
SUMMARY OF PROJECT

“KINETICS AND MECHANISTIC STUDY ON BROMINATION OF SUBSTITUTED DIHYDROPYRIMIDINES USING PHENYL TRIMETHYL AMMONIUM TRIBROMIDE”

The birth of chemical kinetics often is taken to have occurred in 1850, and the rate of inversion of sucrose was studied, in which a quantitative approach was made to reaction rates. Wilhelmy interpreted the course of the reaction by the use of differential equation and proposed an empirical equation to express the temperature dependence of the rate. Wilhelmy's work remained almost unnoticed for over 30 years, after which Friedrich Wilhelm Ostwald called attention to it.

Wilhelmy's work was followed by a number of chemists. In 1862 a reaction between ethanol and acetic acid was studied.

Chemical kinetics is the branch of physical chemistry in which study of rates of chemical reactions is dealt. It provides useful information about the mechanism of a chemical reaction and any intermediates if involved. The knowledge of the rate of a reaction is valuable for the success of an industrial process and it enables to select optimum conditions of reactions so as to give maximum yield.

Thus, chemical kinetics is the term applied to the branch of chemistry that is concerned with the rate of chemical reactions and the mechanism by which the chemical reactions occur.

Valuable evidence about mechanisms can be provided by nonkinetic investigations (the detection of reaction intermediates and isotope exchange studies) but knowledge of a mechanism can be satisfactory only after a careful kinetic investigation has been carried out. Even, the mechanism cannot be deduced with certainty, since subsequent investigations may reveal unexpected complications.

A kinetic study can disprove a mechanism but it cannot establish a mechanism with certainty.

Kinetic studies cover a very wide range from several points of view. The half-life of a reactant, the time taken for half of the reactant to be consumed, can range from a small fraction of a microsecond to a period longer than the age of the universe.

Thermodynamics tells about the stability of substances and the possibility of occurrence of reactions where as chemical kinetics tells us about the time a reaction takes to reach a particular stage or equilibrium under a given set of experimental conditions. Velocity of a reaction is a measure of “How fast a reactant is consumed up in a chemical reaction or how fast a product is formed.” The rate observed for different reactants vary widely. Thus, thermodynamics is a vigorous and exact method concerned with equilibrium conditions of initial and final states of chemical changes. Whereas, chemical kinetics, is less vigorous and deals with a more chemical aspect of chemical phenomena, namely, the rate of change from initial to final state under non-equilibrium conditions. Two methods are related, thermodynamics which yields the driving potential, a measure of one state the tendency of a system to change from one state to another serves the foundations upon which chemical kinetics is built.

Chemical kinetics provide useful rate equations to describe the speeds of chemical reactions, and attempts to describe exactly how each reaction occurs. It does so in terms of one or more elementary steps, which are reactions having observable intermediate chemical species.

The ultimate goal of chemical kinetics is a theory interrelating energies, structure, and time for these single chemical events.

Macroscopic kinetics describes the branch of kinetics because the result relate to the behaviour of a very large group of molecules in thermal equilibrium. Experiments depending on “bulk” or “bulb” are macroscopic type.

The microscopic kinetic investigations, that have been carried out, have led to considerable insight into what is taking place at the molecular level during the course of reaction, called microscopic kinetics.

Reactions may be i) fast reactions and slow reactions. Reactions which occur very rapidly and so are over in microseconds are fast reactions. There are reactions which take months for completion like rusting of iron or millions of years such as those in geological processes. These are so slow reactions that changes in reactants are too small to detect.

Thus the chemical kinetics, is concerned with the experimental measurement of reaction rates and interpretation of the kinetic data.

However, of the greatest interest to chemists is the fact that kinetic helps in studying the mechanism of reaction. The reaction may really occur in several consecutive stages which are not represented by the stoichiometric equation. The presence of such series of stages may often be searched by the study of chemical kinetics. Thus, the study of chemical kinetics may provide a complete picture of reaction involving the equilibrium state. This involves the complexities where often postulations have to be made and consequently the application becomes very difficult, the primary reactants and products of the slow step in a reaction sequence cannot be detected from the kinetic results. However they can be detected by the knowledge of empirical formula of the activated complex.

The rate of a reaction is determined principally by intrinsic properties of the participating molecules. The main factors influencing the molecular concentration 'c' at the instant of measurement, the pressure 'P' and temperature 'T' of solution and the nature of the solvent, and assuming that the solution is free from impurities, of which the most insidious is dissolved.

The idea of the wide scope and significance of chemical kinetics is given by the following table which indicates some important branches of science to which the subject is relevant.

Sr. No.	Branch	Applications of kinetics
1.	Biology	Physiological processes, bacterial growth
2.	Chemical engineering	Reactor design
3.	Electrochemistry	Electrode processes
4.	Geology	Flow processes
5.	Organic Chemistry	Reaction mechanisms
6.	Inorganic Chemistry	Reaction mechanisms
7.	Pharmacology	Drug action
8.	Physics	Viscosity, diffusion, nuclear processes
9.	Psychology	Subjective time, memory

The study of oxidation of organic compounds and its mechanisms have led to the understanding the nature of life processes undergo redox reactions. Oxidation reaction is always accompanied by reduction; such reactions are called redox reactions.

Mechanism of redox reaction can vary greatly with the oxidising or reducing agent employed. Mechanism of redox reactions classified into the following categories⁸.

- a) Direct electron transfer.
- b) Atom or group transfer.
- c) Formation of intermediates.
- d) Displacement mechanism.
- e) Addition elimination mechanism.

The Kinetics provides the useful information about the mechanism and rate of chemical reaction, which helps to run a chemical reaction successfully by a way of selecting optimum condition as to get maximum yield. The kinetic study also helps us to study the factors which influence the rate of reaction like temperature, pressure, substrate concentration, oxidant concentration, composition of reaction mixture and catalyst.

The reaction kinetics plays a very important role in the investigation of the reaction mechanism. Bromination of organic compound carried out by brominating agentt like NBS,Br₂/AcOH have been used to carry out the kinetics and mechanism of various organic compounds.

Pyrimidinones or 3, 4-Dihydropyrimidin-2(1*H*)-thiones (DHPMs) are well known for their wide range of bioactivities and their applications in the field of drug research. This fact has stimulated the invention of a wide range of synthetic methods for their preparation and chemical transformations. DHPM nucleus with structural variations in the aromatic ring at 4-position as well as the modification of basic pyrimidine skeleton at 2,3,5 and 6- positions are known as calcium channel blockers. These dihydropyrimidines have found wide spread use in cardiovascular medicine (antihypertensive activity) and have also served as important tools for the study of calcium channel structure and function.

In general, acetoacetates are employed in the Biginelli reaction and therefore in most cases a methyl group is placed at the C-6 position of the pyrimidin ring. Functionalization of this methyl group is easily achieved by bromination.

There is a wide utility of bromomethyl compound for making functionalized DHPMs nucleus at C-6 position. Functionalization of DHPMs nucleus at C-6 position has been carried out with bromine in acetic anhydride, bromine in water, bromine in DMF, N-bromosuccinimide, dioxane dibromide. Polymer-supported brominating reagent and with lithium bromide in presence of ceric ammonium nitrate (CAN) bromination of other positions of the pyrimidinone ring has been carried out with phosphorus tribromide, through substitution of the carbonyl oxygen by the bromine atom. On the other hand, phenyltrimethyl ammonium tribromide (PTAB) has been found to be much easier to handle and it maintains the desired stoichiometry in comparison with bromine.

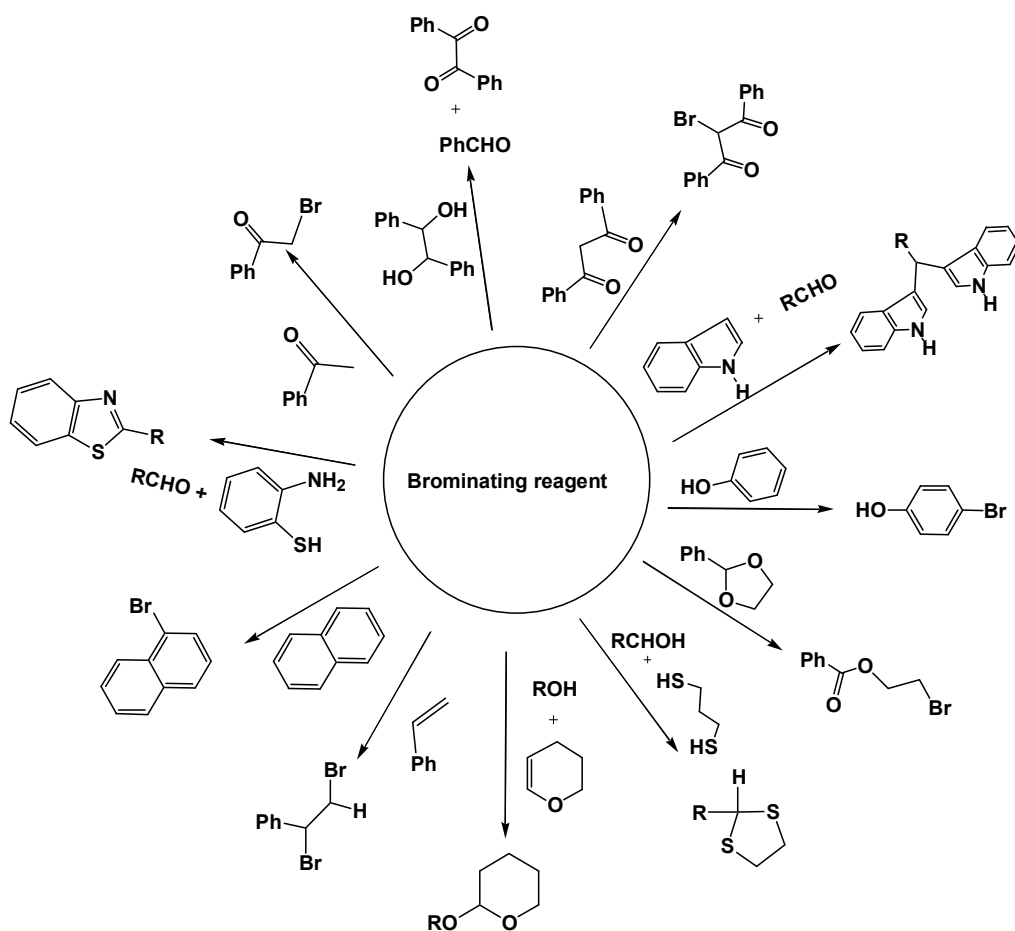
The use of PTAB was more advantageous and attractive than that of Br₂ in organic synthesis. Hence in this project, we wish to report a kinetic study for the facile and direct substitution of bromine at C-6 position of DHPMs under different conditions.

In the preparation of synthetic intermediates and pharmaceuticals/agricultural chemicals, the bromination of organic substrates is very decisive and vital step. Molecular bromine has been employed as a general method to prepare such brominated compounds and in doing so the environmental hazards pertaining to its transport, handling etc., becomes predictable; especially the storage of bromine possesses great concern. Thus there is a growing need for the replacement of molecular bromine by solid and easy to handle brominating reagent.

As a result of this urgency, several crystalline organic ammonium tribromides (OATB) comes at the rescue as they constitute a convenient source of bromine because of their high molecular weight, high stability, safe and easy to handle etc. Moreover these OATB are known to be promising reagents in organic synthesis, to bring about variety and easy transformations.

Some of the illustrative reactions have been given in the fig. 1. Apart from that the attractive feature is mostly all reactions are accomplished under appreciably mild conditions of the brominating reagent.

Several OATB reagents like pyridine hydrobromide perbromide (PHPB), cetyltrimethyl ammoniumtribromide (CeTMATB), tetramethyl ammonium tribromide (TMATB), tetra butylammonium tribromide (TBATB), benzyltrimethyl ammonium tribromide (BTATB) and phenyltrimethyl ammonium tribromide (PTAB) etc., are well known solid brominating reagents.



Applications of several brominating reagents in organic transformations :

Includes importance of chemical kinetics in various fields i.e. chemical kinetics provides useful rate equations to describe the speed of chemical reactions and attempts to describe exactly how each reaction occurs.

It describes the importance of PTAB in bromination of various compounds and also some oxidation reaction.

While studying the solvent effect, the rate of bromination reaction has been observed to it increases with increase in concentration of substrate and reactants.

Dr. A.G. Jadhav

Principal investigator