SUPRAMOLECULAR APPROACH IN TUNING MOLECULAR PROPERTIES: POSSIBLE APPLICATIONS

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Dr. Haridas Pal is the recipient of the DAE Homi Bhabha Science & Technology Award for the year 2008

Abstract

In this article we present some selective results from our studies using supramolecular approach to tune molecular properties. It is observed that using microheterogeneous media like micelles it is possible to modulate photoinduced electron transfer (ET) reaction so significantly that Marcus inversion can be easily observed even for bimolecular ET reactions, though such behavior remains obscured in homogeneous solution. Our studies involving macrocyclic host molecules show that supramolecular interactions can efficiently modulate various properties of organic dyes, namely acid-base properties, fluorescence properties and conformational changes, etc. which can have potential applications in areas like pharmaceutical chemistry, fluorescence sensors, on-off molecular switches and many other. We have also demonstrated the operation of a supramolecular based aqueous dye laser system having performances better than organic solvent based dye laser systems.

Keywords: Supramolecular chemistry, Microheterogeneous media, Macrocyclic hosts, Electron transfer, Marcus inversion, pK_a tuning, Conformational changes, Aqueous dye laser.

Introduction

Supramolecular chemistry is an extensively evolving area having immense importance in various disciplines of chemistry and biology. In broad sense, supramolecular chemistry deals with complex chemical systems that are spontaneously formed by the association of compatible (both chemically and structurally) molecular units via non-covalent interactions. Such systems are special not only in their structures but also in bringing out interesting properties that can find many useful applications in various areas. Since supramolecular systems are formed only due to noncovalent interactions (hydrophobic, hydrogen bonding or Coulombic interactions) and because these interactions are much weaker than the covalent bonds, for the stability of such systems their constituent units are generally of large molecular sizes so that there are multiple and extensive interactions among the constituent units. In nature, supramolecular interactions lead to the formation of very complex spatial structures that play vital roles in determining the course of various biological processes. Considering their direct relevance to biology and their widespread applications in various areas, the studies on supramolecular interactions have sustained tremendous research interests in chemical sciences for long time.

Micelles, reverse micelles, vesicles, etc. are the well-known self-assembled supramolecular systems. The microenvironments of such systems have been used very extensively in various studies, to improve solubility, enhance stability and control reaction dynamics for the entrapped chemical species. In our research group, we have contributed quite significantly in the understanding of the photoinduced electron transfer (ET) reactions in various microheterogeneous media. Some selective results of these studies will be presented in this short review.
Macrocyclic host molecules (also called the cavitand molecules) possess intramolecular cavities and suitable guest molecules can be encapsulate into these cavities simply due to noncovalent interactions, resulting the formation of supramolecular host-guest complexes, having applications in various areas like pharmaceutical chemistry, food technology, chemical industry, sensors, etc. Among different macrocyclic hosts, cyclodextrins (CD; composed of glycopyranose units joined by ether linkages) and cucurbiturils (CB; composed of glycoluril units joined by pairs of methylene bridges) have been investigated very extensively in recent years, mainly due to their nontoxic nature and reasonably good solubility in water. In our group, we are actively pursuing fundamental research on host-guest interactions with an aim to suitably modulate the properties of chromophoric dyes and thus to explore their possible applications in various areas. Some selective results of these studies are also be presented in this short review.

Results and Discussion

Modulation of electron transfer dynamics in microheterogeneous media

Studies on the mechanism and dynamics of ET reactions in microheterogeneous media like micelles, reverse micelles, etc. have attracted considerable research interests in recent years, mainly due to their relevance in areas like nanosynthesis, solar energy conversion, tuning chemical reaction, etc. Such studies also have considerable academic interests, especially to understand the effect of topology of the microheterogeneous media on the chemical reactions. The most important prediction of Marcus ET theory is the inversion (decrease) of ET rate beyond a certain exergonocity (negative of the free energy change; $-\Delta G_0$), commonly known as Marcus inversion (MI). Marcus theory expresses ET rate constant in its simplified form as,

$$k_{et} = \nu \exp \left( -\frac{(\Delta G^0 + \lambda)^2}{4k_BT} \right)$$ (1)

where $\nu$ is the frequency factor and $\lambda$ is the total reorganization energy. It is evident from eq. 1 that $k_{et}$ will be maximum at $-\Delta G_0 = \lambda$ and its value will decrease on either side of this exergonocity resulting MI. Though MI is well documented for intramolecular ET reactions, it is still illusive for bimolecular ET reactions, because in these cases reactant diffusion limits the maximum observable rate to diffusion-controlled rate ($k_d$). Expected MI and the diffusion-control on observed rate constant are schematically shown in Fig. 1. Following this figure, though inversion can still be expected at very high exergonocity, such an extreme situation, however, is practically not realized mainly due to the nonavailability of suitable donors and acceptors that can give such a high exergonicity. It however transpires that if by some means one can overcome the influence of reactant diffusion and bring down the $\lambda$ value it would be possible to observe MI more easily even for bimolecular ET reactions. We felt that microheterogeneous media like micelles, reverse micelles or vesicles can, by and large, satisfy the above conditions. The restricted geometry of these supramolecular assemblies can restrict the reactant diffusion and thus ET will take place only between spatially fixed donor and acceptor pairs, making the bimolecular reaction effectively similar to intramolecular ET. Moreover, solvent relaxation being extremely slow in these systems, one can expect that solvent reorganization will only partially contribute to $\lambda$, shifting MI towards lower exergonocity region. With this viewpoint, we investigated bimolecular ET reactions involving various donor-acceptor systems (aromatic and aliphatic amines as donors and coumarin and substituted anthraquinone dyes as acceptors) in different micellar media. In all the systems studied the ET rates are seen to display clear MI behavior (cf. Fig. 2). To be mentioned, ours are the first report to demonstrate MI for bimolecular ET reactions in microheterogeneous media. Following this report, there have been very extensive follow up work from different research groups, aiming to understand more about MI in such systems, especially to explore the possibility of tuning MI for its better utilization in different areas. Our subsequent studies have in fact shown that MI can really be tuned along the exergonocity scale simply by changing the hydration characteristics of the micelles (cf. figure 2). These results are expected to help in designing ET
systems for their maximum utilization in different applied areas.9-16

Effect of macrocyclic host cucurbit[7]uril (CB7), on the acid-base properties of a biologically important dye (as pH indicator), neutral red, has been investigated in detail. In aqueous solution the dye has a pKₐ value of 6.8 and hence it exists as protonated form (NRH⁺) in acidic solution and as neutral form (NR) in basic solution. Both the forms binds quite strongly with CB7, though the binding is about two order of magnitude higher for NRH⁺ (Kₑq⁰ₙ NRH⁺·CB7 = 6.0x10⁵ M⁻¹) than NR (Kₑq⁰ₙ NR·CB7 = 6.0x10³ M⁻¹).21-23 Such a large difference in the Kₑq values suggests a large upward pKₐ shift for the CB7 bound dye. In fact, the measured pKₐ value for the CB7 bound dye is found to be as large as 2 units higher than that of the free dye (cf. Fig. 3). This further suggests that the CB7 bound dye is 100 times stronger base than the free dye.

Significantly higher Kₑq value for NRH⁺ is understood to be due to the ion-dipole interaction involving the highly polarized carbonyl portal of CB7. Since CB7 is a good cation receptor, it was expected that metal cations will show a competitive binding with CB7, disturbing the NRH⁺-CB7 interaction and thus will shift the pKₐ value again towards that of the free dye. This is in fact found to be so on gradual addition of salt (cf. figure 3). To explore the applicability of this salt-induced pKₐ shift to a biological system, we extended this study in the presence bovine serum albumin (BSA), with which NR binds stronger (Kₑq⁰ₙ NR·BSA = 1.0x10⁴ M⁻¹) than NRH⁺ (Kₑq⁰ₙ NRH⁺·BSA = 6.1x10³ M⁻¹). In the dye-CB7-BSA system, the pKₐ of the dye modulates in the range of 8.3 to 6.3, with the gradual addition of the salt (cf. Fig. 4).

**Host-guest interaction to tune acid-base property: Salt-induced guest relocation**

- Fig. 1: Schematic presentation of expected Marcus inversion, saturation of observed rate at kₐ and expected inversion at extremely high exergonocity for bimolecular ET

- Fig. 2: Marcus inversions observed for bimolecular ET involving coumarin acceptors and aromatic amine donors in TX100, DTAB and SDS micelles. Marcus inversion region can be shifted by about 0.7 eV by using these micellar systems

- Fig. 3: Modulation in the pKₐ value of Neutral red-CB7 system with the addition NaCl

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modulation in turn realized to promote the relocation of the dye from the CB7 cavity (where NRH\(^+\) binds stronger) to the biomacromolecular BSA pocket (where NR binds stronger), especially at a biologically relevant pH ~7, which is schematically shown in the lower panel of figure 4. Present results demonstrate that host-guest interactions can serve as an interesting tool to stabilize potential drugs through host-assisted protonation. The addition of salt could then offer a simple but effective stimulus for the controlled release of the drugs towards biological targets. Such a strategy thus can have a direct relevance to pharmaceutical chemistry.

Conformational changes by monitoring the intrinsic fluorescence from this chromophoric moiety. In aqueous solution FAD fluorescence is strongly quenched due to photoinduced ET from the adenine moiety to excited isoalloxazine moiety. It is understood that in aqueous solution FAD preferentially exists in its “closed” conformer where the flavin and the adenine moieties are stacked together, resulting an efficient intramolecular ET process. In its “open” conformer, the donor-acceptor moieties in FAD are well separated and hence there is no intramolecular ET. We have investigated the conformational changes of FAD on its interaction with β-cyclodextrin host (βCD).\(^{24}\) From detailed photophysical studies it is revealed that FAD binds to βCD through its adinine moiety, keeping its isoalloxazine moiety free. Interestingly, however, there is a large fluorescence enhancement for the system which is normally not expected considering that the isoalloxazine moiety remains free in the FAD-βCD complex. We infer from detailed studies that the binding of FAD with βCD actually promotes a conformational change, from its “closed” structure to “open” structure (mainly due to the steric reason), and thus inhibits intramolecular ET process. Accordingly, there is a large enhancement both in fluorescence intensity and lifetime for FAD on its binding to βCD host. It is expected that present results will aid in the studies and interpretations of the conformational dynamics and activity of flavoproteins, which are based on the intrinsic fluorescence measurements of FAD in the flavoproteins concerned.
Supramolecular host-guest interaction for aqueous dye laser systems

Dye lasers are the indispensable tools in fundamental and applied research. In addition to the safety hazards concerning organic solvents and the associated disposal problem of degraded dye solutions, the organic solvents have less efficient thermo-optic properties causing distortion of the laser beams at high laser output power. Numerous efforts have been made to use water as the medium to overcome the disadvantages of the organic solvent based dye laser systems. As most organic dyes undergo detrimental aggregation in aqueous solution, additives like surfactants, emulsifiers, etc. have been tested, but invariably with limited success, mainly because of large amounts of additives required that add to some other associated problems with the dye stability and laser beam quality. In our study, we have used a simple supramolecular approach where strong host-guest complexation helps to operate an efficient rhodamine 6G (Rh6G) dye laser in aqueous solution. Rh6G forms very strong inclusion complex with CB7 ($K_w = 5 \times 10^4$ M$^{-1}$). Thus, for a typical dye concentration of ~1 mM, usually required for a dye laser operation, a CB7 concentration of just few mM is sufficient for almost quantitative binding of Rh6G with the host. Binding of Rh6G with CB7 also suppresses dye aggregation in solution and dye adsorption on cell walls, increasing the efficiency of the laser. Moreover, the photostability of the CB7-bound Rh6G in aqueous solution is about three times higher than that of the dye in ethanol solution. All these effects add beneficially to give an efficient CB7 based aqueous dye laser system for Rh6G. Fig. 7 compares the lasing efficiency of this laser with that of a standard dye laser in ethanol solution. At about

![Fig. 6: Schematics of the conformational changes in FAD on its binding with βCD host](image_url)

![Fig. 7: Lasing efficiency for aqueous Rh6G-CB7 system with varying CB7 concentration. Dashed line is the reference for Rh6G dye laser in ethanol](image_url)
8-9 mM CB7 concentration the efficiency of the laser saturates where it is quite comparable to that of the ethanol solution. Fig. 8 presents the beam profile for the present CB7 based aqueous Rh6G laser system along with that of the dye laser in ethanol solution. As it is evident, the more efficient thermo-optic property of water makes laser beam profile much more symmetric in the present case than in ethanol solution. In brief, present study suggests that the supramolecular based aqueous dye lasers are not only practically viable but also they offer a better photostability and improved laser beam quality, especially may be very useful for high power and high repetition rate dye laser operations.

**Conclusion**

To summarize, present article demonstrates that the dynamics of bimolecular ET reactions can be suitably modulated by using micellar media where reactant diffusion is largely suppressed and solvent reorganization only partially contributes resulting the MI to shift significantly towards lower exergonocity region such that the MI behavior is easily observed for bimolecular ET reactions though such behavior is normally remained obscured in homogeneous solutions. In supramolecular host-guest interactions, present review shows that encapsulation of potential guest molecules into the cavity of the macrocyclic hosts (e.g. CB7 and bCD) can efficiently modulate various properties of the guests. Thus, modulation in the pKₐ value of neutral red dye, its’ tuning by added salts and salt induced dye relocation from host cavity to a biomacromolecular pocket has been demonstrated, which is having a direct relevance to pharmaceutical chemistry. Host induced conformational changes in a biomacromolecule FAD has been demonstrated and the results might be useful in understanding the conformational dynamics and activity of flavoproteins. Present article also demonstrates that supramolecular host-guest interaction can be used suitably to develop an efficient aqueous dye laser system.

**Acknowledgement**

I sincerely thank all the co-authors and collaborators of the published works⁹-²² that are summarized in this short review. I am especially thankful to my sectional members for their tireless efforts to carryout the best quality of research works. I also take this opportunity to thank my RPCD and TCS colleagues for all their help and support. My special thanks are due to Dr. S. K. Sarkar, Head, RPCD and Dr. T. Mukherjee, Director, Chemistry group, for their constant help, support and encouragement in all our scientific endeavors.
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