBOXYL GROUPS IN PEPTIDE SYNTHESIS - A REVIEW