Phase Solubility Method in Supramolecular Chemistry

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Abstract

Phase solubility analysis is useful and widely applied analytical approach in this context. This technique is based on the equilibrium solubility of a chemical substance in a given solvent at a given temperature. These phase solubility systems not only allow a qualitative assessment of the complexes formed, but it can also be used to derive the equilibrium constants. Supramolecular host-guest chemistry provides a promising means to achieve selectivity in a wide range of biological reactions. In general, the supramolecular host acts in two ways. One approach is to position the target sites of substrates close to the reaction center for preferential attack. Another approach is through the inclusion of a reaction center to constrain the approach of non-target sites of substrates. As a result, the selectivity of response at target sites will increase.

Introduction

Cyclodextrins are water-soluble supramolecular compounds with hydrophobic cavities and hydrophilic surfaces, largely employed as ideal hosts in supramolecular catalysis. Reversible formation of host-guest complexes by CDs can affect the microenvironment of guest molecules and alter the state of the conventional reaction to improve the shield.

CDs can also alter the rate of reactions by various non-covalent means. Here inclusion of the substrates into the CD cavity provides a microsolvent effect, which is highly solvent dependent and reported in Diels-Alder, decarboxylation and bromination-debromination reactions. Alternatively, the CD may bind a guest in one conformer rather than another for geometrical reasons.

Ali Reza et al. have studied the catalytic activity of þ-cyclodextrin by immobilized it on Dowex resin, as an efficient solid-liquid phase transfer catalyst, for the synthesis of alkyl thiocyanates and phenacyl derivatives in water (Scheme 1.1).

Scheme 1.1: CD Catalysed Nucleophilic Substitution Reactions

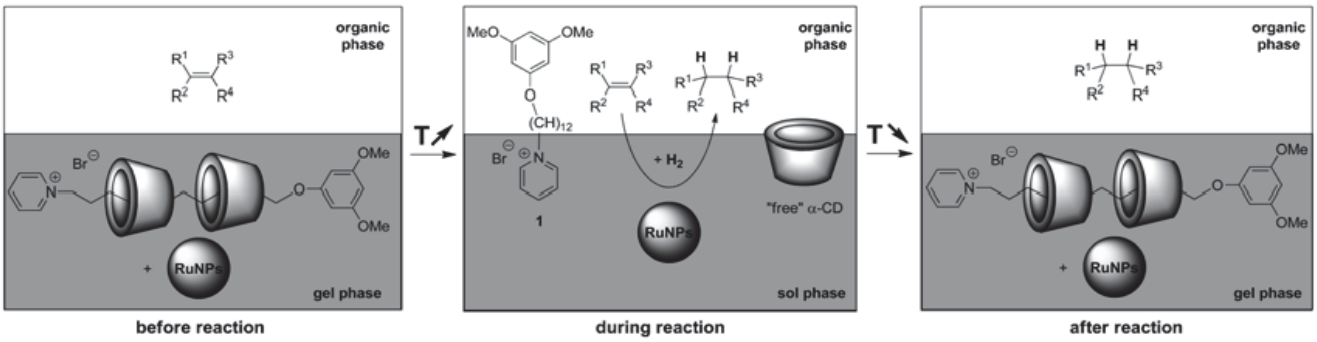
Shin et al. have synthesized 1,4-disubstituted-1,2,3-triazole (Scheme 1.2) from azides and terminal alkenes in excellent yields in water in the presence of þ, -CD as the catalytic amount of phase þ-CD.

Scheme 1.2: Synthesis of 1,4-disubstituted-1,2,3-triazole in the Presence of þ-CD

Monflier et al. have embedded ruthenium-nanoparticle catalysts on a supranuclearcyclodextrin-based hydrogel matrix that allows stabilization at room temperature and activation of Ru NPs at high

temperatures. When heated, the gel phase changed to a sol phase, in which the alikene could be efficiently hydrogenated. When cooled, the reaction products and metal catalysts can be easily separated (Scheme 1.3).

Scheme 1.3: Thermo-regulated RuNPs-catalyzed Hydrogenation of Alkenes using the 1-(a-CD)$_2$hydrogelmatrix



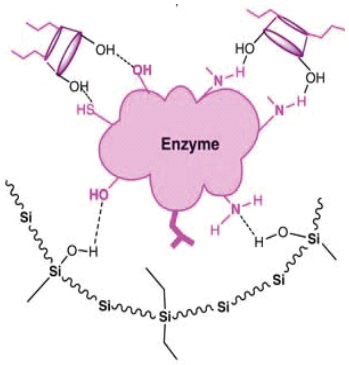
Monflier et al. have also reported that native or modified þ-cyclodextrins showed very opposite behavior, depending on their neutral or ionic nature, when mixed with water-soluble phosphine to self-combine into micelles is capable of in the post-micellar field, the neutral þ-CD led to a micelle destructor. In contrast, the micelles remained stable over a well-defined range of ionic þ-Cd concentrations. In that case, micella destruction was only observed when using a large amount of ionic þ-CD. Thecatalytic performances of these micellar systems have been evaluated in a rhodium catalyzed hydroformylation reaction of 1-decene.

Li et al. have reported efficient procedure for the preparation of urapidil, under various inverse phase-transfer catalysis (IPTC) conditions. They found that þ-CD is the best catalyst owing to its excellent catalytic activity and eco-friendly nature compared to the same conditions with no inverse phase-transfer catalyst (Scheme 1.4).

Yilmaz and Sezgin have encoded an enzyme, Candida rugoza lipase, within a chemically inert sol-gel support prepared by polycondensation with tetraethoxoxycillin and octyltriethoxoxylene in the presence of an þ-CD-based polymer (þ-CD-hexamethylenediisocyanate).

The catalytic activity of encapsulated lipases (Scheme 1.5) was evaluated in both antisoluble hydrolysis of p-nitrophenylprimate and racemic naproxen methylar.

Scheme 1.5: Schematic Illustration of Sol-gel Encapsulation of Enzyme on þ-CD

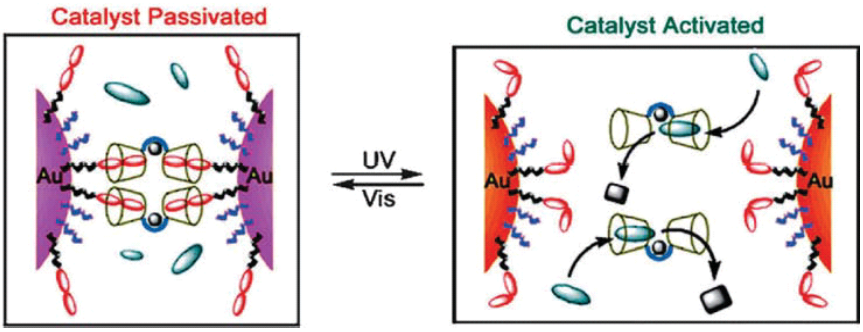


The inclusion complex of isatoic anhydride with þ-CD was formed as a result of intermolecular interaction between isatoic anhydride with þ-CD From application of complex, herein Dalal et al. have described a simple and efficient protocol for synthesis of 2,3-dihydroquinazoline-4(1H)-one derivatives (Scheme 1.6) by one pot condensation of isatoic anhydride, ammonium acetate or amine and aldehyde using þ-CD as a supramolecular catalyst in aqueousmedia.

Nageswar et al. have synthesized a-hydroxyphosphonates from aromatic/heteroaromatic aldehydes with triethylphosphite in the presence of þ-CD in an aqueous medium (Scheme 1.7). The þ-CD can be recovered and reused without loss of catalytic activity.

Zhao et al. have synthesized zone (II) -coordinated þ-CD dimer catalysts with azobenzene units on the surfaces of gold nanoparticles and were used as a photovoluble supramolecular catalyst for esters (Scheme 1.8) is. Trans azobenzene units, the catalyst now recognizes the substrate and hence its catalytic activity is dissociated.

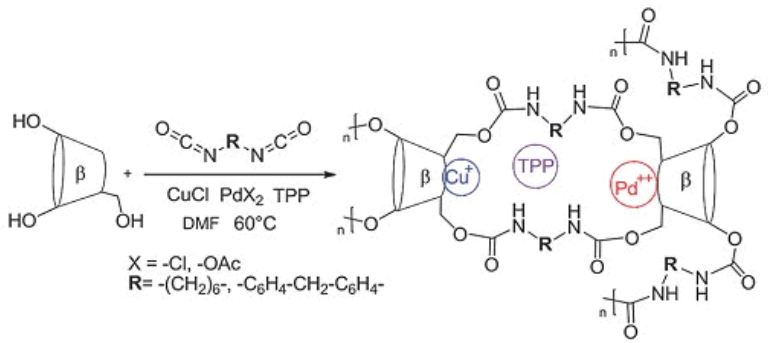
Scheme 1.8: Zn(II)-coordinated þ-Cddimerphoto Switchable Supramolecular Catalyst for Esterhydrolysis



Kissat et al. used water-insoluble þ-cyclodextrin-polyurethane polymer (þ-CDPU) as a catalyst for the nucleophilic substitution reaction of benzyl halides with thiocyanate and acetate ions in water (Scheme 1.9). There is no evidence for the formation of a by-product, for example is othiocyanate and the products were obtained in pure form without further purification.

Cravotta et al. have arranged a Pd/Cu stacked polymeric cyclodextrin impetus by means of in-situ reticulation with diisocyanates under sonochemical conditions. Excellent yields were watched for Sonogashira responses completed in water and glycerol and the impetus could undoubtedly be recouped and reused multiple times without a noteworthy misfortune in synergist action (Scheme 1.10).

Scheme 1.10: Preparation of Poly-þ-CD/Pd/Cu Nanoparticles



Modified Cyclodextrins

- **Approaches to Selective Modification of Cyclodextrins**

Changing CDs so that the size and shape can be adjusted and new utilitarian gatherings are presented for more noteworthy usefulness and host-visitor particularity have increased a lot of consideration lately. Monflier et al. announced that synthetically adjusted cyclodextrins can be utilized to (I) increment fundamentally the rate and selectivity of responses catalyzed by water-solvent organometallic edifices, (ii) structure new water-dissolvable ligands for watery organometallic catalysis, (iii) balance out chemically dynamic honorable metal nanoparticles in water and (iv) favor the scattering and initiation of the palladium on charcoal in water.

All changes of CDs are done at the hydroxyl gatherings, and since these are nucleophilic, the underlying response includes an electrophilic assault on these gatherings. Notwithstanding, because of their wealth and likeness, these hydroxyl bunches go after the reagent and make specific adjustment troublesome. Of these three kinds of hydroxyl gatherings, those at the 6-position are the most essential and frequently most nucleophilic, those at the 2-position are the most acidic (pKa~ 12.1) and those at the 3-position are the most in available.

The optional side is more packed than the essential side because of the nearness of double the quantity of hydroxyl gatherings. Hydrogen holding between hydroxyl bunches at the 2-and 3-positions makes them unbending and less adaptable when contrasted with C-6 hydroxyl gatherings. Every one of these elements make the optional side less responsive and harder to specifically functionalize than the essential face.

Since essential hydroxyl bunches are more nucleophilic than their optional partners, they are effortlessly changed into other utilitarian gatherings. Particular permodification of all the essential hydroxyl bunches is moderately simpler than mono-, di-or trisubstitution in light of the fact that even replacement is accomplished when the response is permitted to run for a more drawn out time with proper measures of reagents.

Exploration in the field of multivalent CDs to date has to a great extent concentrated on the amalgamation of persubstituted CDs, in which all the hydroxyl bunches are adjusted. Perhalogeno-6-deoxycyclodextrins are legitimately arranged by responding cyclodextrins with triphenylphosphine and bromine or iodine in DMF. Segregation and filtration of the Vilsmeier-Haack reagent [(CH3)2NCHBr] +Br-before response with cyclodextrin maintains a strategic distance from serious issues of expulsion of triphenylphosphine oxide in this response. Per-6-iodo-þ-cyclodextrins are significant percursors for aminocyclodextrins. Alkylamines respond with per-6-iodo-þ-cyclodextrins at a high temperature to create auxiliary amines in an awesome yield. Per-6-azido-þ-cyclodextrinsare combined by responding with sodium azide in DMF at high temperature in an exceptionally high return. Decrease of the azido gathering by Ph3P in fluid smelling salts arrangement followed by treatment with weaken hydrochloric corrosive yields the comparing amine salt. This is a fairly clear technique for making amino cyclodextrins and other subbed amino subsidiaries.

- **Aminocyclodextrins**

Aminocyclodextrins, in which the essential face comprises amine bunches instead of the hydroxyls of CD itself and the optional face was unmodified, methylated or acylated, speaks to the parent particle for

a group of monofacially subbed aminocyclodextrins which give the accompanying potential biomimetic restricting spaces: the hydrophobic pit, the cationic annulus and the crown shaped by the pendant tendrils.

- **Biological Importance of Aminocyclodextrins**

Aminocyclodextrins were appeared to specifically perceive changed glycosaminoglycan sulfate (GAGs) and in essential cell culture to restrain and additionally give a substrate to neurite development, Demonstrating selectivity for little anionic visitor atoms, for example, nucleotides and aryl phosphates. These examinations show that aminocyclodextrins contrast fundamentally from other CD subsidiaries. Venton et al. revealed that aminocyclodextrins hinder self-get together of a conceivably neurotoxic type of þ-amyloid protein (Aþ) involved in Alzheimer's malady utilizing an Aþ explicit immunoassay. Aminocyclodextrins hinder self-get together of Aþ into neurotoxic amyloid determined diffusible ligands (ADDLs) with nanomolar strength through a mix of electrostatic and hydrophobic acknowledgment. Amino-cyclodextrins can be seen to introduce a geography of restricting locales similar to a counter acting agent like restricting pocket however without the inborn issues in immune response therapeutics.

- **Catalysis by Per-6-amino-þ-cyclodextrin(per-6-NH_2-þ-CD)**

Amino groups not only can act as ligands for transition metal in coordination complexes, but also act as base in organic reactions. Similarly per-6-NH_2-þ-CD (pKa value 6.6-8.5)is also used as a supramolecular ligand for transition metal complexes and as a catalyst for base catalysed organic reactions. Nearness of chiral hydrophobic cavity with amino gatherings on the essential side delivers this CD a one of a kind nano response vessel for different synthetic procedures and changes.

Per-6-NH_2-þ-CD catalyzes the Kemp elimination of 5-nitro-benzisoxazole by 210-680 folds at physiological pH (Scheme 1.11).[80a] Amino CDs are used to facilitate deprotonation.[80b] Per-6-amino-þ-cyclodextrin enhances the rate of deprotonation of 4-tert-butyl-a-nitrotoluene to a greater extent than native CDs.

Utilization of per-6-amino-þ-cyclodextrin (per-6-NH2-þ-CD) as a base and chiral inductor is accounted for in the awry Michael expansion of nitromethane and thiols to trans-chalcone in watery medium at room temperature (Scheme 1.12).[81a] In this response per-6-NH2-þ-CD plays out a double job, acting both as a base to catalyze the response and furthermore as a chiral inductor by upgrading the enantiomeric overabundance. Water is utilized (with no cosolvent) as an eco-accommodating dissolvable and the impetus is reused with no misfortune in its action. Great enantioselectivities are watched even at room temperature. Different focal points incorporate simplicity of recuperation and nonattendance of dangerous outer acids and bases.

Per-6-NH2-þ-CD is utilized as a proficient ligand for CuI as impetus in N-arylation of imidazole with a wide scope of aryl and heteroaryl bromides which give magnificent yields under milder conditions (Scheme 1.13).[81b] This system maintains a strategic distance from a dormant air, which is a typical imperative with prior works.

A basic, green and effective convention is created with per-6-NH2-þ-CD which acts at the same time as a supramolecular have and as a productive strong base impetus for the dissolvable free blends of

different dihydropyrano[2,3-c]pyrazole subsidiaries including a four-part response (Scheme 1.14).[81c] This particle affordable convention, announced just because with ketone likewise, incorporates an a lot milder strategy, keeps away from dangerous reagents/side-effects and results in close to quantitative yields. The impetus can be reused at any rate multiple times with no adjustment in its catalyticactivity.

An exceptionally proficient enantioselective Henry response has been done utilizing per-6-NH2-þ-CD as a supramolecular chiral host and advertiser to give the comparing adduct with high return (up to 99%) and enantiomeric abundance up to 99% (Scheme 1.15).[81d] Per-6-NH2-þ-CD likewise advances the diastereoselective Henry response in a syn-particular way to give the adduct up to 99% yield with 99:1 syn/hostile to selectivity. The enantiomeric abundance of the syn-adduct is 99%. The impetus is recuperated and reused without misfortune in its activity.

Effective cyanation of aryl halides is accomplished utilizing less harmful K4[Fe(CN)6] as the reagent and amino-þ-cyclodextrins as supramolecular ligands for CuI. Four diverse aminocyclodextrins viz. per-6-amino-þ-CD, per-6-methylamino-þ-CD, per-6-n-butylamino-þ-CD and mono-6-amino-þ-CD are arranged and examined. Aryl and heteroaryl nitriles are gotten in acceptable to phenomenal yield for even bromo subsidiaries of flavone and 2-aminopyrans. This framework utilizes reactant sums (10 mol %) of both copper iodide and per-6-amino-þ-cyclodextrin (Scheme 1.16).[81e]

An effective three segment response of fragrant aldehyde, malononitrile and 1,3-cyclohexanedione/dimedone was created just because utilizing per-6-amino-þ-cyclodextrin, as a supramolecular have for aldehydes and a proficient base impetus, which delivered different subbed 2-amino-4H-benzo[b]pyrans in great to incredible yields, under dissolvable free conditions.[81f] The impetus can be reused at any rate multiple times with no checked change in its reactant action (Scheme 1.17).

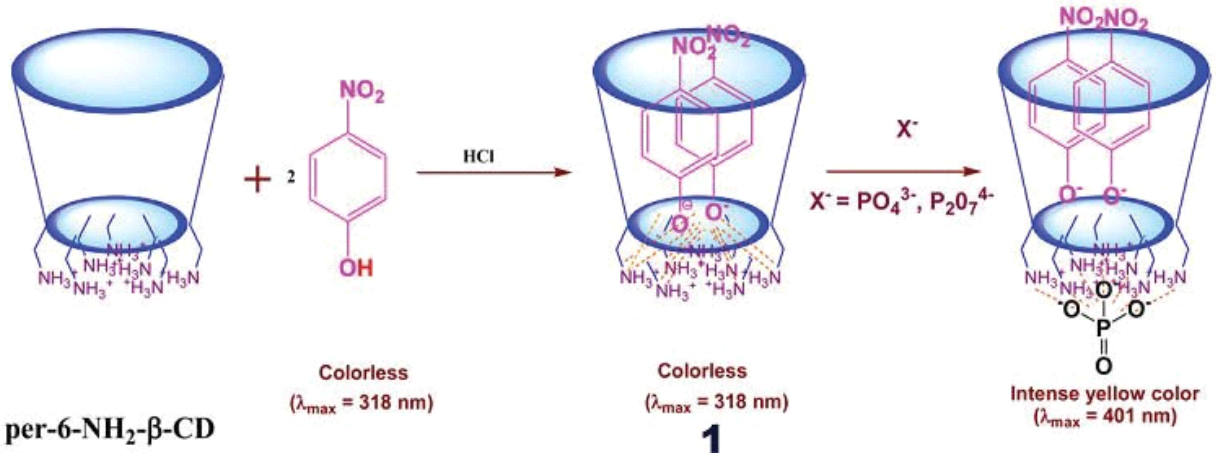
A profoundly productive one-pot blend of enantiomerically improved 2-aryl-2,3-dihydroquinolin-4(1H)-ones was done just because utilizing per-6-NH2-þ-CD as a supramolecular have, chiral base impetus, and a reusable advertiser to give the relating platform with high return (up to 99%) and enantiomeric overabundance (up to 99%). The impetus was recuperated and reused without misfortune in itsactivity.[81g]

A colorimetric and ratiometric sensor for progress metal cations, for example, Fe3+, Ru3+ and an overwhelming metal Bi3+ in water utilizing per-6-NH2-þ-CD as a supramolecular host and p-nitrophenol as a spectroscopic test was created in our lab.[81h] Other metal particles like Ag+, Cu+, Mn2+, Fe2+, Cu2+,Zn2+, Cd2+, Hg2+, Pb2+, Cr3+, Ln3+ and Eu3+ are not detected by this technique. This metal particles detecting by basic shading change from serious yellow to dry, can be used readily for their naked-eye detection (Scheme 1.19).

Scheme 1.19: Mechanism of Cation Sensing in Water

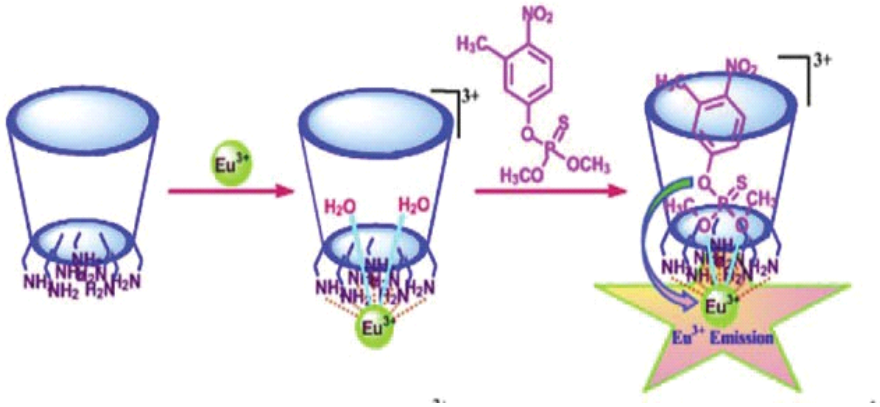
Utilizing per-6-ammonium-þ-cyclodextrin (per-6-NH3+-þ-CD) as an anion restricting site and p-nitrophenol as a spectroscopic test, a colorimetric sensor is created for phosphate and pyrophosphate anions in water.[81i] Per-6-NH +-þ-CD shapes a 1:2 incorporation complex with p-nitrophenol (1 in Scheme 1.7) as portrayed by NOESY and ESI-MS spectra and it experiences a particular shading change from dreary to extreme yellow upon presentation to phosphate or pyrophosphate anions over different anions including perchlorate, ATP2-, ADP2-and AMP2-. The seven ammonium gatherings of 1, tie phosphate (described by ESI-MS) or pyrophosphate anions explicitly by electrostatic communication (Scheme 1.20).

Scheme 1.20: Mechanism of Anion Sensing in Water



An exceptionally particular fluorescent chemosensor for fenitrothion utilizing per-6-NH2-þ-CD:Eu(III) complex is accounted for in our research facility. This sensor framework is fit for particular detecting of fenitrothion over different organophosphorus pesticides to be specific paraoxon, methylparaoxon, parathion, methylparathion, fenitrothion, profenofos, fenchlorophos, quinalphos and malathion. The astounding selectivity towards fenitrothion detecting, includes a retention vitality move discharge (AETE) process (Scheme 1.21).[81j]

Scheme 1.21: Mechanism of Enitrothionsensingbyper-6-NH_2-þ-CD:Eu(III)complex in Water



Charged type of per-6-amino-þ-cyclodextrin (per-NH3+-þ-CD) has been utilized in chiral acknowledgment of an amino corrosive subsidiaries.[82a] Per-NH3+-þ-CD structures solid buildings with the (S)-enantiomers of N-acetylated Trp, Leu and Val in their anionic structures more specially than the (R)-enantiomers, however the coupling constants (K) between the enantiomers is little. Local CDs show an extremely low capacity to separate between the enantiomers of amino acids. Stability of the complexation is rationalized by the intermolecular coulombic interactions between the amino acid and charged CDs. Binary complex of pyrene/per-6-ABCD acts as a chiral selector at two pH values for amino acids like phenylalanine, methionine and histidine and the stability of the ternary complex of pyrene/per-6-PABD/amino acid is determined by spectro-fluorimetric measurements. Per-6-NH_2-þ-CD is used as a chiral selector for the enantiomer separation in different classes of anionic analytes in capillary electrophoresis.

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