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Role of Polymeric Solid in Organic Synthesis

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Abstract* – *The application of functionalized polymers for affecting a host of organic chemical transformations has achieved wide-spread acceptance ever since the introduction of the solid-phase peptide synthesis. For the last 3 decades, a number of such systems which find applications in the field of organic chemistry, analytical chemistry, bio-chemistry, biology and medicine have been developed.

When polymers are used as supports for organic reagents or catalysts, the reactivity and selectivity of these attached functions are seriously affected by the so-called polymer effects. These may be physical in nature as in the case of diffusion effects, steric effects, site isolation effects and local concentration effects. It can also be chemical, like, micro environmental interaction and coordination unsaturation. The earlier concept about the polymers as only passive supports can no longer be perceived now.

A cross linked macromolecule can behave as a gel if the degree of cross linking is low. Thus the reactions using lightly cross linked polymers could be viewed as taking place in the gel-phase. In these polymeric systems, reactive functions are attached to the macromolecular matrix so as to perform the desired chemical transformations. Here the microscopic properties of the reagent functions attached to the macro molecular are taken into account, rather than the bulk properties of the polymers. Reactive polymers could be produced either by the fictionalization of preformed polymer or by the co-polymerization of functional monomers with an extra functionality which does not participate in polymerization.

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INTRODUCTION

Cross linked polystyrene supports are of two types, the micro porous and macro porous resins. The gel-type resins are generally lightly cross linked. They have a permanent porosity type, but swell to varying: degrees in many organic solvents. The spaces between the cross links are occupied by the swelling solvents and may be considered as small pores. These spaces do not only contain solvents, but must be considered as volknes of semi-dilute solutions of polymer segments, linking cross links or the cores of tiny micro gels. Macro porous resins are obtained when polymerization is carried out with 5-6% of DVB and in the presence of diluents. During the polymerization, phase separation occurs after extraction of the diluents and 'on drying permanent pores or holes of various sizes are created. On contact with organic solvents, the size of the pores may change, but they generally survive. Small organic molecules can diffuse more or less freely. The diffusion of the small organic molecules may however be restricted in very small pores because of the capillary forces and also because they may be absorbed inside the polymer domains where the crosslink density causes a very high viscosity.

In order for a polymer to be usable as a support for an organic reagent, it should have sufficient mechanical stability under the reaction conditions. In the practical run, a compromise has to be attained between the mechanical stability and reactivity. Dual – type polymers with very low crosslink density may be desirable as reagents since diffusion control of the reactions inside the polymer are limited, but they are too easily handled and cannot be used %n a column reactor. On the other hand macro porous resins with large pore volumes are very brittle and will disintegrate to very fine particles upon attrition in a stirred reactor. In other cases the swelling-deswelling process which may occur during the life of the supported reagent may cause it to disintegrate into smaller particles.

A required functional group can be introduced onto a support in two ways. It can either be incorporated during the synthesis of the support itself or by chemical modification of a preformed polymer matrix. Copolymerization of an appropriate functional monomer is a very general method, provided that the relevant monomer is available. A number of functional groups can be attached to styrene or acrylic residues, both of which are easily polymerized. This gives a possibility of predicting the relative position of functional groups inside the polymer chain when the reactivity ratios of the co monomers are known. Here the degree of fictionalization of products were readily controlled, the structure of the required croup can be unambiguously ascertained by analysis of the relevant co monomer prior to polymerization. The ability to control the loading and distribution of a group can be crucial.

The introduction of a particular functional group onto a support by chemical modification is the most commonly employed method. This method has the advantage of avoiding the synthesis of a complex monomer. A wide range of supports of a very high quality and varying physical parameters are commercially available. It is particularly attractive for the preparation of cross linked polymeric reagents. After the chemical modification, generally, the final functionalized polymer has the same physical form as the original polymer. But this method is not without problems. The reaction conditions used must be carefully chosen to ensure 'that the reagent can penetrate the cross linked matrix throughout the reaction sequence. There should not be any side reaction. The distribution- of the functional groups in the final cross linked product is almost certainly different to that obtained by direct copolymerization. Chemical modification will occur generally at the more accessible sites.

Usual chemical methods of analysis applied to low-molecular weight species have been found to be satisfactory with linear polymers. But with insoluble cross linked polymers such methods which require solubilisation of the sample cannot be applied. Detection and estimation of the specific elements can be carried out by means of elemental analysis. Although carbon and hydrogen analyses are often carried out routinely, this is not much useful. The different functional groups are detected qualitatively by the general chemical tests available for them. Quantitative determination is done by non-aqueous volumetric methods.

If reactions are carried out with reasonable gravimetric accuracy, from the difference in mass during chemical transformations, reliable measurement of transformed functional groups can be achieved. IR spectroscopy is of much use as a tool for the characterization of the functional polymers. The occurrence of slow reaction is a major problem associated with the polymer-supported reagent. The decrease in reactivity of the functional groups may be attributed to the close proximity of the polymer backbone. This is more conspicuous in the case of cross linked polymers, where the active functional groups are either flanked by the cross links or buried in the interior of the polymers. Such groups are not readily accessible to reagents and substrates in the continuous phase. The reactivity and the rate of reaction involving the supported reagent is enhanced considerably when they are anchored through spacer groups.

One major factor affecting: the reactivity of the reagent function anchored on a polymer-support is the extent of cross linking of the support. This determines the distribution and accessibility of the functional groups on the polymer- backbone. In the case, of cross linked polymer, the accessibility of the functional groups is diffusion-controlled and penetrates transport causes some sort of molecular relaxation making the functional group buried deep in the polymer. By control of the crosslink ratio, a thermodynamic and/or kinetic control of substrates attempting to gain access to a reactive site can be achieved.

Proxy acids prepared by treatment of polymeric carboxylic acids with hydrogen peroxide was found to be efficient in carrying out oxidation. The carboxylic acid formed as the by product in the oxidation reaction can easily be reconverted to the per acid. With the use of large excess of the reagent greater conversion rate can be achieved. But when a very high molar ratio was used, the yields of the peroxides decreased probably due to the difficulty in efficiently recovering the product from the relatively large amount of the resin.

Certain selectivity was noticed in the oxidation of long chain alkenes. Thus with cyclododecene, the isomer was converted into the peroxide selectively and the selectivity was markedly higher at low temperature. This may be due to the increased steric interactions between the polymer matrix and the cyclododecene which is caused by the lowering of molecular motions. In some oxidation reactions, the participation of neighboring hydroxyl group and the steric hindrance near the double bond has been reported as important factors.

REVIEW LITERATURE:

The diverse nature of the chemistry of N-halogen-N-metallic' reagents is a consequence of their ability to act as a source of halonfum cations, hypo halite species, N-anions which act as bases and nucleophiles and nitrinoids in limited cases. As a result, these reagents react with a surprising range of functional groups effecting an array of molecular transformations. Historically the important early developments in the area stemmed from the synthesis of chloramines-T and related aryl sulphonamide derivatives.

Polymeric reaction takes place smoothly only when there is an effective interaction between the reagent function attached to the macromolecular matrix, the substrate and the reaction medium. This in turn depends on the nature of the functional CI'OUP, degree of functionalisation, solvent and temperature. Influence of the concentration of the reagent function, solvent, temperature and crosslink density on reactivity of N-bromo resin was studied using the oxidation of benzoic to benzyl as a model reaction. For this, standard solutions of benzoic and benzyl of different concentrations were prepared in chloroform and absorbances were measured at 390 run. A calibration curve w a s drawn by plotting absorbance against concentration. The reactions were done by varying the conditions or parameters, under investigation. The extent of reaction was followed by determining the concentrate ion of benzyl at different intervals: The reactivity was found to depend very much upon the conditions. In polymeric reactions, even if the bulk concentration of the reactive function is low, the effective local concentration will be high enough to cause substrate conversions.

Conversions of benzoic to benzyl by differently cross linked N-bromo resins were followed in five solvents. In all the reactions, a three-fold molar excess of the reagent was used. The solvents were chloroform, benzene, cyclohexane, tetra hydro furan and acetonitrile. In all the solvents the reactivity was found to decrease as the extent of cross linking increased. The variation of the relative reactivity of the N-bromo resins in different solvent systems as a function of degree of cross linking.

In the various solvent systems studied, the behavioral patterns of the differently cross linked N-bromo resins were almost similar. For the oxidation reaction of benzoic to benzyl chloroform was the best solvent. Chloroform, comparably polar, was able to swell the resin matrix and it could efficiently penetrate through the pore structure of the resin so that the reactive sites could be made accessible to the substrates make the reaction easy. Thus with chloroform as the solvent, a comparably good value of 30% conversion was achieved after using the 20% cross linked resin as against - the almost complete conversion using 3% cross linked resin. As the crosslink density increases, the reactivity drastically decreases. The percentage of benzyl obtained was only 10% for the 20% cross linked resin.

When the solvent was changed to benzene, a highly non-polar solvent, the relative reactivity decreased considerably. This was true both for 3 and 20% resins. When a 3% cross linked resin was used here, only 58% conversion was obtained even after reaction. For 20% cross linked resin the percentage conversion was only 20.

Polystyrene-supported hypo halite resins were prepared from supported t-alcohol resins by treatment with hypo halite solutions. The hypo halite reagents were used for oxidation of alcohols, N-halogenations of amides and halogenations of ketones. In all these cases hypochlorite resin was found to be more reactive than hypobromite resins. In the case of N-halo-N-sodium polystyrenesulphonattes, N-bromo resin is more reactive than N-chloro resin. The reactions using polystyrene supported hypohalites were not affected by the presence of catalytic amount of acid.

Polystyrene- supported hypo halite reagents are very much less reactive than the supported bromamine-T. For example, a three-fold molar excess of hypochlorite resin in chloroform solvent requires 27 hours for complete conversion for the oxidation of benzoic to benzyl while the time required is 6 hours for the N-bromo-N-sodio polystyrene sulphonanide resin. Similar observations have been made in the N-halogenations of amides and a-halogenations of carbonyl compounds.

RESEARCH METHODOLOGY:

The procedure for the oxidation or bromination involved stirring of a suspension of the resin with the substrate dissolved in suitable solvent. The spent resins were filtered and the filtrate on evaporation afforded pure products. The effects of temperature, molar excess of reagent, catalyst and solvent used on oxidation reactions were followed by taking the conversion of benzoin to benzyl as model reaction. Chloroform was found to be the best solvent. The reaction rate increased with increase in temperature. A three-fold molar excess of reagent gave optimum results. Wetting of the resin with dilute sulphuric acid catalyzed all the reactions.

The N-bromo resin was found to be capable of converting ketones to a-bromo ketones. Another reaction undergone by the N-bromo resin was bromine addition to compounds. Unsaturated hydrocarbons like stilbene and styrene were converted to their di-bromo derivatives in near quantitative yields. Reaction of cinnamyl alcohol with polymeric bromamine-T resulted in preferential double bond bromination. When equimolar reagent was used, while simultaneous bromination and oxidation of alcoholic group occurred on using a large-excess of the reagent. In the case of dibenzosuberenol, the oxidation of the secondary alcoholic group and double bond bromine addition take place with equal ease.

N-Halogenation of amides was possible only with N-chloro resins. The N-bromo resins failed under these conditions. Investigations of the effect of crosslink density on the extent of functional group conversions and on the course of synthetic reactions were carried out. Divinylbenzene-crosslinked polystyrenes of varying crosslink densities were prepared by suspension polymerization. The extent of functionalisation as well as the reactivity of the reagent were found to be dependent on the crosslink density.

One of the advantages of these reagents is the possibility of regeneration of the spent resin through a single step. The resin after the oxidation and halogenation reactions, on sodium hypohalite treatment gave the N-halo resins without loss of activity. These reagents were stable under ordinary and hydrolytic conditions. They are easily filterable through sintered glass filters of medium porosity. The resin can also be stored for months without any appreciable loss in capacity.

The study of kinetics of oxidation of differently substituted a-phenyl ethanols using polymeric bromamine-T were carried out in dichloromethane solvent. Studies were also carried out using low-molecular bromamine-T under identical conditions. The kinetic parameters obtained were compared with the use of polymeric bromamine-T and the trends of variations on p-substitution were found to be similar . This suggests the possibility of mechanism of the reaction using polymeric bromarnine-T being similar to that in the case of low-molecular bromamine-T. The heterogeneity of the reaction impises restrictions in arriving: meaningful quantitative comparison in such studies.

N-Benzyl, N-methyl and N-ethyl substituted N-halopolyCstyrene- codivinylbenzene sulphonanlides were prepared by the treatment of corresponding amides with sodium hypobromite solution. The amides were obtained by the treatment of polystyrenesulphonyl chloride resin with the appropriate amines. The reactivity of these resins were compared with that of polymeric bromamine-T.

The reactivity was found to decrease on alkyl substitution. Thermal studies were done using polymeric bromamine-T and its precursor resins. Some broad informations are obtained about the decomposition patterns of the various resins involved. The thermal behavior of polystyrene has been changed considerably on functionalisation. The introduction of functional groups onto the cross linked polystyrene matrix changes the structural environment considerably. These informations give an insight into the thermal stability of functionalized polystyrene resins which could help in the design of reagent with better stability.

The efficiency of polymeric bromine-T and chloramine-T is compared with that of other reported polymer-supported oxidizing reagents like polystyrene hypohalites, N-halo polyacrylamides, N-bromo acetamido polystyrene and polyvinyl pyrrolidone-bromine complexes. In terms of yield and duration of reaction, polymeric bromamine-T is a better reagent than many of the reported reagents.

SCOPE OF THE STUDY:

The study deals with the preparation and synthetic applications of polystyrene-supported analogues of chloramine-T and bromamine-T, N-chloro,A-bromo,N-sodio-polystyrene sulphonamides which have proved their efficiency as conventional low-molecular oxidizing and halogenating reagents. The various reaction parameters which could affect the course and the extent of the synthetic - reactions are also analyzed.

Benzene was used as the solvent in this case. In the second method, chlorosulphonic acid was used instead of thionyl chloride and solvent used was chloroform. The procedure involves the stirring of the sulphonic acid resin in chloroform under reflux for overnight. The total chlorine in the product resin was estimated by modified Volhard's method. The chlorine content was in the range 4.5 - 5.0 equiv. of chlorine per gram of the resin corresponding to 84 - 94% conversion.

The presence of some unconverted sulphonic acid groups has some advantages. The sulphonyl chloride group although reactive, is hydrophobic and the presence of hydrophilic sulphonic acid group might facilitate the further conversion of acid chloride to amide using ammonia. The IR spectrum of the resin showed peaks at 1170 cm-I and 1370 cm-I which are characteristic of sulphonyl chlorides.

The polymeric chloramine-T and bromamnine-T were found to be stable under ordinary laboratory conditions and under hydrolytic conditions. The resins retain the bead form characteristic of the styrene-divinylbenzene copolymers prepared by suspension copolymerization. They are easily filterable through sintered glass filters of medium porosity. The resin can be stored for months without any appreciable loss in capacity.

RESULT:

The alcohols used in the present study, a-phenyl ethanol, p-chloro-a-phenyl ethanol, p-methyl- phenyl ethanol and p-methoxy-phenyl ethanol, were prepared from their corresponding ketones by reduction using sodium boro-hydride. All the oxidation reactions were carried out in dichloromethane and the resins were made wet with 2ml of 2N sulphuric acid. The reactions were followed by measuring the concentration of ketones formed at definite intervals of time by spectro-photometric method. For this, standard solutions of corresponding ketones were prepared and absorptions were measured at the maximum of the ketones. A standard curve is prepared and the unknown concentrations were measured from the calibration- curve.

The second order rate constants obtained were found out graphically by plotting time against – log C<b-x>/<a-x>1 , where, a is the initial concentration of a-phenyl ethanol and b is that of N-bromo resin. The slope of the curve will be k<b-a>/2.303 from which the second order rate constant k can be calculated.

The ratio of concentration of alcohol to that of the resin used is 1:3. In the case of low-molecular weight bromamine-T, the reactions were done using equimolar concentrations of alcohol and bromamine-T. The decrease in concentration of bromamine-T is followed by iodometric iteration. The equation used in this case is k = i / C - l/Co where Co is the initial concentration and C that at time t. A plot of t against I/C is drawn. The slope will give the rate constant.

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