CHAPTER 1

Molecular Electron-Transfer Systems and Artificial Enzymes

1.1 MOLECULAR BUILDING BLOCKS

It is common in science to dismantle, both conceptually and physically, complex structures into their component parts. By studying the simpler components it is often possible to more fully understand the complex system as a whole. In the field of chemistry the concept of deconstructing macromolecules into smaller constituent sub-units is also well established. A glance at any modern biochemistry textbook will reveal analyses of the main classes of biologically important compounds in terms of their components or 'building blocks'. This is not surprising as many of these compounds are polymeric and consist of repeated monomeric units. Understanding the building blocks of complex biological macromolecules allows some insight into the behaviour of the whole system, especially when one considers how each of these units may interact with each other both intra- and inter-molecularly. The polymeric biological compounds of importance include proteins, nucleic acids and carbohydrates.

The building blocks of proteins are amino acids. There are only about twenty naturally occurring amino acids. A large number of amazingly complex protein structures, which vary widely in functionality, can be 'built' from this small library of molecular components. Nucleic acids (DNA and RNA) are polymers constructed from just four different monomer units joined together by phosphodiester linkages. Understanding the complex structure of nucleic acids and their ability to act as information storage devices largely depends upon an understanding of the way individual nucleic acid residues are able to interact with one another. Finally, carbohydrates can also be described in a similar manner. Carbohydrates may be monomeric (e.g. glucose), oligomeric (e.g. maltose) or polymeric (e.g. starches such as amylose). The variation in number and type of monomers used to form carbohydrates explains the versatility of this class of compounds. Not only are these compounds important energy sources but also they are important structural materials and they even participate in molecular recognition events on the surfaces of some cells.

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This modular view of different classes of biological macromolecules has aided in the design and synthesis of a great variety of large chemical systems. This includes both biologically based and artificial compounds. Some recent examples from various specialised research areas are the design and synthesis of: porphyrin-based photonic, intramolecular electron transfer and catalytic systems[1-3]; photoluminescent polymeric arylenevinylene-type materials[4]; cross-conjugated enyne macrocycles (expanded radialenes)[5]; dendrons and dendrimers[6,7]; 'molecular belts' and 'molecular coils'[8]; rotaxanes and catenanes[9-16]; and peptides, including those based on glycosamino acids.[17-20] A recent materials science review article has focused on 'the development, characterisation and exploitation of novel materials based on the assembly of molecular components' as 'molecules enable a substantially greater ability of control than atoms as building blocks for new materials'.[21]

1.2 ELECTRON AND ENERGY TRANSFER SYSTEMS

1.2.1 NATURAL SYSTEMS

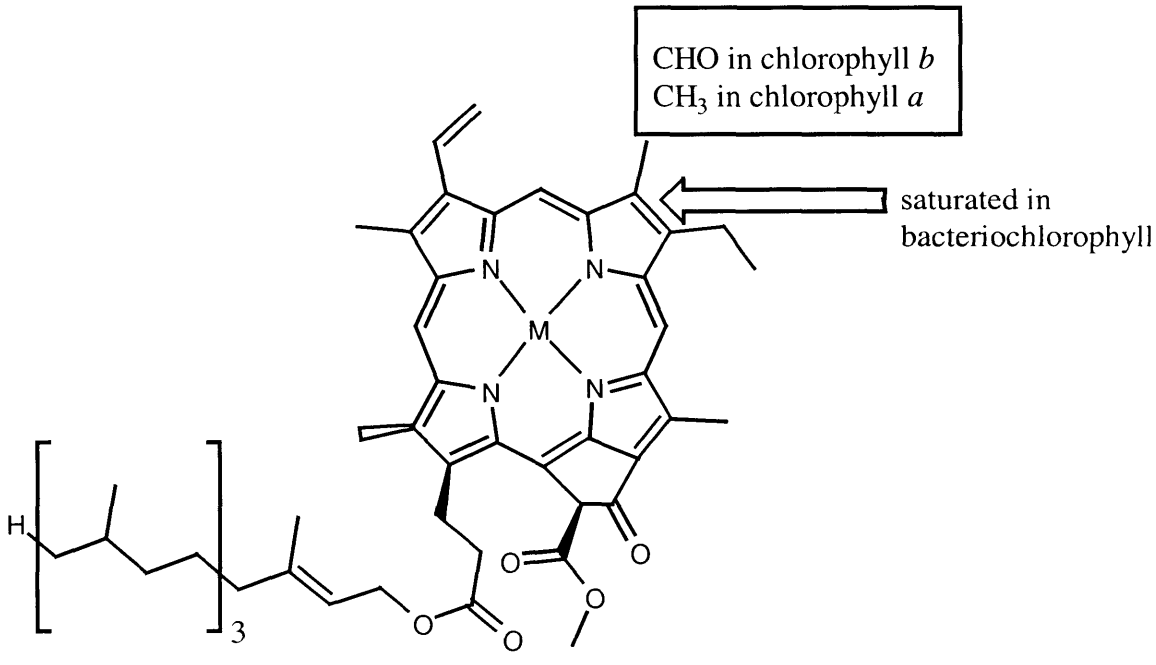

Figure 1.1 Structure of chlorophyll.

Photosynthetic organisms have, over many millions of years, evolved a set of chromophore pigments, which can absorb visible or near infrared light of particular wavelengths. It is, therefore, no coincidence that the wavelengths of light that these chromophores absorb correspond closely to the wavelengths of the sun's radiation that reach the earth's surface. Some of the most important classes of natural chromophores contain porphyrin derivatives. These include the energy harvesting chlorophylls (Figure 1.1) of plants and photosynthetic bacteria. The tetrapyrrole π-system has an associated low-energy π–π* transition corresponding to strong absorption in both the blue and yellow regions of the visible spectrum. This absorption pattern leads to the characteristic green colour exhibited by most plants. The bacteriochlorophylls absorb light of a longer wavelength than chlorophyll due to the difference in the level of saturation of their respective porphyrinic units. Chlorophylls and bacteriochlorophylls bind the otherwise labile Mg^{2+} ion.

The presence of magnesium is essential for the proper orientation and operation of each chlorophyll unit within the light-harvesting array. There are two free axial coordination sites on the octahedral Mg^{2+} centre which, along with the hydrophobic side-chain, binds the chlorophyll units in a well defined and highly ordered manner. Magnesium is naturally abundant and is the right size for coordination within chlorophyll. The relatively low reduction potential and small spin-orbit coupling constant of magnesium are both essential characteristics for the efficient electron transfer processes to occur.

The natural photosynthetic system is very large and complex. Determinations of the x-ray crystal structures of several bacterial photosynthetic reaction centres (PRCs) have enormously aided our understanding of the way they work.[22-28] By analysing the key features of the natural system, both functional and structural, it may be possible to apply some of the principles learnt toward the synthesis of effective and practical artificial photochemical devices.

In the reaction centre of *Rhodopseudomonas viridis* (Figure 1.2) the bacteriochlorophyll dimer or 'special pair' (P) lies in the centre of the approximate C_2 symmetry axis. The special pair absorbs long-wavelength light (λ_{max} = 960 nm) supplied from the multichromophoric 'antenna'. This absorption leads to an excited singlet state which results in a very rapid electron transfer (3 ps) to a nearby bacteriopheophytin (BP) molecule. This electron transfer step is assisted by a monomeric bacteriochlorophyll (BC) either through a superexchange or step-wise mechanism.

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Each of the two BCs is at a distance of 13 Å from P and is at an interplane angle of 70° to P. The BC-BP interplane angle is 65° and a distance of 11 Å separates them.

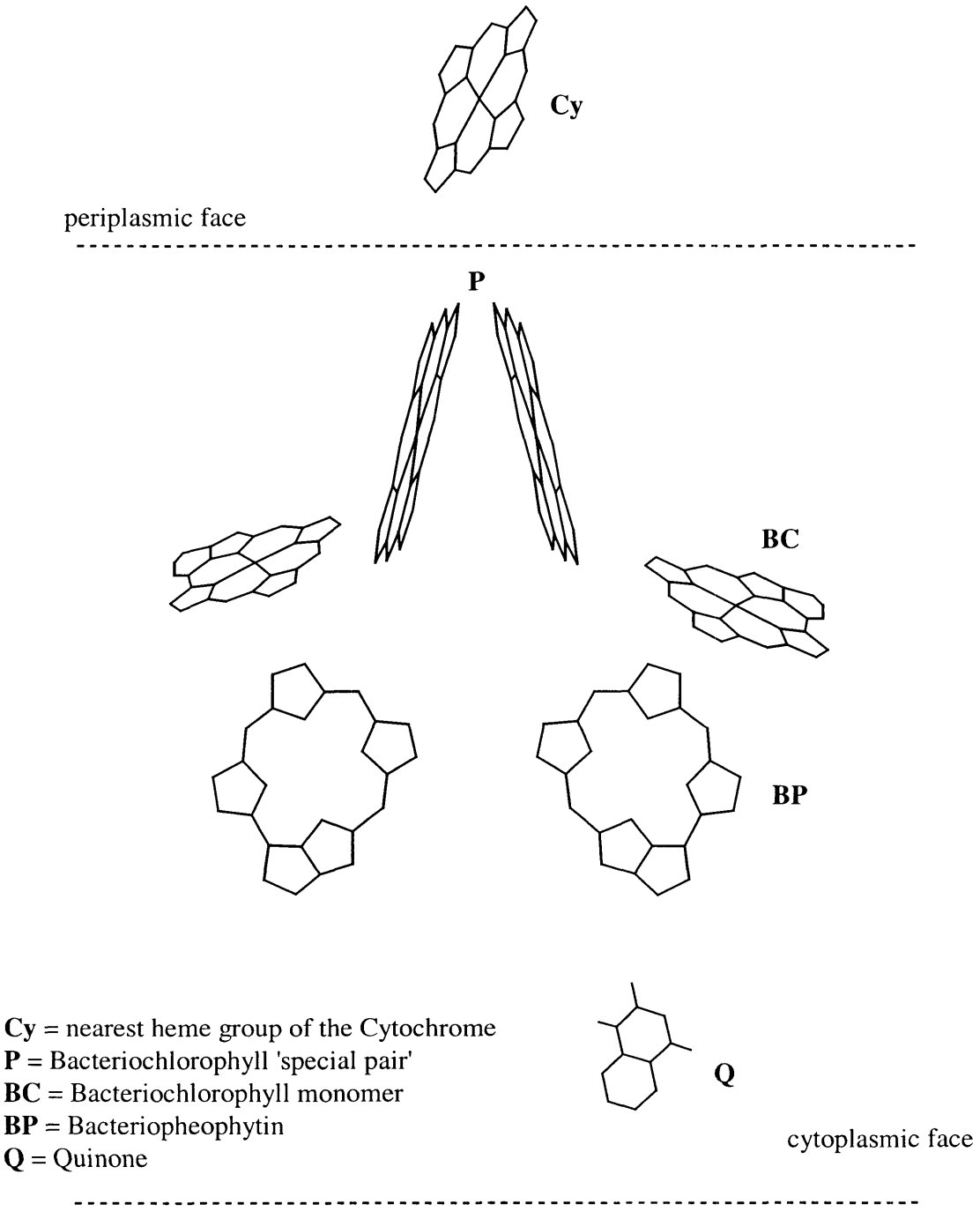

Figure 1.2 Arrangements of the chromophores in the reaction centre of *Rps. viridis*.

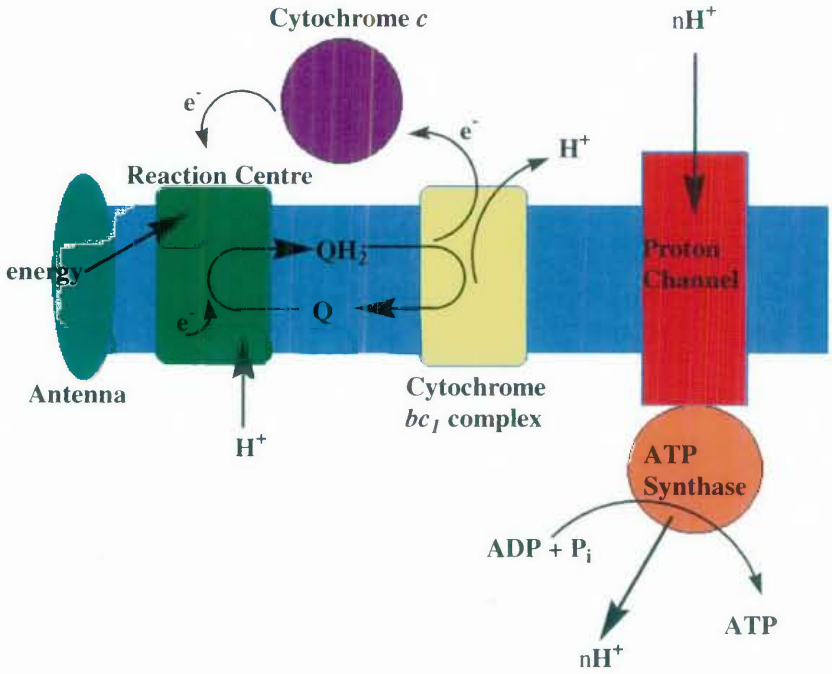

Figure 1.3 Bacterial photosynthetic membrane.[28,29]

This precise geometric configuration is essential for the proper functioning of the reaction centre. A second much slower (200 ps) electron transfer from the BP to a quinone (Q) molecule then follows. Q is then reduced to a semiquinone and finally to a hydroquinone (QH_2). This step is accompanied by the uptake of two protons from water on the cytoplasmic side of the membrane and two photoinduced electron transfers. The QH_2 then diffuses to the cytochrome bc_1 complex that oxidises the QH_2 back to Q with an associated release of energy.

This energy is used to translocate H^+ across the membrane. This establishes a proton motive force (pmf) across the membrane. This pmf drives the production of adenosine triphosphate (ATP), the energy 'currency' of the cell. The positive charge left on the special pair is neutralised by an electron transfer from a cytochrome heme porphyrin (Cy) on the periplasmic side of the membrane (Figure 1.3). This occurs 200 ns after the electron transfer from BP to Q. The end result is a long-distance (~30 Å), long-lived trans-membrane charge separation via a series of short-range rapid electron transfer steps.

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1.2.2 BIOMIMETIC SYSTEMS

Recently, research in the area of biomimetic* chemistry has used models of natural systems, which incorporate one or more key features, in order to gain control over electron and energy transfer processes. The deconstruction of the complex PRC into simpler components has proven to be a rewarding approach to understanding these systems as a whole. The simplest PRC model is to dissolve one or more of the reaction centre components in a solvent and study the resulting solution. While much has been learnt from this approach there are several reasons why it is inadequate. In the natural photosynthetic system the relative position and orientation of each pigment, donor and acceptor group is strictly controlled with respect to one another. As a result, very efficient and rapid energy and electron transfer events occur. This type of control is not possible in solutions of separated donor and acceptor molecules. In solution the electron transfer reactions are rate-limited by diffusion and the picosecond time scales of natural reaction centre electron transfer processes are impossible. Another difficulty is that in most solution studies at normal concentrations longer-lived triplet excited states of the pigments are evident whereas excited singlet states are known to be involved in the natural system. Even if photoinitiated charge separation were achieved it would be difficult to counteract diffusion controlled charge recombination that acts to shorten the lifetime of these species. It is also difficult to obtain mechanistic information from a bimolecular system as the unimolecular electron transfer step and the geometries within the "encounter complex" are masked by solution dynamics.

In order to counter these difficulties many research groups have explored systems that have the donor and acceptor moeities covalently bound in the one molecule. Molecular dyads, which have just one donor (D) and one acceptor (A) group, covalently attached, constitute the simplest of these models. Either flexible linkers or rigid-spacer groups may join the D and A groups. Photosynthetic models using rigid-spacer groups ameliorate complexities introduced from the various conformational changes inherent in flexible-spacer models (Figure 1.4) and so rigidly spaced systems will be the main focus of the following discussion. Many research groups have studied rigid dyads consisting of a variety of different D, A and spacer groups. A few are presented here to illustrate some of the important design principles involved.

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* R. Breslow was the first to use the term "biomimetic" in 1972. (30) Breslow, R. *Chem. Soc. Rev.* **1972**, *1*, 553.

where;
hν = excitation energy
$h\nu_f$ = emission energy (fluorescence)
$h\nu_f^{ex}$ = exciplex emission energy (fluorescence)
k_{el} = rate of electron transfer
k_{ret} = rate of back electron transfer (charge recombination)
k_{ex} = rate of exciplex formation

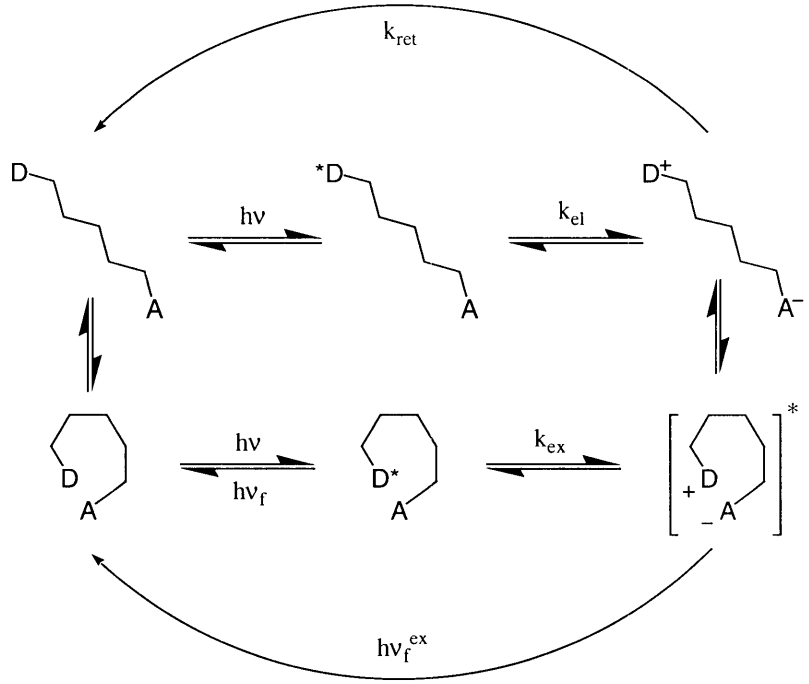

Figure 1.4 Photoinduced electron transfer in donor-acceptor (D-A) systems joined by a flexible linker. The dynamic motions associated with the flexible spacer introduce added complexity e.g. competition between exciplex formation and direct electron transfer which is dependent on chain length and solvent system as well as steric considerations.

At a minimum, the design of a model reaction centre must include; (1) a chromophore that absorbs visible light, (2) an electron acceptor or donor moiety and (3) an organisational principle that controls the electronic interactions. An ideal system will maximise the quantum yield of the ion-pair (ϕ_{IP}) and the lifetime of the charge-separated species (τ_{IP}). This can be achieved by controlling the energy differences between the ground state, excited state and ion-pair by judicious choice of D and A groups and by the use of an appropriate spacer group.

Early work by Paddon-Row and co-workers investigated the effect of distance on photoinduced intramolecular electron transfer between D and A groups. These studies were done on a series of dyads that had a dimethoxynaphthalene donor and a dicyanoethylene acceptor group separated by rigid saturated polynorbornyl spacers of varying length (Figure 1.5).[31-34] In these systems a through-bond mechanism of electron transfer was proposed with the rate of the forward and reverse processes varying according to separation distance between the D and A groups. The forward rates of electron transfer, producing a charge separated species (D^+-spacer-A^-), range between about 10^9 and 10^{12} s^{-1}. The rates decreased with increased separation of D and A. Charge

recombination was slower than the forward electron transfer process due to a relatively large energy difference between the ion-pair and ground states (k_{ret} decreases with increasing ΔG_{ret}). The rates of charge recombination were also found to be dependent on the number of bonds that separated the D and A groups. Paddon-Row has extended this work to further investigate the role of solvent-mediated and through-bond electron-transfer processes using a number of different multichromophoric rigid molecules of various shapes and sizes.[2,35-43]

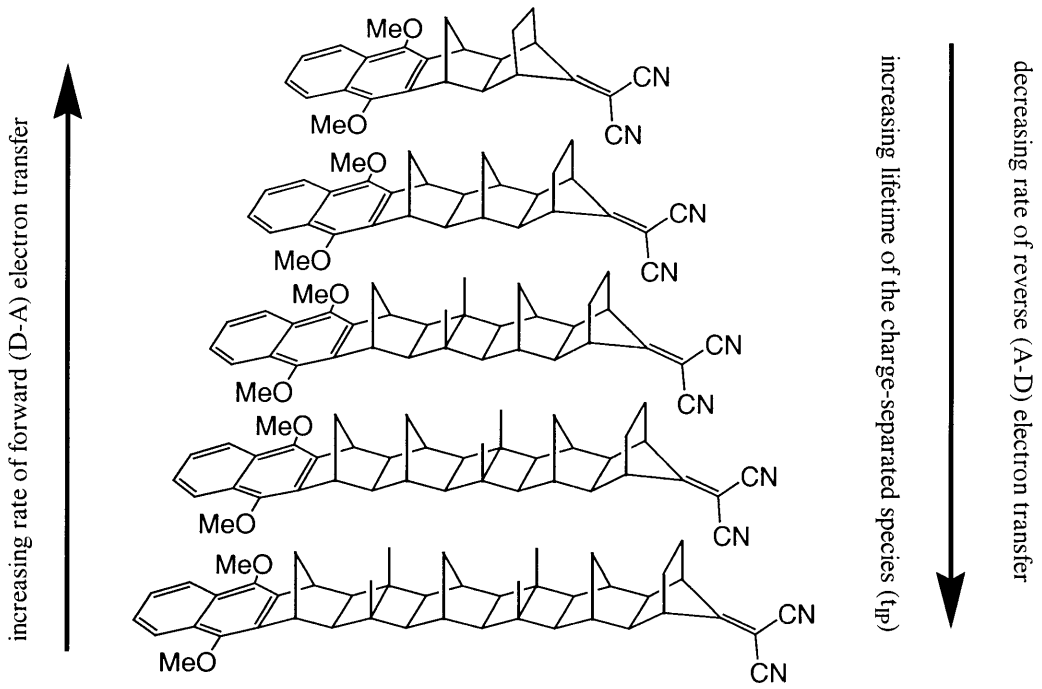

Figure 1.5 Effects of distance on electron transfer rates in a series of molecular dyads.[31-34]

One of these systems of particular interest is a giant U-shaped tetrad (P-DMN-NQ-MV) bearing spatially separated (10 Å) cofacially-oriented terminal porphyrin and viologen units (Figure 1.6).[44] The system was designed and constructed using a building block approach for the purpose of investigating solvent-mediated electron transfer processes. The tetrad was found to undergo an efficient photoinduced electron transfer (ET, $\phi = 78\%$) between the donor group and the terminal acceptor group thereby generating a charge-separated state ($P^{\cdot+}$-DMN-NQ-$MV^{\cdot+}$) with a lifetime of 330 ps. A complex charge recombination process occurred with a short-lived major component (500 ns $\approx$ 70%) and a substantially longer lived (tens of microseconds) minor component. Although the exact mechanistic details were not determined three possible mechanisms were

proposed for the observed electron transfer dynamics: (i) a direct solvent-mediated ET from P^* to MV^{2+}; (ii) a direct through-bond mediated ET from P^* to MV^{2+} through the orbitals of the bridge and the DMN and NQ units; (iii) a two-step ET process in which a through-bond mechanism generates an intermediate $P^{\cdot+}$-{bridge}-$NQ^{\cdot-}$ charge-separated state followed by thermal ET from $NQ^{\cdot-}$ to MV^{2+}.

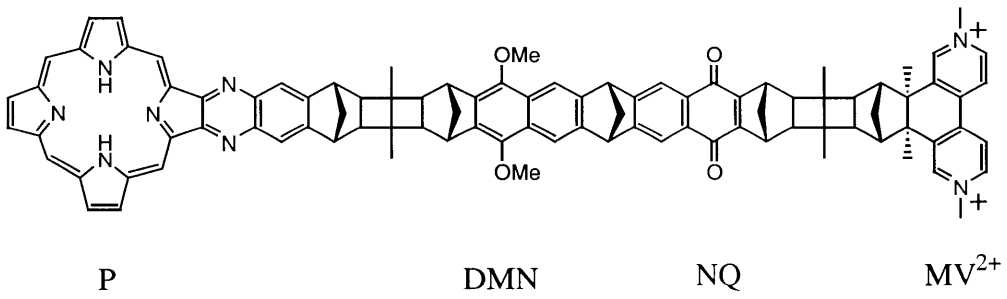

Figure 1.6 A giant U-shaped tetrad with spatially separated (10 Å) cofacial donor (P) and acceptor (MV^{2+}) units. A photoinduced electron transfer between P and MV^{2+} was measured followed by a biphasic charge recombination process consisting of a dominant short-lived (500 ns) event and a second much slower (tens of μs) process.[44]

A group of much simpler systems that have been designed to mimic the natural photosynthetic centre have a porphyrin donor group covalently linked to a quinone acceptor. There are hundreds of examples of these types of systems dating back to 1979.[45] A few early examples of these Porphyrin-Quinone (P-Q) systems include those with saturated or partially saturated spacers such as trypticene and bicyclooctane(s).[46,47] The latter system also shows a strong dependence of electron transfer rate on D-A separation. Other early research focused on unsaturated linkers, such as the polyenes, and comparisons were made between them.[48] It was found that the all-*trans* polyenes act as highly conductive molecular wires allowing for very rapid energy and electron transfer processes to occur (k_{el} = 10^{11}-10^{12} s^{-1}). A strong donor-acceptor electronic coupling is facilitated by these conjugated rigid spacer groups.

One of the effects of this is a less than straightforward relationship between separation distance of the P and Q moieties and electron transfer rates unlike the previous systems discussed. The polyene groups in these dyads act, not as a simple bridge, but as active components of the donor-acceptor systems. Structural effects in rigidly spaced P-Q systems have been investigated through a comparison of two systems that are largely identical in all aspects except for mutual orientation of the donor and acceptor groups.[49]

Other researchers have adopted an approach based on assembling the various components through reversible non-covalent interactions. A substantial benefit in using self-assembly methods is the ability to more easily vary the sub-units used to form the overall system. Examples of this approach include a P-Q system based on metal-ligand coordination[50], a coplanar chlorin-naphthalene diimide dyad based on a juxtaposed three-point hydrogen bonding interaction[51], a ternary complex formed between a zinc-porphyrin and a macrocycle with two different binding sites[52] and finally, several complexes formed between N,N-dimethyl-4,4,-*bis*-pyridinium salts and different π-donor capped zinc-porphyrins.[53]

The major shortfall of the Dyad systems generally is due to the rapid return electron reaction between the reduced acceptor and oxidised donor moieties. This makes them useless for practical applications where a long-lived ion-pair is required. Typical lifetimes for the ion-pairs resulting from photoinduced electron transfer in dyads are usually below 10^{-8} s.

The natural photosynthetic system once again gives us a clue as to how this problem may be overcome. The incorporation of multiple energy and electron transfer components resulting in oxidised and reduced products remote from one another is a key feature of the natural system. Following this lead, molecular triad, tetrad and pentad systems were developed. Although a large number of such systems have been made it will suffice here to concentrate on just a few triads which exemplify the advantages these give over an analogous dyad.

The work of Gust, Moore and co-workers have, over the years, provided some very interesting biomimetic photoactive compounds which feature a porphyrinic component linked to various acceptor groups. Early work on triads included systems that had carotenoid and quinone components attached to a porphyrin chromophore.[54] A more recent version replaces the quinone with a buckminsterfullerene as the final electron acceptor component but retains the porphyrin and carotenoid electron donor components.[29] The analogous dyad, which lacks the carotenoid unit, was found to undergo a rapid decay from the charge separated ion-pair back to the ground state whilst the triad ion-pair lifetime is significantly longer (Figure 1.7).

In order to imitate more closely the electron transfer processes between the special pair, the monomeric bacteriochlorophyll and the bacteriopheophytin in the reaction centre artificial triad systems were devised which contained two porphyrins and an ultimate acceptor group. One such series of compounds was the subject of a seminal research project described by Sessler and co-workers.[55] These triads were constructed by covalently linking two porphyrins via a phenylene

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group. A quinone moiety was directly attached to one of the porphyrins. The structural relationship between the porphyrin units was varied by changing the linkage from *para* to *meta* bonding on the phenylene linker.

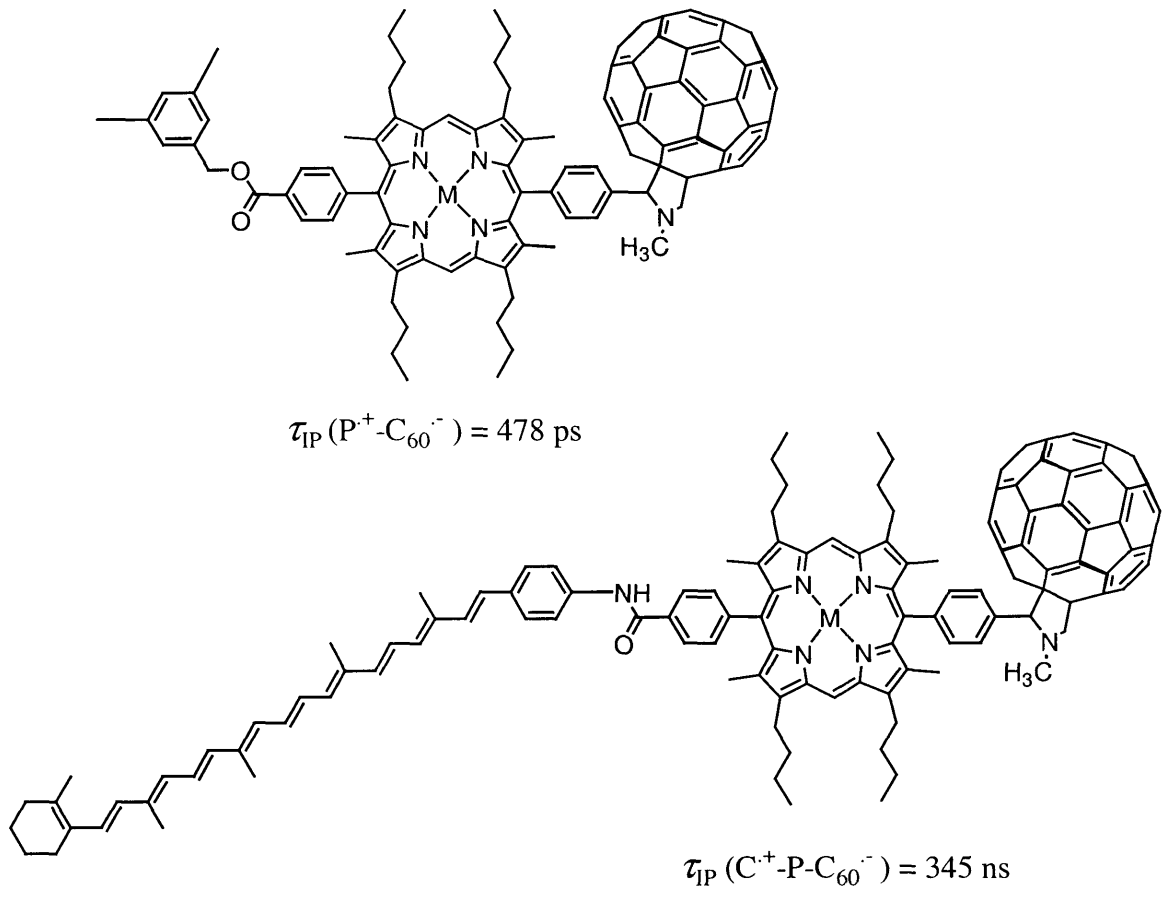

Figure 1.7 A comparison of dyad and triad ion-pair lifetimes.[29]

This resulted in two systems, one of which was a 'gable' type and the other a 'flat' type. The electronic properties of these systems varied according their overall geometry and to the metallation pattern employed. The electron transfer rate (k_{ET}) was increased in the 'gable' compared to the 'flat' systems and was found to be significantly faster in the ZnP-H_2P-Q configuration compared to H_2P-ZnP-Q systems (Figure 1.8).[64]

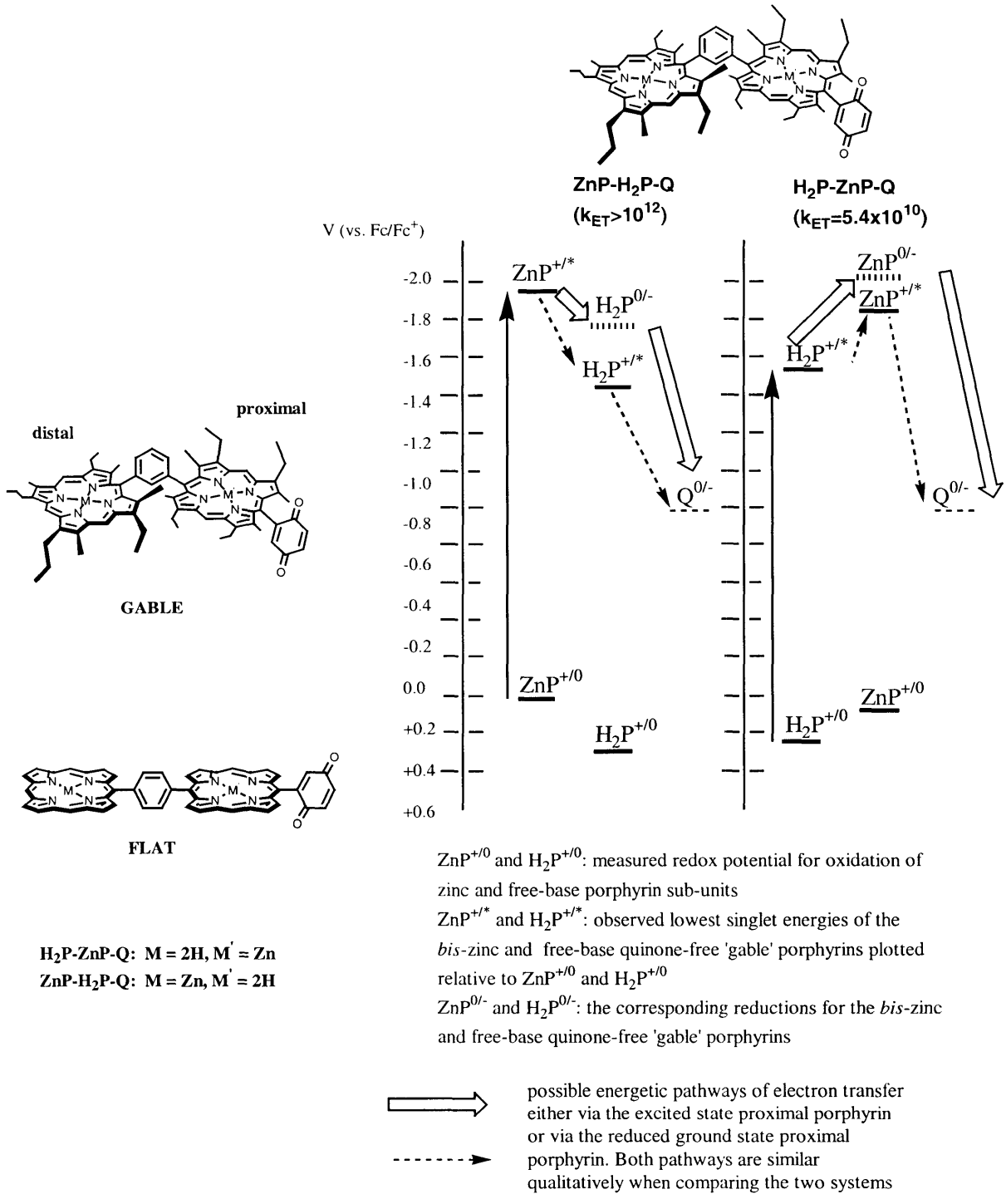

Figure 1.8 Structures of Sessler's 'gable' and 'flat' triads and an energy diagram showing the dependence of electron transfer pathways on orientation and metallation of *bis*-porphyrins.[55,56]

The difference in k_{ET} values due to metallation pattern used can be explained in terms of the relative redox potentials of each of the sub-units, as indicated in Figure 1.8. In these systems when the distal porphyrin is metallated (Zn) and the proximal porphyrin is a free base then there is a

cascade from higher to lower energy for the electron transfer process. The k_{ET} values for these systems are comparatively larger ($\sim 10^{12}$ s^{-1}). If, on the other hand, the distal porphyrin is a free base and the proximal porphyrin is metallated (Zn) then there is an energy barrier to electron transfer which explains the smaller values of k_{ET} ($\sim 10^{10}$ s^{-1}) for these systems. Both the structural and the distal/proximal metallation effects were found to be additive. This was one of the first model systems to bear directly on the question of the mechanistic possibilities of electron transfer in the initial steps of the reaction centre process. Later studies gave evidence of a superexchange mechanism in the electron transfer of the H_2P-ZnP-Q triad.[57,58]

Sessler's method of obtaining porphyrin dimer redox gradients by the combination of zinc and free-base porphyrins is not the only one that has been used. Smith et al. used unsymmetrical porphyrin-chlorin and porphyrin-corrole heterodimers.[59] Many more important biomimetic models of the PRC have been synthesised and analysed. Some of these, which differ from those already discussed, have focussed particularly on the special pair. The structure of the special pair in the PRC of the photosynthetic bacteria can be described as a dimer consisting of two bacteriochlorophyll monomer sub-units held apart at a distance of approximately 3.6 Å. There is an approximate interplanar angle between the two macrocyclic sub-units of around 10° and full π overlap between the pyrrole-1 rings of each macrocycle. This arrangement can be described as an offset stacked geometry. A simplified diagram (side chains omitted) showing the top and side views of the special pairs from the PRCs of both *Rps. viridis* and *Rb. sphaeroides* is presented in Figure 1.9.

A number of different cofacial porphyrin dimers, which, in general, have small inter-porphyrin distances, have been used to model the special pair. Covalently linked pyropheophorbide dimers are an example.[60] A number of different bridging groups (ester, anhydride, 1,2-phenylenediamide and 1,8-naphthylenediamide) were used resulting in optically different *bis*-porphyrins and two cofacial *bis*-porphyrins. The analysis of the naphthalene bridged cofacial *bis*-porphyrin was rationalised in terms of a forced face-to-face geometry in comparison with an apparent offset face-to-face geometry for the phenylene-bridged dimer (Figure 1.10).

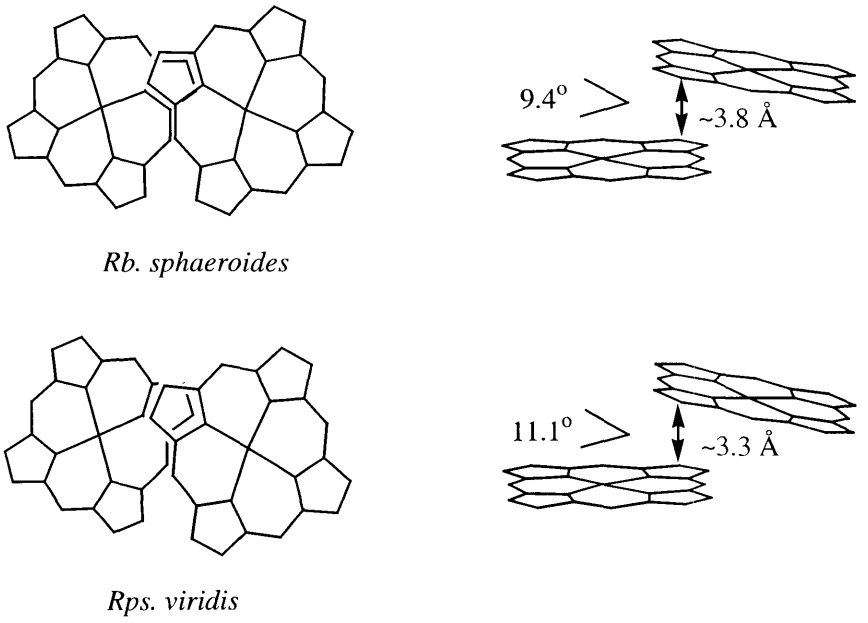

Figure 1.9 Geometrical relationships between the porphyrin–type macrocycles found in bacterial PRCs.

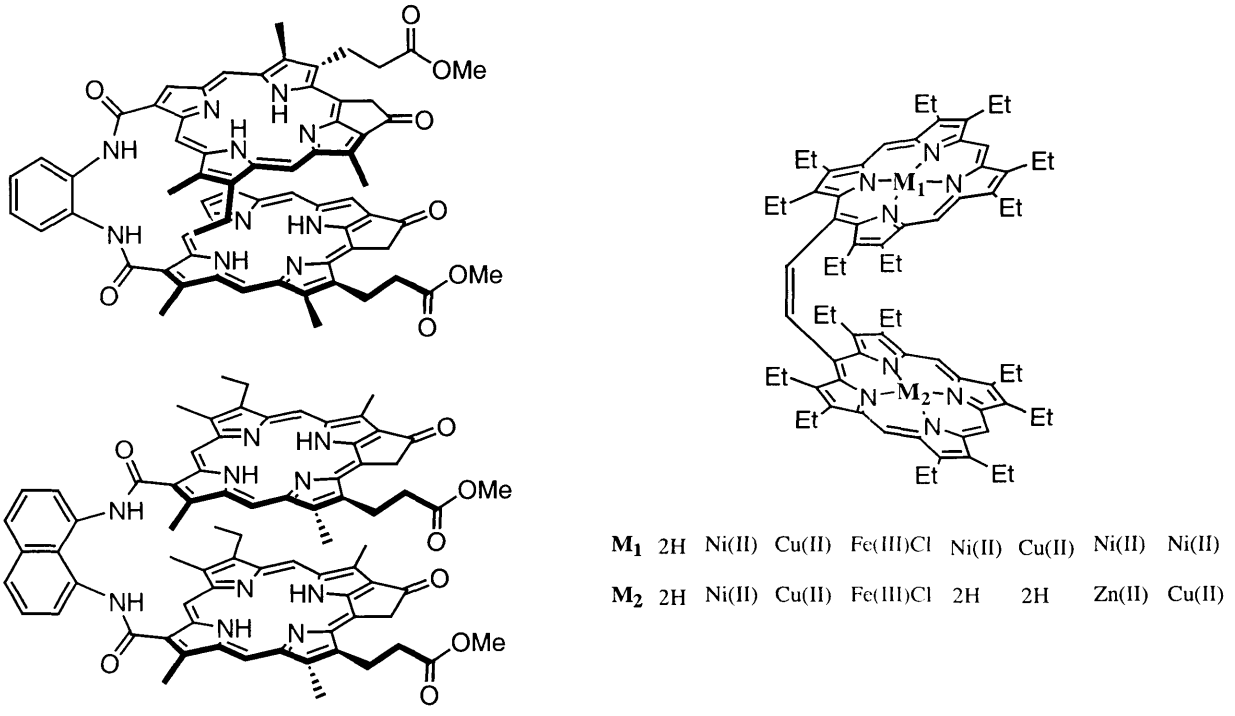

Figure 1.10 Examples of 'special pair' biomimics based phenylenediamide, naphthalenediamide[60] and 1,2-ethene bridged[61] systems.

The measured electrochemical properties of these systems were significantly different to the analogous monomeric porphyrins and the naphthalene-bridged dimers were similar to those found for the special pair of *Rb. sphaeroides*. Other porphyrin based dimers which have been reported to have similar structural features to the natural dimers, such as significant π–π overlap, include a series of 1,2-ethene linked co-facial *bis*-porphyrins (Figure 1.10), an amine tethered Zn-porphyrin dimer formed from a mutual coordinate covalent bonding interaction between two identical monomers, a chlorin-spirochlorin dimer formed unexpectedly from a *bis*-chlorin dimer and bridged by a tetrahydrobenzophenanthrene group and a number of *bis*-porphyrin metal (IV) sandwich complexes.[61-63]

It is neither practical nor often even desirable to try to synthesise natural energy transduction systems *in toto*. Natural systems are extremely structurally complex and only perform a set task for which they have evolved under a narrow set of chemical and physical conditions. The motivation for research into simpler, more robust and functionally flexible systems that can be designed to perform new tasks far removed from nature is increasing. An example of this is the ever-growing effort by many research groups to explore the possibilities of a 'bottom up' approach toward the manufacture of nano-scale electronic devices.

1.2.3 ARTIFICIAL SYSTEMS

1.2.3.1 Background

In 1945 the Electronic Numerical Integrator and Computer (ENIAC), regarded as the first successful general digital computer, contained over 18000 vacuum tubes, occupied approximately 1672 m^2 and weighed about 27 tonnes. The ENIAC was initially used by the U.S. military to calculate ballistic firing tables and was able to perform roughly 5000 calculations every second.[64] A modern PC, which weighs several kilograms and fits onto a small desk, is more than 20000 times faster than this and uses only a small fraction of the energy to operate. It is estimated that both the number of transistors contained on a computer chip and the processing speed of computers currently double every 18 months.[64] It seems there is no end to the miniaturisation of electronic components; however, things may not go so smoothly in the near future as fundamental technical difficulties begin to thwart efforts to continue the shrinking trend.

The size and spacing of patterns stencilled, by photolithographic techniques, into the silicon of a microchip have resolutions no less than about 100 nm. An integrated circuit measuring 10 mm on one side can contain thousands of transistors, diodes, resistors and other circuit elements. There are several problems with going smaller than this with current technology. As circuits become smaller the build-up of heat increases. This is especially relevant when the conducting properties of the silicon-based diodes are rendered ineffective above about 200°C. A more fundamental challenge lies in the photolithographic method itself. To make structures with separations of ~100 nm, U.V light of wavelength less than 250 nm is required. This is nearing the limit for resolution by the materials used as lenses and increasingly expensive specialised techniques are required to make smaller structures. There is of course a huge research effort going into extending current technologies and some progress in this effort is very likely. New techniques being studied include electron beam lithography, x-ray lithography and relatively low tech soft lithography methods.

Instead of these 'top-down' methods some researchers have suggested a fundamentally different approach from the 'bottom-up'. The idea is to assemble nano-scale structures using atomic and molecular building blocks. Complex structures in the range 2-10 nm can be obtained using either covalent bonding or more commonly self-assembly of sub-units through carefully designed non-covalent interactions. The difficulty lies in going one step further and forming reproducible and concise interconnected patterns essential for making nano-scale electronic devices. The art and science of forming usable nanoelectronic devices is still in its early stages with the main focus on producing individual molecular components.

So a search of the literature will reveal many reports of nanodevices of various types ranging from molecular wires to molecular switches and rectifiers. The most relevant of these to the current project are the molecular switches especially those that incorporate a photosensitive porphyrin moiety. It is important to realise that the potential usefulness of such systems is not only related to their being incorporated into some complex molecular computer circuitry in the distant future but also in their own right, they are of interest in understanding the fundamentals of how light and electron transfer may be controlled in discrete chemical systems. More immediate applications may be as photochemical or electrochemical sensors in the field of analytical chemistry or as electron sources for the performance of chemical work in solution. A 'many and varied' approach has the advantage of revealing general trends as well as subtle differences between the functional activity of a large number of related and even unrelated systems.

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1.2.3.2 Molecular Switches

A molecular switch is in some ways analogous to a simple mechanical switch. Switches in the macroscopic world are often mechanical devices operated either manually or electromagnetically. Other switches may be coupled to some other device that changes its properties gradually until a response is triggered when a certain threshold is met. In any case the fundamental properties of a switch are that (i) it resides in one or more stable states (e.g. two states 'on' or 'off') that either allow or disallow the transfer of energy and (ii) the system is reversible. Solid-state electronic switches, relying on semi-conducting rather than mechanical properties, also operate by residing in one of a number of stable states depending on the electrical input signal.

There are various types of molecular switches acting by different mechanisms. In general they must (i) respond to some input signal, (ii) reside in either one of two or more stable configurations, (iii) effect a chemical or physical change as a result of being addressed and (iv) have the ability to return to the original configuration (reversibility). The natural PRC, as described earlier, can be seen as a very effective and complex molecular switching device that is coupled to a long range electron transfer system, the action of which produces a proton motive force across a membrane driving a molecular machine (proton pump). The fundamentals learnt from studying biomimetic systems continue to apply in the world of molecular switches and here too porphyrins and their derivatives have been used as the key building blocks.

Lindsey and co-workers have recently given an in-depth account of a molecular architectural motif used for studying excited state and ground-state electronic communication between covalently linked arrays of tetraphenylporphyrin derivatives.[65] Depending on the arrangement of the porphyrin units the various arrays could be made to operate as a molecular wire, a linear gate or a T gate. Various relationships between electronic coupling and porphyrin substitution, metallation and linker attachment site were elucidated.

The principal findings for these alkyne-linked systems were that ultra fast excited-state energy transfer and ground-state hole hopping occur mainly via a linker-mediated through-bond mechanism. These processes could be tuned by (i) changing the steric interactions between the linker and the porphyrin and/or (ii) variation of the porphyrin frontier molecular orbital symmetry which in this case was itself found to be dependent on the substitution pattern on the phenyl rings of the tetraphenylporphyrin sub-units and/or (iii) changing the site of porphyrin attachment to the

linker (*meta* versus *para* position) and the site of attachment of linker to the porphyrin (*meso* versus β-pyrrole position).

Non-pairwise superexchange interactions were found to be important in both ground-state and excited-state electronic communication along with rapid quenching of excitation emission by adjacent oxidised porphyrin units. The excited-state processes occurred much more rapidly than those occurring in the ground state. These properties were incorporated into the design of linear and T-shaped optoelectronic gates. The operation of this type of switching device relies on the system being in one of two states as illustrated for the linear version in Figure 1.11. When the output free-base porphyrin unit is adjacent to a neutral Mg-porphyrin the gate is in an "on" configuration. The oxidation of the Mg-Porphyrin to a π-cation radical effectively quenches the emission from the output unit resulting in the gate being switched to an "off" position.

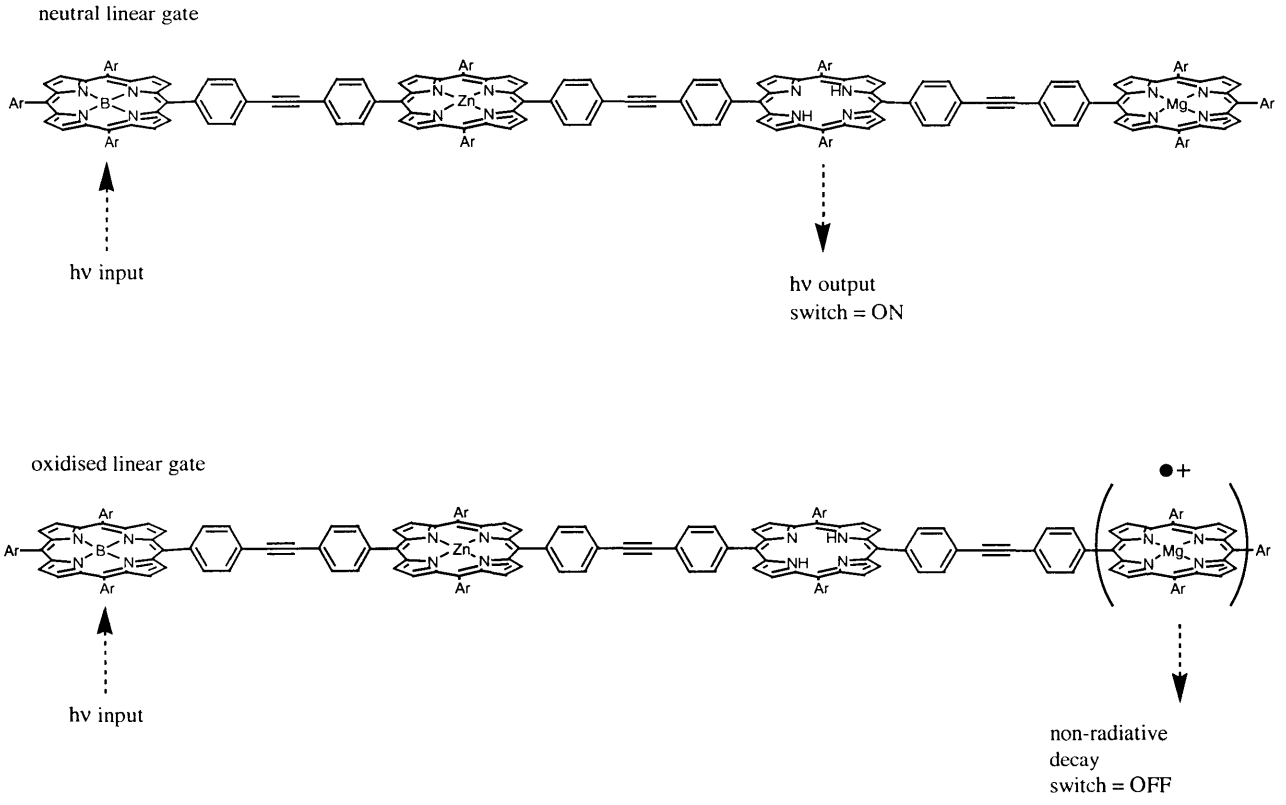

Figure 1.11 A multiporphyrin optoelectronic molecular switch based on a redox gating mechanism.[65]

Another example of a covalently assembled molecular switch has two different donor units joined by two aromatic acceptor groups, D_1-A_1-A_2-D_2 (Figure 1.12).[66,67] The donor units can be

individually addressed using different wavelengths of light thereby producing different electronic states upon which 'molecular logic' can be generated. The porphyrin donor group, D_1, is first addressed with a blue femtosecond laser pulse, which leads to the formation of the D_1^+-A_1^--A_2-D_2 ion-pair. A red femtosecond laser pulse used to address a perylene imide donor group, D_2, follows this leading to the D_1^+-A_1^--A_2-$^{1*}D_2$ excited state. Electron transfer from $^{1*}D$ to A^- is inhibited by the initial formation of the ion pair resulting in an enhanced output efficiency.

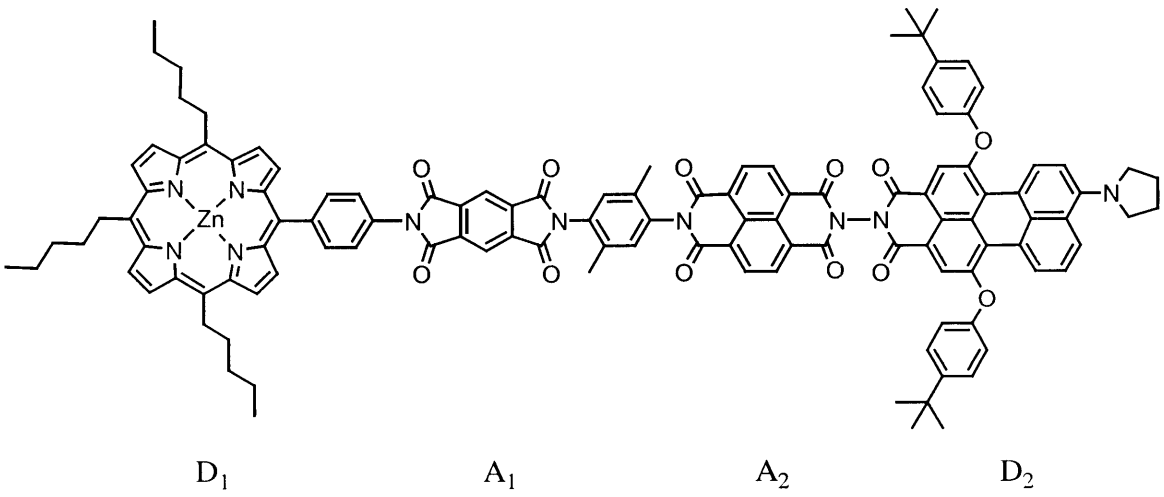

Figure 1.12 A covalently assembled molecular switch based on a D_1-A_1-A_2-D_2 arrangement.[66,67]

A supramolecular approach toward making molecular switches has been used by various workers including those based on mechanically interlocked molecules. Various catenanes and rotaxanes have been synthesised over the last two decades based on using template directed and molecular recognition methods. During much of this period Stoddart and co-workers have synthesised a number of elegant catenane and rotaxane molecules using a self-assembly approach.[8-15,68-70] An example of a redox active catenane that acts as a molecular switch has been described (Figure 1.13).[70,71] One of the interlocked macrocycles of this catenane contained a tetrathiofulvalene (TTF) unit and a 1,5-dioxynaphthalene ring. This was interlocked with a tetracationic cyclo-*bis*-(paraquat-*p*-phenylene) macrocycle ($CBPQT^{4+}$). Prior studies had shown that the $CBPQT^{4+}$ was able to bind TTF much more strongly (K_a > 8000 M^{-1}) than 1,5-dioxanaphthalene ring systems (K_a < 5000 M^{-1}). Another important difference between the sub-units was their redox behaviour. TTFs are readily oxidised to their cations ($E_{1/2}$ = 320 mV) and dications ($E_{1/2}$ = 720 mV) whereas 1,5-dioxanaphthalenes are much more difficult to oxidise. It

was expected then that the $CBPQT^{4+}$ ring of the neutral catenane would predominantly reside around the TTF unit whereupon oxidation it was expected that the $CBPQT^{4+}$ would migrate to the 1,5-dioxanaphthalene position and this type of switching behaviour was experimentally verified (Figure 1.13). Similar catenanes, which incorporate a photoactive porphyrin moiety, have also been made and photoinduced electron transfer processes studied.[16,53,72,73]

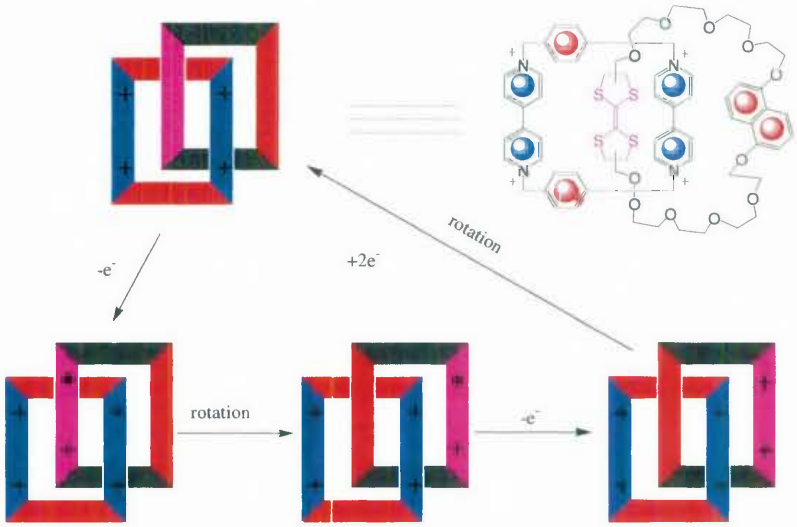

Figure 1.13 A redox-controllable [2]-catenane switch.[70,71]

1.3 ENZYME CATALYSIS

'I believe that the same mechanism, dependent on a detailed complementariness in molecular structure, is responsible for all biological specificity. I think that enzymes are molecules that are complementary in structure to the activated complex of the reactions that they catalyse, that is, to the molecular configuration that is intermediate to the reacting substances and the products of the reaction for these catalysed processes...I believe that it is molecular size and shape, on the atomic scale, that are of primary importance in these phenomena, rather than the ordinary chemical properties of the substances involving their power of entering into reactions in which ordinary chemical bonds are broken and formed'.[74]

Linus Pauling, 1948

1.3.1 NATURAL ENZYMES

Enzymes are nature's metabolic machines rapidly gluing together and pulling apart the building blocks of life from the veritable molecular soup in which they exist. These complex proteins are able to accelerate reactions with high substrate selectivity and maximum efficiency. Many enzymes have evolved to perform so efficiently that they exhibit second-order rate constants approaching diffusion limits ($\sim 10^9$ $Lmol^{-1}s^{-1}$). To help get some perspective on this, it has been pointed out recently that in the absence of enzymes some of the reactions with which they are associated have half-times approaching the age of the earth![75,76] As with the previous discussion on the energy transduction machinery of living systems, an understanding of enzyme activity can be illuminated through a deconstructive study of their key functioning components. There are many different types of enzymes present in different living organisms catalysing a large and diverse range of reactions. Despite this they share many common characteristics.

Enzymes are large polypeptides (molar mass > 10 kDa) with complex structural and functional behaviour, the sum total of which is determined by the order and identity of the amino acid building blocks. Changing one or more amino acid residues can have significant structural and functional consequences. This is due to the highly ordered intramolecular and intermolecular interactions upon which the formation of each protein's secondary and tertiary structure depends. A fine balance between these attractive forces and the entropy costs, associated with the formation of highly ordered structures, is maintained. The unique conformation of each enzyme includes various clefts and grooves that act as binding sites. Binding of a substrate or substrates occurs through numerous intermolecular forces including salt-bridges (ion-ion), H-bonding (dipole-dipole), aromatic interactions (π–π stacking) and metal-ligand coordination. There have been several theoretical models proposed for the mechanism of enzyme activity.

1.3.2 THEORETICAL MODELS OF NATURAL ENZYME ACTION

Emil Fischer proposed a 'lock and key' hypothesis as long ago as 1894.[77] This concept relies upon the notion that there is some geometric match or template effect between an enzyme and a substrate molecule and that as a result an enzyme-substrate complex forms. This hypothesis helped to explain some of the changes in physical and chemical properties of proteins (enzymes) in the presence of other substances, for example; the properties of invertase and sucrose from studies of

fermentation processes.[78,79] The concept of an enzyme-substrate complex was an essential part of the kinetics equations developed by Haldane in 1930 [equation (1)].[80] These mathematical equations are still the cornerstone of modern enzyme kinetic studies. Koshland made a further modification of Fischer's key-lock hypothesis in 1958.[81] Koshland proposed that the structures of enzymes are somewhat flexible and can be induced to change conformation upon binding of a substrate. The 'induced fit' hypothesis stated that there is a requirement for the precise alignment of catalytic groups; a change in the three-dimensional relationship of amino acid residues upon substrate binding and the induced structural changes bring about the required alignment only when the 'correct' substrate is bound. The induced fit hypothesis was able to explain certain anomalies that were not explicable using the more rigid view of enzymes embodied in the lock and key model including; non-competitive inhibition and the strong binding of certain substrate analogues without concomitant catalysis.

$$E + S \rightleftharpoons ES \longrightarrow EP \rightleftharpoons E + P \qquad (1)$$

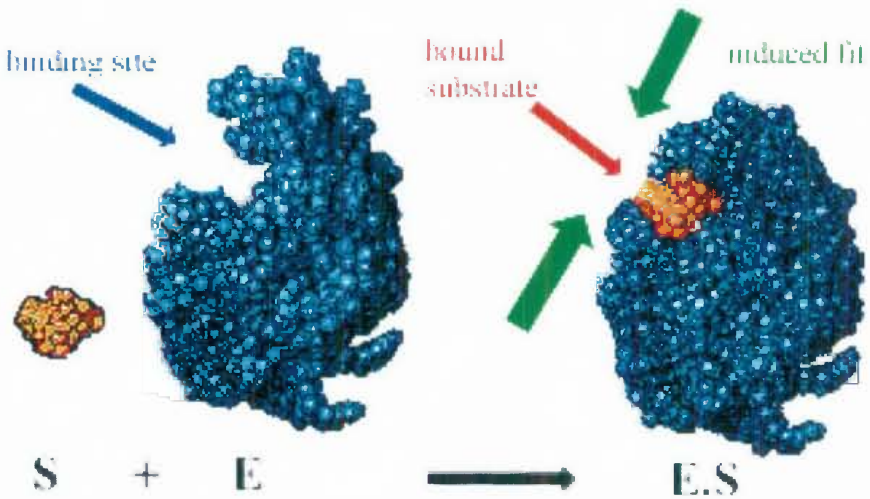

Figure 1.14 Conformational change associated with binding of a polysaccharide chain (substrate: orange) by lysozyme (enzyme: blue).[82]

A classic example of this is Lysozyme, an enzyme present in human tears and saliva that actively breaks down the cell membrane of bacterial invaders. X-ray structures of lysozyme were

amongst the earliest obtained. Studies revealed that a conformational change occurs upon binding of the polysaccharide substrate in accordance with the induced fit theoretical prediction (Figure 1.14).[82]

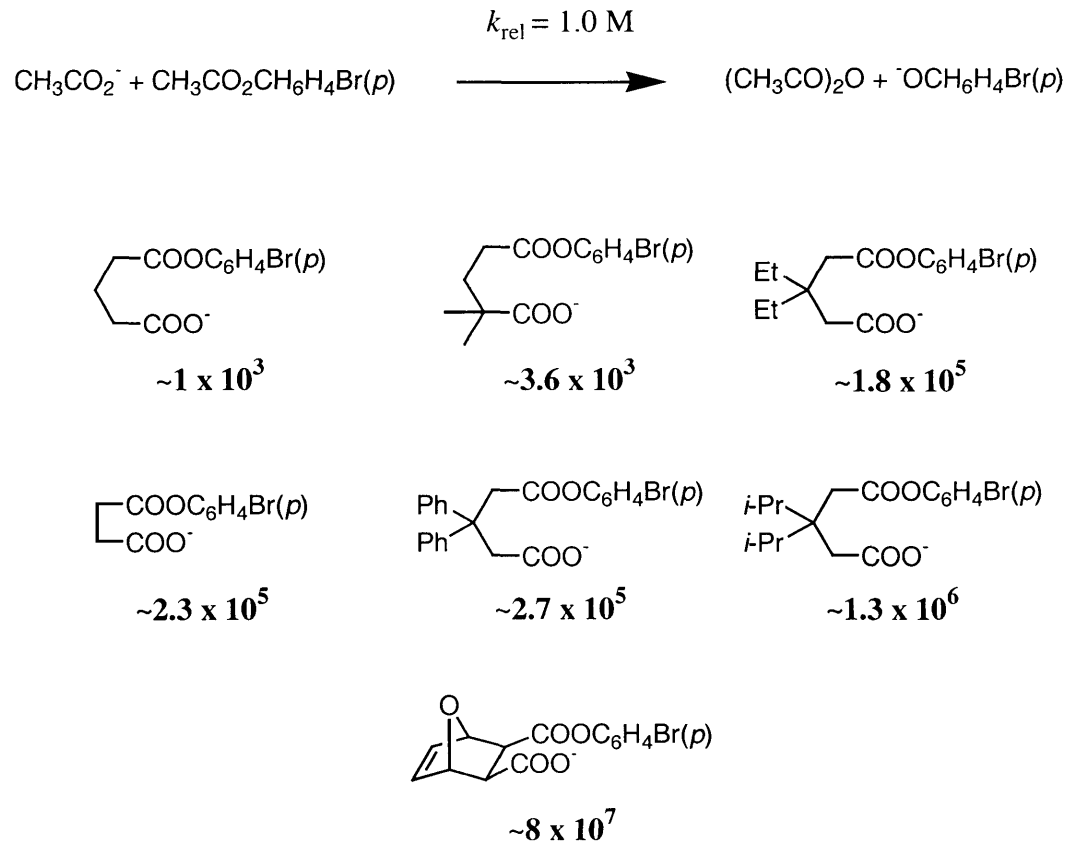

Figure 1.15 Early models of enzyme catalysis: relative reaction rates for a number of related intramolecular-nucleophilic-catalysed hydrolysis reactions.[83]

Pauling first enunciated the most profound and influential contribution to theories on enzyme activity in 1946.[74,84-86] He believed that an enzyme binds the transition state of a particular chemical reaction in preference to the ground-state substrate, thereby lowering the activation energy of the reaction compared with the same reaction in the absence of the enzyme. Page, Jencks and others later developed this theory.[83,87-91] They interpreted the relatively large reaction rates of a number of intramolecular nucleophilic catalysed hydrolysis reactions in terms of the freezing out of translational and rotational motions compared with analogous bimolecular processes (Figure 1.15). It was surmised that a similar entropy trap was operational in reactions involving enzyme substrate complexes.

The intuitive logic relating rate accelerations found in both intramolecular reactions and enzyme catalysed reactions to the chelate effect noticed in the binding of various polydentate ligands to particular metals provided a satisfactory explanation for many chemists. Thus it was the entropy difference between a bimolecular analogue and the quasi-intramolecular enzymatic process that was conjectured to be the main driving force in the remarkable enzymatic rate enhancements. Theoretical calculations by Page and Jencks predicted relative reaction rates of 10^8 based on an entropic driving force. Although not always couched in terms of entropy changes, a review of the literature reveals that Pauling's elegant transition-state hypothesis is widely accepted.[75,92-98]

The use of transition-state analogues for the development of catalytic antibodies has met with some success with reaction rate enhancements of the order 10^3-10^4 being measured.[99-104] These rates are often several orders of magnitude less than the rate enhancements typical for some enzymes; nonetheless, some workers have interpreted them as proof of the transition-state stabilisation hypothesis.[98] A recent review brings together the various aspects of transition state stabilisation, enzyme kinetics and entropic driving forces with respect to transition-state analogues.[105]

An alternative explanation given by Pandit and Bruice for the enzyme-like rate enhancements found in such intramolecular reactions, as illustrated in Figure 1.15, does not rely on an entropic driving force. They showed that for these types of reaction there was a strong correlation between the proximity and juxtaposition of reactant groups found in the ground state and the observed reaction rate.[83,106] Along with several other researchers, they have recently challenged the classic Pauling hypothesis of selective transition-state binding as well as Page and Jenck's entropy arguments. In particular Bruice et al. have recently proposed a theoretical model based on computationally calculated statistical distributions of 'Near Attack Conformers' (NACs) using a combination of stochastic search and molecular mechanics techniques.[107,108] These NACs are ground-state structures that are similar to the calculated transition state and close in energy to it. This model has been tested further on a number of enzymatic reactions, for example; the chorismate mutase catalysed Claisen rearrangement of chorismate to prephenate and the reduction of 7,8-dihydrofolate to 5,6,7,8-tetrahydrofolate by the enzyme dihydrofolate reductase found in *E.coli*.[109,110] These studies incorporated molecular dynamics simulations starting from ground-state x-ray coordinates and derived coordinates for the transition state and related the results obtained to detailed kinetics data. The basic argument is that the role of the enzyme is to

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effectively increase the mole percent of the NACs compared with the solution phase process and that the accompanying free energy change can be dominated by enthalpy and/or entropy changes depending on the enzyme and substrate(s) in question. The enzyme, therefore, directs the reactant(s) toward one of many conformations that resemble the transition state through selective stabilisation of these very same ground state NACs. Support for some of these concepts come from recent calculations of enthalpy and entropy contributions in some enzyme catalysed reactions.[111,112]

Menger has also argued against what he calls "the fundamentalist position" on enzyme catalysis embodied in the following statement by Schowen: 'The entire and sole source of catalytic power is the stabilization of the transition state; reactant-state interactions are by nature inhibitory and only waste catalytic power', as implied by the usual interpretations of energy diagrams such as Figure 1.16.[113]

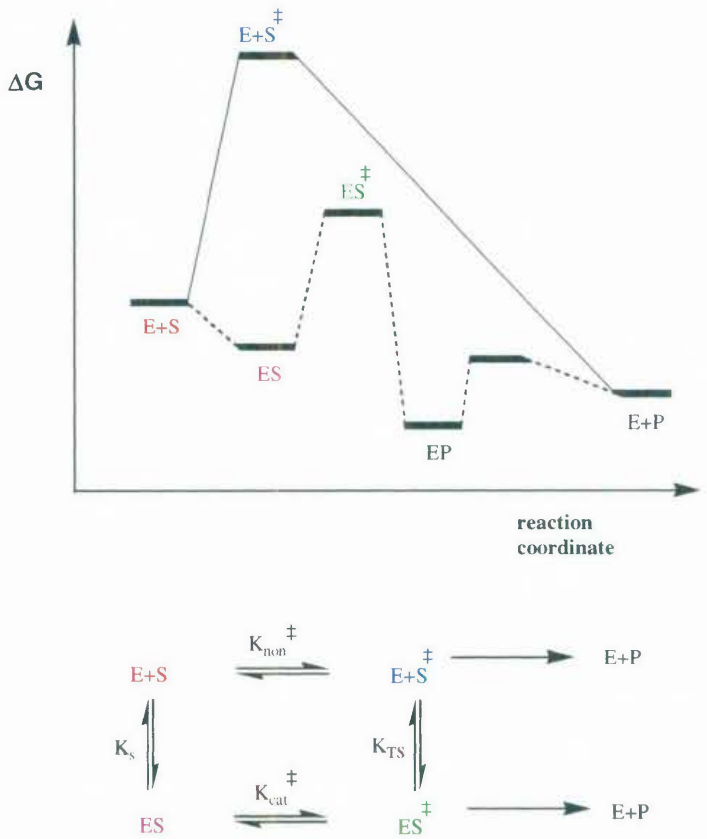

Figure 1.16 Energy profiles for enzyme catalysed (dashed line) and uncatalysed (solid line) reactions of a substrate (S) and a thermodynamic cycle used to calculate the equilibrium constant (K_{TS}) for the dissociation of the transition state (TS) species.

It was demonstrated using a 'split-site' model coupled with thermodynamics considerations that other possibilities besides a transition-state stabilisation can be rationalized for enzymatic rate enhancements, including stabilisation of the enzyme-substrate ground-state complex. Shortcomings of the thermodynamic arguments for the transition-state model, based on a direct comparison of the transition state in the uncatalysed reaction and the enzyme-catalysed reactions, were identified. The difficulties involved in defining precisely the nature of transition states and interesting questions about how enzymes could evolve to selectively bind such transient species were among them.[105,114] Menger has proposed a 'spatiotemporal' hypothesis relating forced or induced short (desolvated) contact distances in the ground state to enzyme reaction rate enhancements. This hypothesis has been thoroughly tested on a number of enzyme model compounds using kinetic measurements coupled with computationally calculated structures and energy barriers.[115]

1.3.3 EXPERIMENTAL MODELS AND MIMICS

The comparison of intramolecular reactions with enzyme catalysis is valid with respect to the reaction rates relative to bimolecular reactions; however, it is obvious that there are significant differences in terms of complexity and the types of bonds used to position reacting groups. Even though an intramolecular reaction may be thought of as catalytic in the sense that a huge increase in reaction rate is realized and that the 'catalytic group' is eventually regenerated unchanged, it cannot be said that such systems exhibit 'turnover'.[96] The positioning of catalytic and reactant groups in an intramolecular reaction is through strong, irreversible covalent bonding. Enzymes, in contrast, rely on a collection of intermolecular non-covalent bond types which, taken individually at least, are relatively weak and reversible.

A unique feature of natural enzymes in living cells is their interaction with a range of small molecules besides the primary reactant substrates. Their activity level is also often dependent on the activities of other enzymes present in the cell. A good analogy is that of a machine doing a particular job in an assembly line. For this chemical 'assembly line' to work a number of different feedback-control mechanisms are known to operate. Basically enzyme activity can be switched off or on through the binding of small molecules that may (competitive) or may not (non-competitive) resemble the primary reactant substrate molecule(s). Globular enzymes exhibit even more complex allosteric control mechanisms. It would be a daunting task to try to synthesise molecules the size

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of an enzyme using usual organic chemistry synthetic methods. Even if this were not the case it is a good question to ask if such large molecules are even necessary when the main focus is to emulate the catalytic power of an enzyme without the added behaviour concerned with selectivity and control essential for living systems. This is especially relevant to research and development of 'artificial' enzymes.* Does size really matter? Are preorganised complementary binding pockets required when substrate selectivity is not necessary?

There have been many different approaches toward making enzyme mimics and models. Some models are rationally designed and synthesised, others are produced using combinatorial libraries coupled with a selection process reliant on selective molecular-recognition events. Other more biologically oriented systems have been made using specialised techniques like site-directed mutagenesis in which the amino acid residues are selectively changed and subsequent effects on activity and structure measured. Due to the breadth and scope of such work it is necessary here to focus on just a few examples relevant to this project.

1.3.3.1 Polypeptides

An obvious approach toward designing an experimental model of an enzyme would be to base it on the very same building blocks. Polypetides that are much smaller than the enzyme proteins have been prepared for this purpose. An early example of a rationally designed catalyst for the decarboxylation of oxaloacetate via an imine intermediate was based on a 14-mer polypeptide synthesised using solid-phase techniques (Figure 1.17).[93]

The secondary structure was shown to be an α-helix which aggregated to form a four helix bundle at higher concentrations. Comparison of reactivity compared with a mutant analogue demonstrated the importance of the α-helical structure. The catalytic activity was related to a measured depression of the pK_a of each of the two closely related systems studied. This was brought about by the interaction of the positive charge on the respective amino group and the α-helix dipole. The rate enhancement of this system is similar to those measured for catalytic antibodies. Interestingly no discrete binding cavity was incorporated in this model. A larger polypeptide (42-mer) with a well-defined hairpin helix-loop-helix structure showed similar relative activity for the catalysis of an acyl transfer reaction of *p*-nitrophenyl esters comparable,

* An 'artificial' enzyme is not designed to mimic any particular 'natural' enzyme and accompanying reaction(s) but rather to mimic essential features of enzyme catalysis for promoting any chemical reactions of interest.

again, to catalytic antibody efficiency. This motif, based on flanking His residues with His^+ residues, along with possible hydrophobic binding contributions was thus shown to be satisfactory. These examples demonstrate the effectiveness of polypeptides as catalysts however difficulties arise in describing details of binding and geometry due to their complex dynamic behaviour. The description of polypetide-substrate binding and catalytic events in these systems is given in fairly general terms. Unlike the flexible and mobile polypeptides described, cyclodextrins are relatively rigid structures that are geometrically well defined.

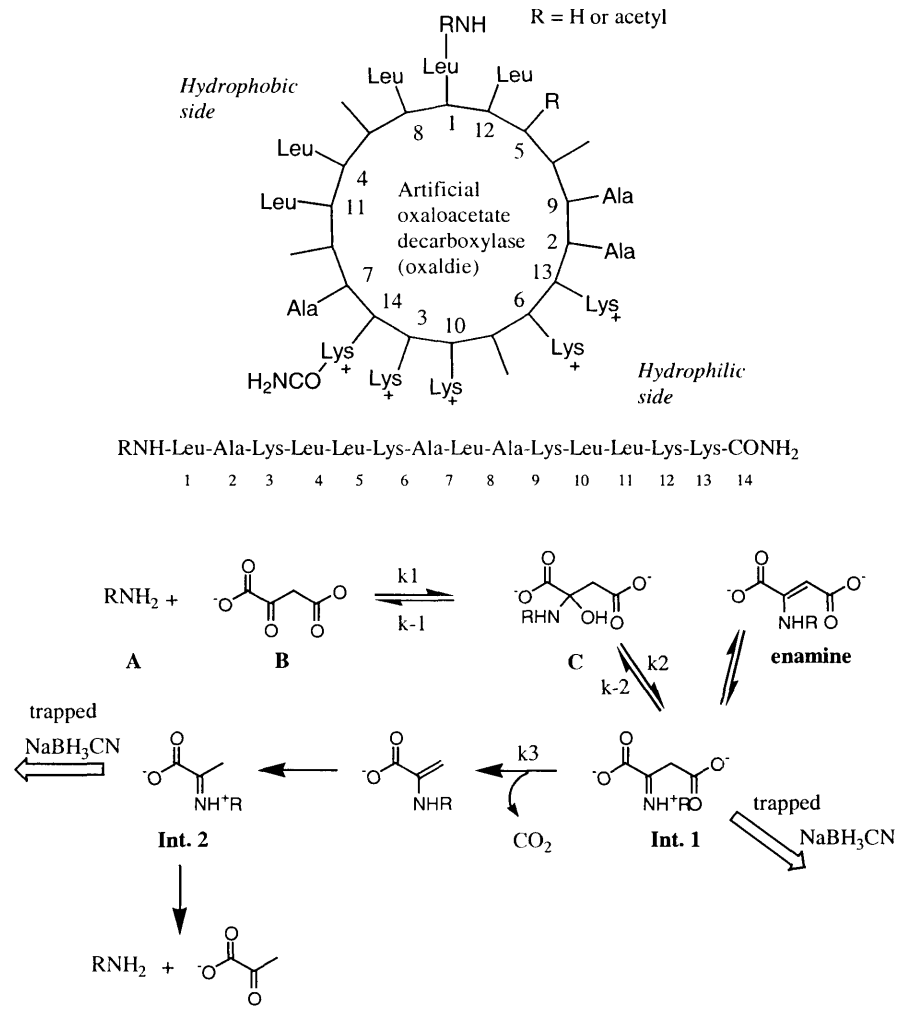
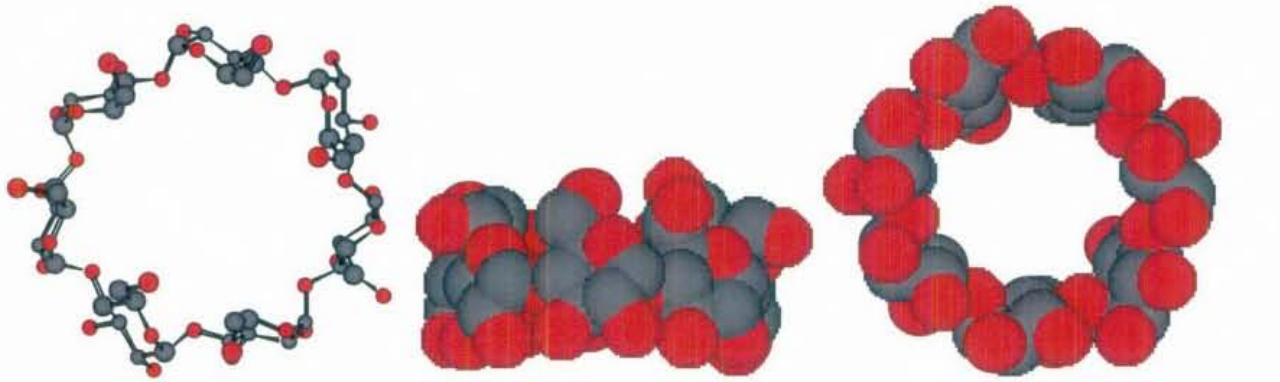


Figure 1.17 An artificial enzyme (oxaldie) based on a polypeptide α-helix that catalyses the decarboxylation of oxaloacetate. Design based on the general amine catalysed reaction mechanism outlined. Amino acid residues positioned in order to bind the tetrahedral high-energy reaction intermediate C and hence the transition state leading to Int. 1 (Hammond Postulate). The reaction rate measured was about three orders of magnitude larger than that catalysed by a simple amine.[93]

1.3.3.2 Cyclodextrins



Cyclodextrins (CDs) are cyclic oligosaccharides usually consisting of six to eight D-glucopyranoside units linked by a 1,4-glycosidic bond. The three most common members of this family of compounds are α-CD, β-CD and γ-CD, which have six, seven and eight glucopyranoside units respectively. The shape of a cyclodextrin can be represented as a tapering torus with a primary face, the narrow rim, and a secondary face, the wide rim. Cyclodextrins have a discrete hydrophobic inner cavity and external hydrophilic regions. It is this hydrophobic cavity coupled with good water solubility that gives the cyclodextrins their unique and well-studied binding properties. Basically the cyclodextrins act as water-soluble host molecules that can bind hydrophobic guest molecules if they are of an appropriate size and shape to fit inside the cavity. Many such systems have been described.

Early interest in cyclodextrins as enzyme mimics came from their reactivity with some ester guest compounds. Although these reactions did not exhibit turnover, and were therefore not truly catalytic, they could be related to the first step of the serine proteases in which an acyl group is transferred to a serine hydroxyl group. *m*-Nitrophenyl acetate transfers its acetyl group to β-CD 100-times faster than hydrolysis in the absence of β-CD.[116] The significance of substrate binding inside the β-CD cavity became apparent when a comparison of its reactivity with *p*-nitrophenyl ferroceneacrylate esters was made. Computational modelling predicted that the tetrahedral transition state of a *p*-nitrophenyl derivative was able to fit inside the cavity much better than the transition state arising from reaction with *m*-nitrophenyl acetate. A 5.9 x 10^6-fold acceleration compared with substrate hydrolysis under the same conditions was a remarkable testament to host-guest complementarity and resultant proximity effects of reactive groups (Figure 1.18).[117]

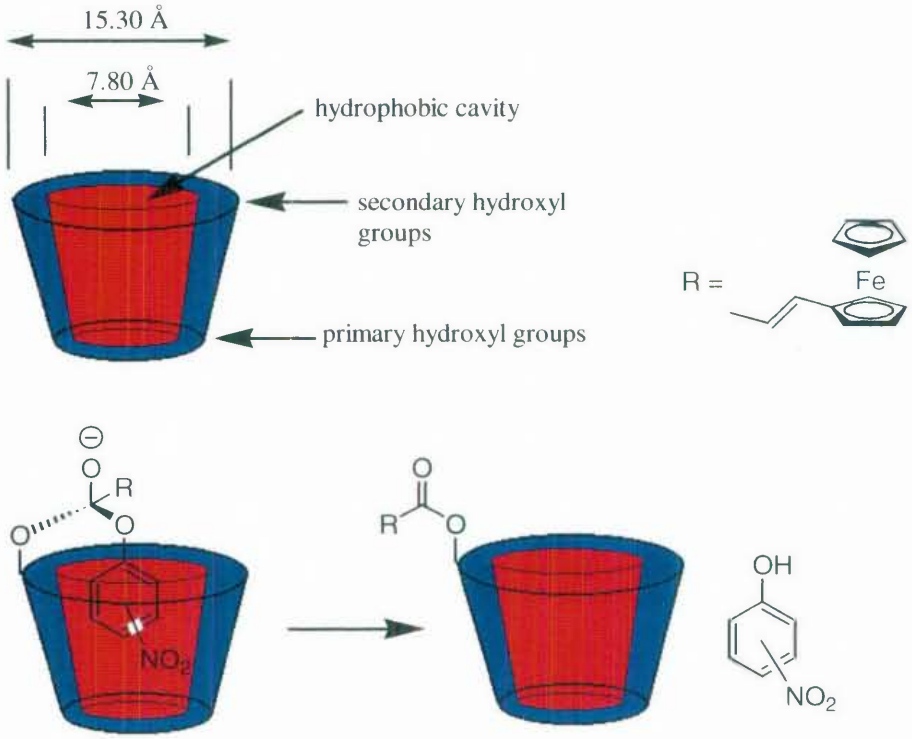


Figure 1.18 The 5.9 x 10^6-fold rate acceleration of acyl transfer for *p*-nitrophenyl ferroceneacrylate esters correlates well with the predicted ability of the tetrahedral transition state to bind inside the cavity by molecular modelling.[117]

An important observation from these studies was that systems that are too rigid are much less reactive. A requirement for a certain amount of geometric mobility along the reaction path was invoked. These sorts of reactions are close analogues to the intramolecular reactions discussed earlier except that the positioning of the reactant groups is initially through reversible non-covalent bonding interactions rather than irreversible covalent bonds. In this way they more closely reflect the *modus operandi* of natural enzymes. Once the correlation between binding and reactivity was established, further development came from the introduction of catalytic groups onto the cyclodextrins.

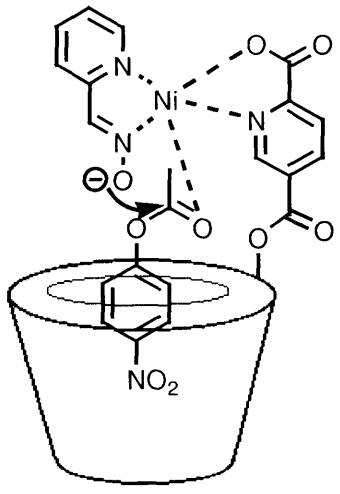


Figure 1.19 Cyclodextrin catalyst for cleaving bound *p*-nitrophenyl esters.[118,119]

True cyclodextrin catalysts were constructed using associated metal binding groups. The importance of metals in enzymes is well known. An example of a CD-metal complex that is able to cleave bound esters with catalytic turnover is shown in Figure 1.19.[118] Cyclodextrins with vitamin B-12 attached have been studied as biomimics of apoenzymes that require this coenzyme for activity and mimics of cytochrome P-450, based on metalloporphyrins with two or four β-CDs attached, have also shown promise (Figure 1.20).[120] The P-450 mimics are able to bind various substrates and show various degrees of catalytic turnover. The two ends of the substrates are simultaneously bound within two β-CDs that are positioned opposite to one another on the porphyrin ring. This double-ended binding arrangement positions the reactive bonds of the substrate directly above the porphyrin metal atom. A variety of substrates and metalloporphyrins have been studied using iodosobenzene as an oxidant. These systems have successfully catalysed alkene oxidation and the hydroxylation of saturated substrates including a regio- and stereo-specific oxidation of the steroid androstanediol.[121]

The usefulness of cyclodextrins is limited to hydrophobic substrates that can fit and bind inside them. Other important porphyrinic enzyme model compounds that do not contain cyclodextrins have also been made and studied.

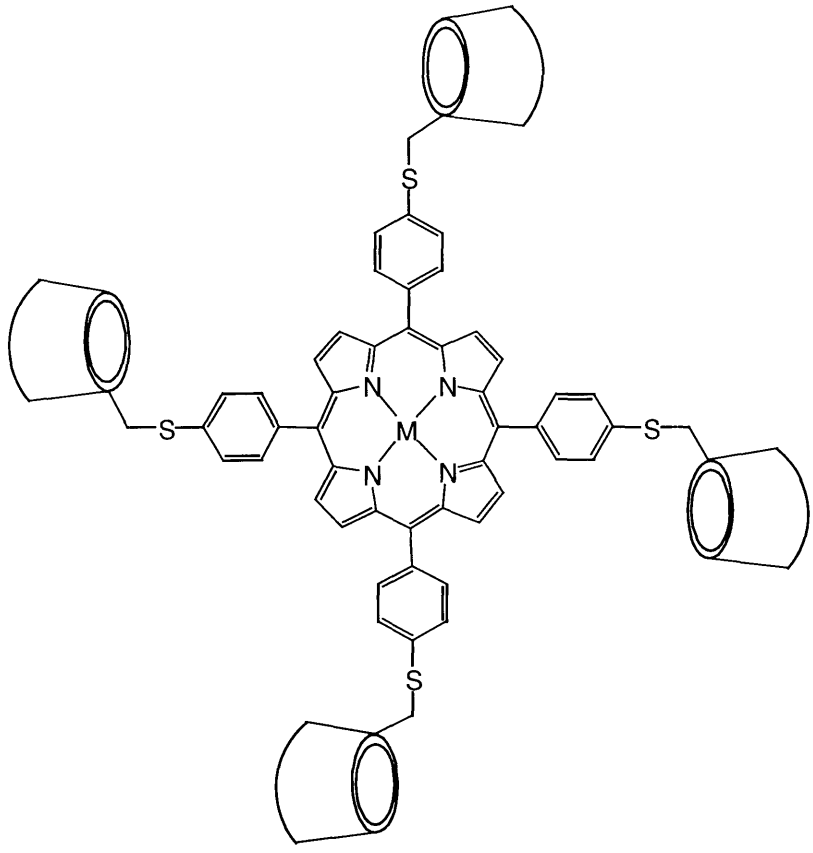


Figure 1.20 A cytochrome P-450 mimic based on a porphyrin electron source attached to a number of convergent cyclodextrin binding units.[119,120]

1.3.3.3 Porphyrin Dimers and Trimers

Porphyrin derivatives are key functioning components of natural small-molecule transport proteins (haemoglobin and myoglobin) and are also present in a number of important natural enzymes (catalases and cytochrome P-450). All these porphyrin derivatives are based on the haem structure. In general the porphyrinic backbone lends itself, via a number of established synthetic approaches, to variation and many different types of porphyrinic assemblies have been studied as either direct enzyme mimics or as artificial enzymes.

A particularly relevant series of porphyrinic systems that has been the focus of a comprehensive artificial enzyme research program are the porphyrin dimers and cyclic trimers of Sanders and co-workers. The design of these catalysts was based on joining tetraphenylporphyrin sub-units together via rigid ethyne or longer butadiyne linkers. A number of other researchers have also made use of ethyne and butadiyne linkage protocols.[122] A series of dimers and trimers were

synthesised and studied according to their potential as catalysts for the Diels-Alder and/or acyl-transfer reactions.[123-126]

The design of these catalysts was based on the simple principle of bringing two reactants together in close proximity via coordination of the substrates to the metalloporphyrin units. The metal chosen was zinc due to synthetic considerations and a known predominance of pentacoordinate geometry; however, the potential to change the metal type in order to modify substrate binding and geometry was an important aspect of the overall design. The substrates were designed to be relatively rigid and complementary to the geometry and cavity size of the dimer and/or trimer catalytic hosts. The rational design of both catalysts and substrates allowed for a higher degree of control over interaction geometries and also allowed for systematic variations of each to be made.

Only a small selection of the whole range of Sanders' compounds will be discussed here in order to illustrate the most salient features, in particular the 2,2,2-Zn_3-trimer, which has three butadiyne linkers, and 1,1,2-Zn_3-trimer, which has one butadiyne linker and two ethyne linkers, were compared as catalysts for a Diels-Alder reaction (Figure 1.21). A comparison of these trimers was made with analogous porphyrin dimers that used either an ethyne or butadiyne linker. The 2,2,2-Zn_3-trimer showed exclusive selectivity in accelerating the formation of the thermodynamically favoured *exo*-adduct. This result was in agreement with expectations based on molecular modelling considerations. The N-N distance of the calculated transition state for the *exo*-adduct was around 13 Å. This correlated well with a calculated Zn-Zn distance of about 15 Å in the 2,2,2-Zn_3-trimer, which presumably allowed for the formation of two strong Zn-N coordinate covalent bonds in a 1:1 complex. The predicted N-N distance of the *endo*-adduct transition state was much less at about 9 Å leading to an expected poor fit within the larger trimer cavity. In contrast a good fit for the *endo*-transition state was predicted within the cavity of the smaller 1,1,2-Zn_3-trimer, which has a calculated Zn-Zn distance of around 12 Å between ethyne bridged porphyrins. Indeed the smaller trimer accelerated the formation of the *endo*-product in favour of the *exo*-adduct at 30°C.

Hydrogenation of the acetylenic linkers resulted in a complete loss of Diels-Alder acceleration. It was concluded that too much flexibility in the host system requires a large entropic cost for bringing the reactants together in a favourable orientation. A limited relaxation of rotational freedom, however, had a much smaller effect with reasonable rate accelerations and

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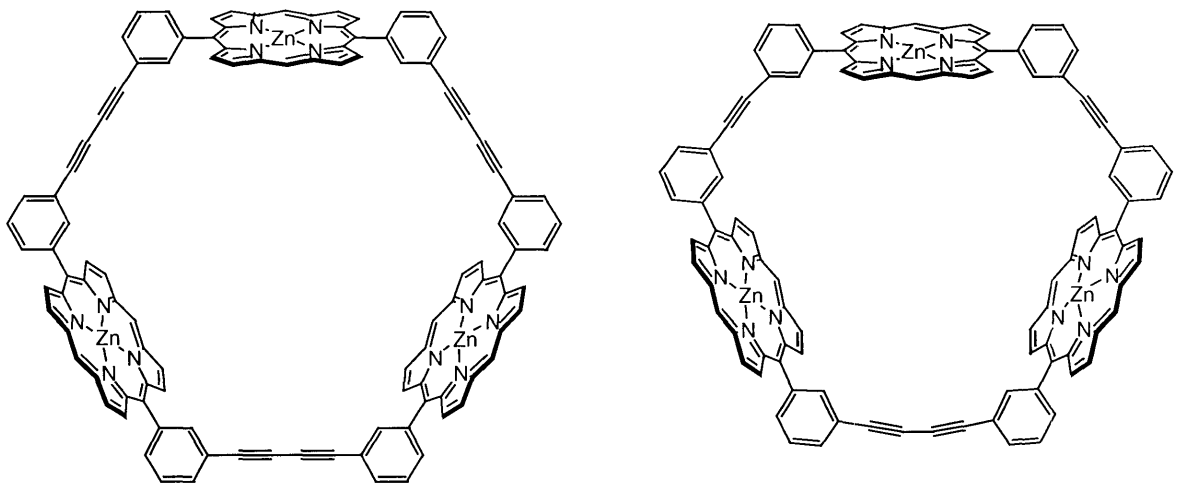
stereoselectivity being maintained for the analogous rigidly linked linear porphyrin dimers. Too much rigidity in catalytic host systems could also be detrimental for catalysis. It was surmised that if the geometries of the host and substrate(s) were not a precise match then a large enthalpic cost would be required to attain a favourable conformation.



2,2,2-Zn_3-trimer **1,1,2-Zn_3-trimer**

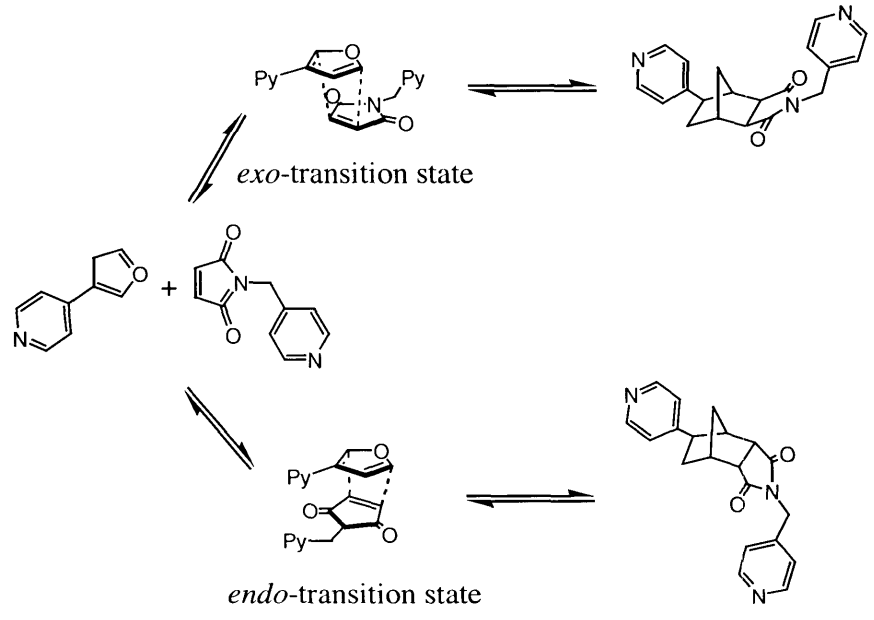


Figure 1.21 Acceleration of Diels-Alder reactions by Zn_3-porphyrin trimers. The trimer with the smaller cavity (1,1,2-Zn_3-trimer) almost exclusively promoted the formation of the thermodynamically and kinetically disfavoured *endo*-product at 30°C in tetrachloroethane. The larger trimer exclusively promoted the formation of the *exo*-product under the same conditions. The calculated N-N distances in the *endo* and *exo* transition states corresponded to the Zn-Zn distances of the particular trimer that showed selectivity for it.[126]

The possibility of such an effect was suggested for an unexpected lack of rate enhancement for the production of the *exo*-adduct by the 1,1,2-Zn_3-trimer. According to molecular modelling the transition state for the *exo*-product should bind well across the butadiyne bridge. Although macroscopic rate enhancements of several hundred-fold were measured no catalytic turnover was evident. This was expected as a doubly bound product was produced from two singly bound reactants thus product inhibition is likely.

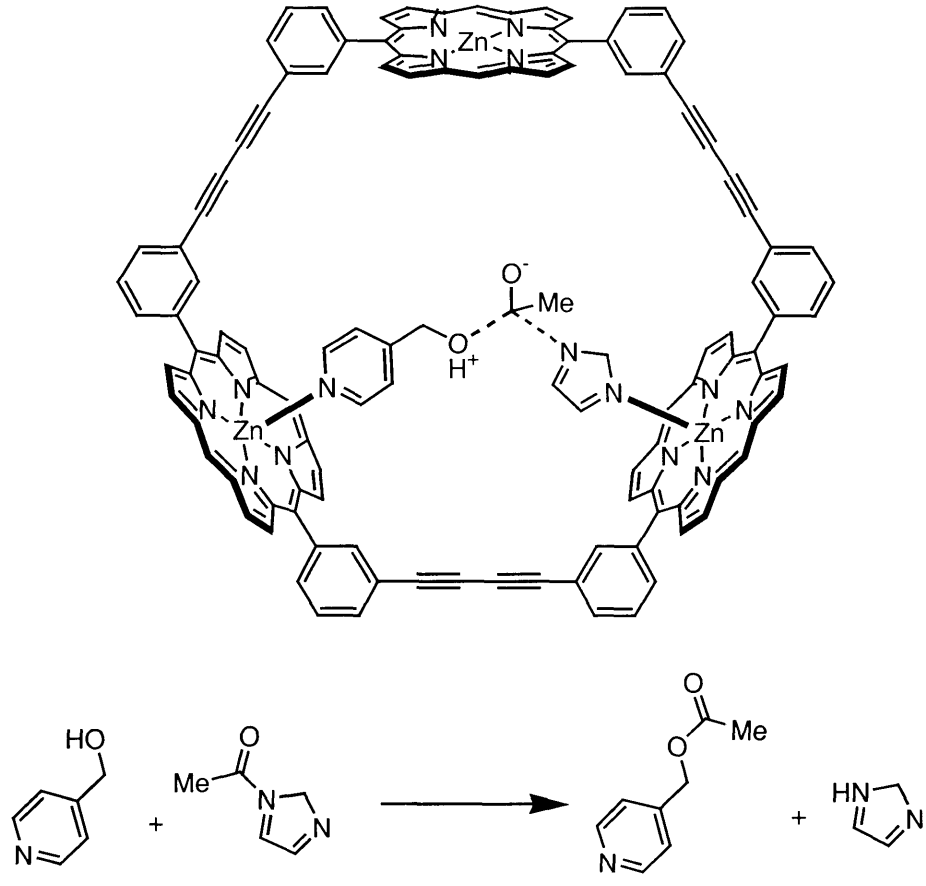


Figure 1.22 Catalysis of an acyl-transfer reaction by a Zn_3-porphyrin trimer with an effective molarity (EM) of 2 M and measurable catalytic turnover.[124]

The 2,2,2-Zn_3-trimer was able to catalyse the acetylation of 4-hydroxymethylpyridine by acetylimidazole (Figure 1.22) with measurable catalytic turnover (25/week/trimer in toluene at T = 70°C). The two reactants were bound in a similar manner to the Diels-Alder substrates, however; only the transition state is thought to be doubly bound to the catalytic host in this case. A dipyridyl transition state analogue (TSA) was found to be an effective competitive inhibitor (cf. K_a for TSA = 2.3 x 10^7 M^{-1}, K_a for pyridine = 1.8 x 10^3 M^{-1} and K_a for N-acetylimidazole = 360 M^{-1}). It was

concluded that the charge distribution and geometry of the transition state was not as good a match for the cavity as the transition state analogue; however, the potential for rationally designing artificial enzymes that catalyse transfer reactions has been clearly demonstrated by this work.

It can be seen from the examples described above that one of the keys to rationally designing an artificial enzyme involves the ability to precisely position various binding sites to which the substrates will be attached. In order to achieve this a geometrically well-defined molecular backbone is required and various strategies have been adopted. One approach involves using large fused polyalicyclic systems formed by connecting various functionalised building blocks.

1.4 SPACER GROUPS

1.4.1 BLOCK DESIGN AND ASSEMBLY STRATEGIES

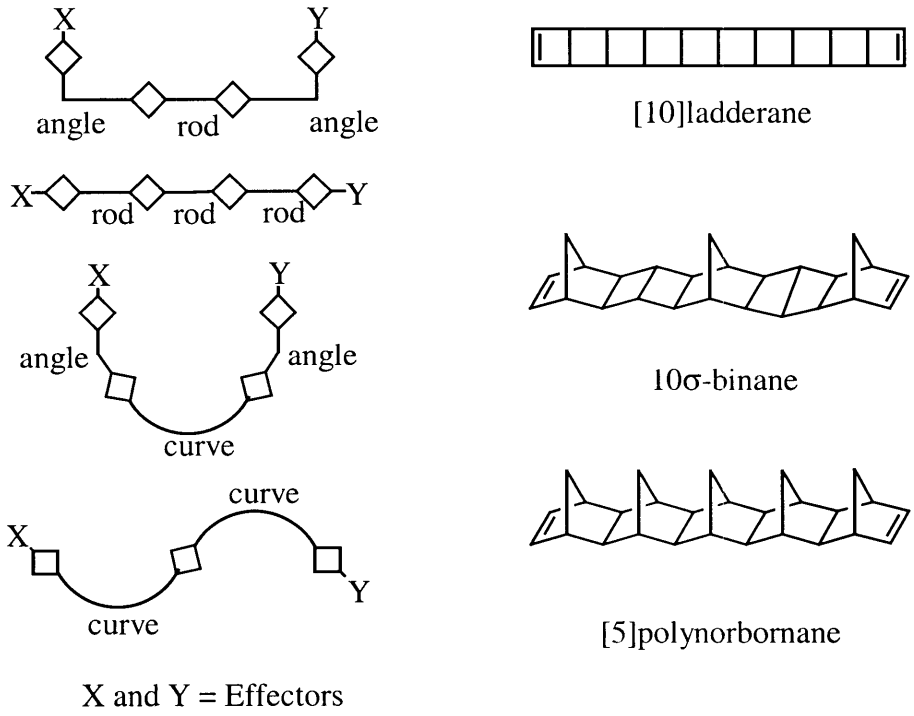


Figure 1.23 BGUs and types of MOLRAC.[127,128]

The block assembly strategy, as enunciated by Warrener, is based on the ability to react two separate reagents in a stereochemically defined way.[128] In its simplest form a set of A-blocks can

be combined with a number of complementary B-blocks. Also dual-blocks that have appropriate functionality on each end of the molecule can be envisaged. It is essential to the building block paradigm that the basic geometric forms of the constituent blocks are both recognised and clearly defined. Various Basic Geometric Units or BGUs have been assigned to a number of molecular types.

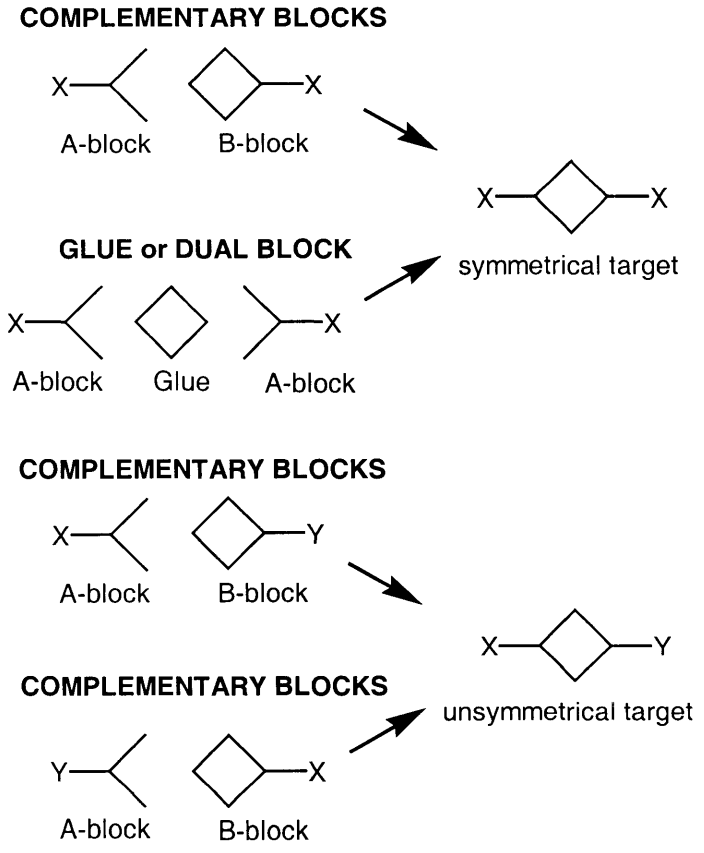


Figure 1.24 Block combinations toward either symmetrical or unsymmetrical target molecules.[128]

There are several well-established blocks that correspond to the BGUs described (Figure 1.23). Two main approaches have been used to produce symmetrical target molecules, either by fusion of complementary A and B blocks or through homocoupling of a single type of block (A or B) via either a second 'molecular glue' molecule or dual-block (Figure 1.24).[129] Examples of relatively small molecular glues that have been used successfully are oxadiazoles, used to fuse norbornenes, and 1,2,4-triazenes, also fusing norbornenes.[130,131] The 1,2,4-triazenes have the added ability of introducing functionality, also called an 'effector', onto the resulting spacer compound. Unsymmetrical targets, having two different effectors (X and Y), can be obtained by the combination of complementary blocks. There are, therefore, two possible routes available to reach

the same product allowing for greater design and synthetic flexibility. The structures of a number of representative A and B-blocks are shown in Figure 1.25. Various effector groups that have been studied using this approach include; porphyrins, crown ethers, β-lactams, bidentate and 1,10-phenanthroline ligands, metal complexes, and peptides.[129,132-138]

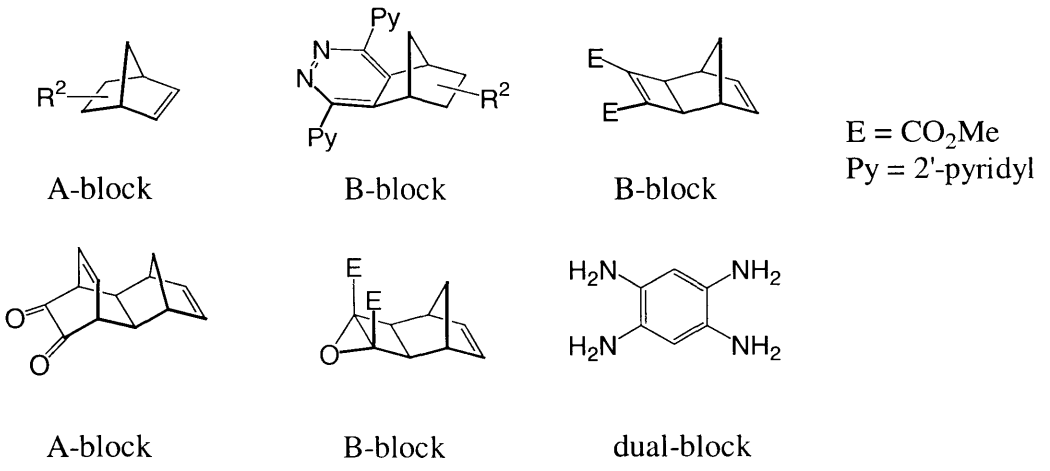


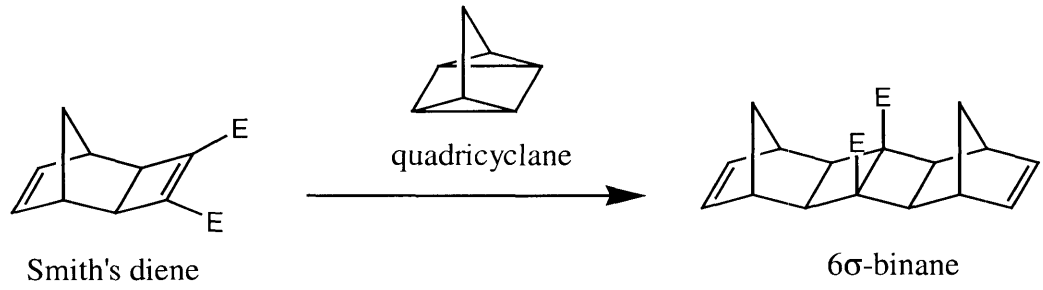
Figure 1.25 Representative A, B and dual blocks.[128,139]

1.4.2 RIGID POLYALICYCLIC SPACER GROUPS (MOLRACS) AND *BIS*-PORPHYRINS

The extensive work done by Warrener's group on various types of polyalicyclic systems forming rigid molecular racks, also called 'molracs', is well documented.[140] There are various types of molracs differing in their overall topology. The *exo,exo*-fused [n]ladderanes, which consist of a straight alicyclic framework (rod), can be contrasted with the curved nσ-binanes and [n]polynorbornanes (curves) (Figure 1.23).

Early synthetic work on molracs focused on the use of successive cycloaddition reactions, which exhibited the necessary stereospecificity. The synthesis of the [n]ladderanes followed a tandem cycloaddition protocol. The archetype [n]ladderane was extended by one cyclobutane ring via a [2+2] ruthenium catalysed cycloaddition reaction with dimethyl acetylenedicarboxylate (DMAD). This reaction is often referred to as the 'Mitsudo reaction'.[141,142] Extension by two cyclobutane rings was achieved via a [4+2] cycloaddition with cyclobutadiene.[127,134,143] The synthesis of the binane series of compounds also used a combination of cycloadditions.[144]

Starting from Dimethyl tricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene-3,4-dicarboxylate, an extremely versatile compound also known as 'Smith's diene', a number of binane systems were made.[145-147] The cycloaddition of Smith's diene and quadricyclane led to a binane system having six bonds (a 6σ-binane) separating the terminal norbornene π-bonds (Scheme 1.1). Further extension of these systems by sequential ruthenium catalysed [2+2] cycloaddition with DMAD and cycloaddition with quadricyclane have afforded 10σ- and 14σ-binanes.[144]



Scheme 1.1 Formation of a binane from Smith's diene.

The [2]polynorbornanes (sesquinorbornanes) were obtained by exploiting the Diels-Alder addition of cyclic 1,3-dienes to norbornadienes, however, this approach was not suitable for the production of larger systems.[148-150] The production of larger hetero-polynorbornanes relied on the building block methodology (Figure 1.26). The A-blocks, norbornene or the 7-hetero-bridged norbornenes, served as 2π reagents. The B-blocks, such as the 1,3-dipolar compounds, acted as 4π reagents. Coupling of the A and B-blocks was through a [4+2] cycloaddition reaction. An extension of this approach used 1,3-dipolar or alkene functionalised dual-blocks.

In the construction of molracs generally, it was essential that a high level of geometric control was possible in order to position functional groups with some precision. It has been found, for instance, that variation of bridgehead oxygen containing groups on quadricyclanes affected the stereoselectivity of the cycloaddition reaction with DMAD. An acyloxy derivative gave a 3:1 mixture of the *syn* and *anti* isomers respectively, whereas only the *syn*-isomers were formed from the reaction with the alkoxy substituted quadricyclanes. This stereocontrol allowed for the synthesis of *syn,syn*-, *syn,anti*, and *anti,anti*-binane isomers. It was thus possible to tune the separation distance within the same molrac spacer (Figure 1.27). An all *syn*-isomer of the 10σ-binane diol was also synthesised.[151] Photodimerisation of the substituted Smith's diene led to the

endo product having the terminal groups on opposite faces of the molrac. Further control of geometry was possible by variation of the methylene bridgehead group of the norbornane moeity within the norbornane containing molracs (see Section 2.1.1).

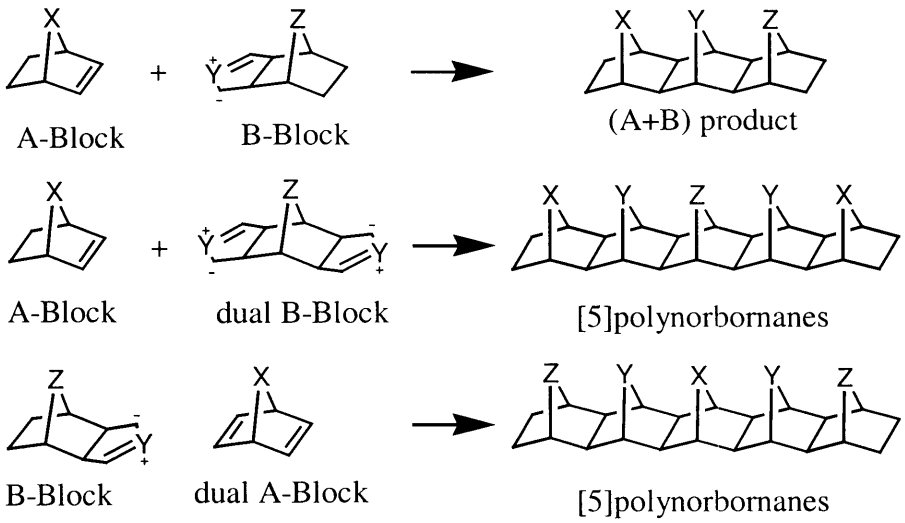


Figure 1.26 A+B building block approach towards [n]polynorbornanes.[152]

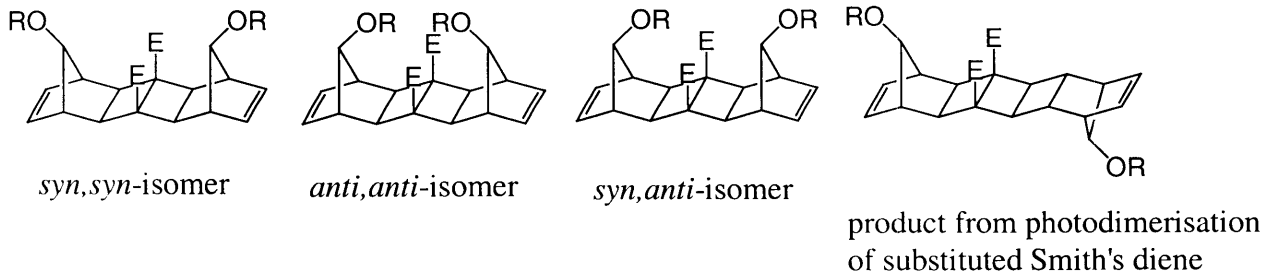


Figure 1.27 Possible isomers of alkoxy and acyloxy 6σ-binanes.[151]

Warrener and Johnston have constructed a number of variously spaced *bis*-porphyrin systems using the principles of block design and assembly outlined above. Several fused-norbornene porphyrin blocks (PBlocks) have been developed and three of these are shown in Figure 1.28, including PBlockC, which has been the most commonly used example.

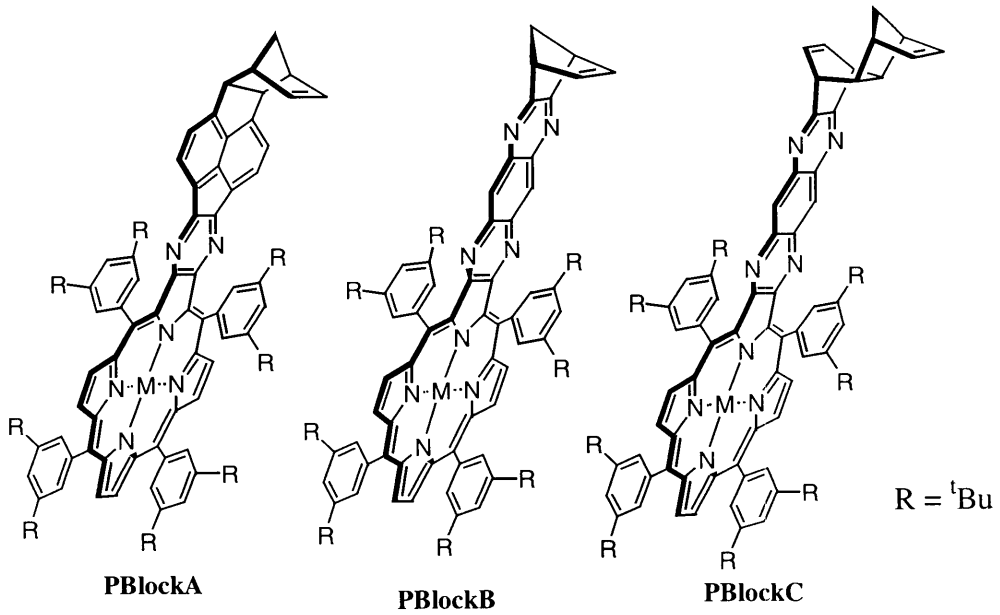


Figure 1.28 Three examples of porphyrin blocks (PBlocks) used by Warrener and Johnston in the construction of various *bis*-porphyrins. A 'right-angled' PBlock (**PBlockA**), a fused-norbornene PBlock (**PBlockB**) and an extended fused-norbornene PBlock (**PBlockC**).[153]

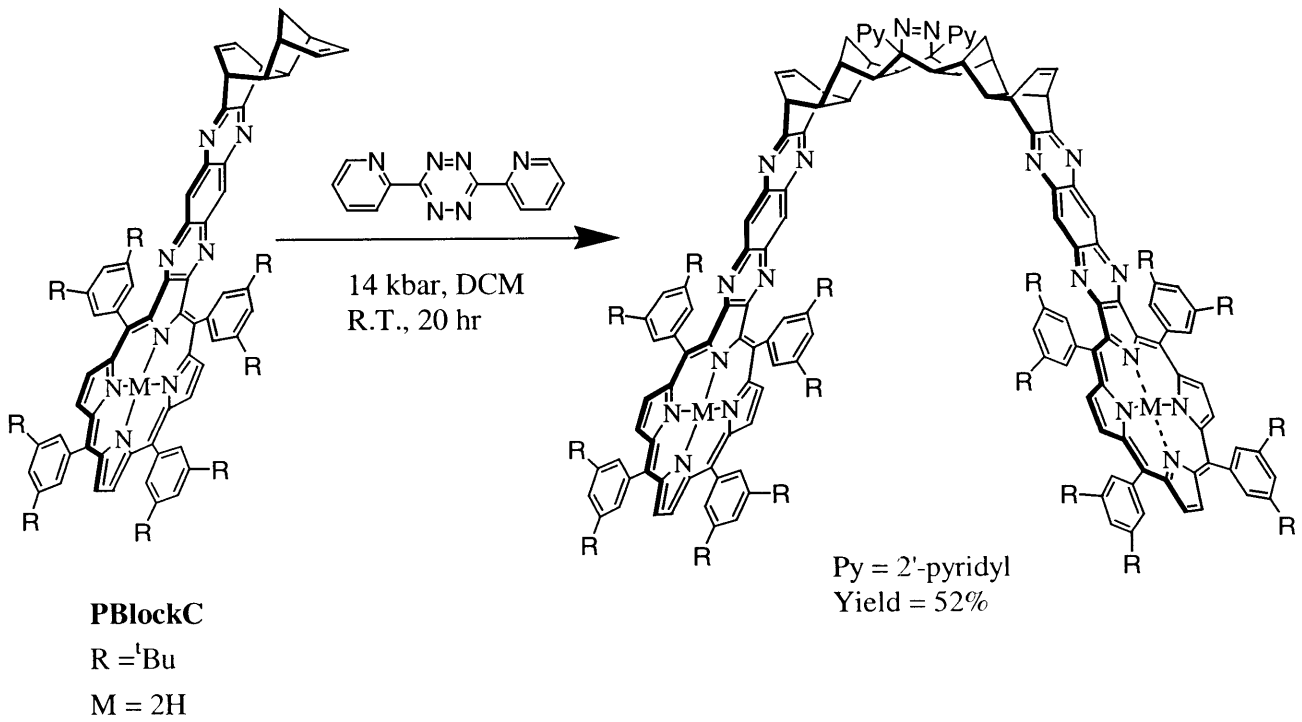


Figure 1.29 A typical example of a *bis*-porphyrin synthesis using the *s*-tetrazine coupling method.[132]

The porphyrin blocks have been coupled together using one of two main techniques. The *s*-tetrazine coupling method involved the use of either 3,6-di(2'-pyridyl)-*s*-tetrazine or 3,6-di(4'-pyridyl)-*s*-tetrazine as the coupling reagent (Figures 1.29 and 1.30). For example, two equivalents of PBlockC and 3,6-di(2'-pyridyl)-*s*-tetrazine were placed under high pressure (14 kbar) at room temperature for 20 hrs to afford the *bis*-porphyrin in moderate yield (52%) (Figure 1.29).[132] The use of the 4'-pyridyl tetrazine along with the insertion of zinc into each of the porphyrin units was reported to lead to the formation of a tetraporphyrin self-assembled dimeric capsule based on the simultaneous formation of four coordinate covalent bonds between the bridge 4'-pyridyl units of one bis porphyrin and the two zinc centres of the other *bis*-porphyrin and vice versa (Figure 1.30).

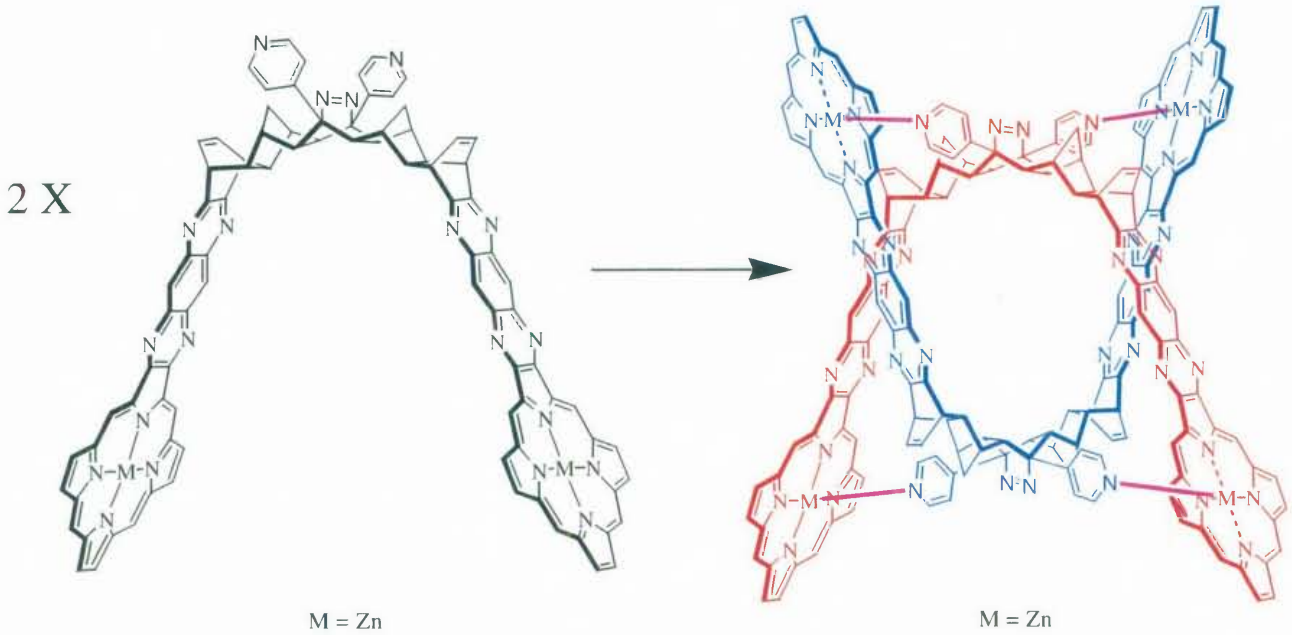


Figure 1.30 Self-recognition of a *bis*-porphyrin to form a molecular capsule (peripheral groups on the porphyrins have been removed for clarity).[154]

The other coupling method used was the ACE reaction* between a 1,3-dipole and a fused norbornene porphyrin block. Several different *bis*-porphyrin systems have been reported. The main dual-block *bis*-epoxides that have been used for this purpose are shown in Figure 1.31 along with the resulting *bis*-porphyrin systems.[153]

* Details of the ACE (**A**lkene + **C**yclobutane **E**poxide) coupling reaction are discussed further in Section 2.5.1

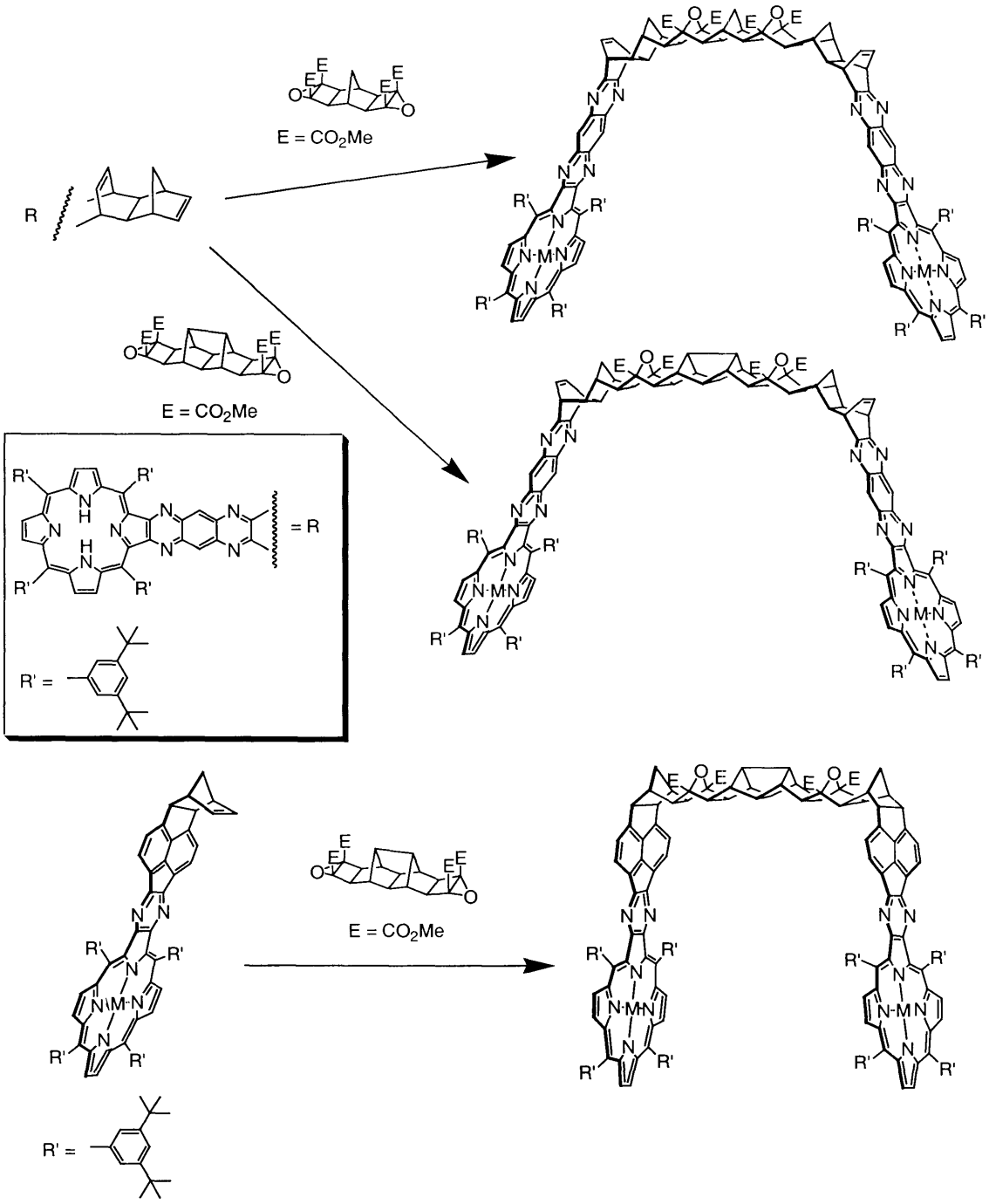


Figure 1.31 Representative *bis*-porphyrins formed using the ACE coupling method.[153]

A number of binding studies between a di-zinc *bis*-porphyrin of the type shown in Figure 1.29 and various *bis*-pyridine guests have been reported and will be discussed further in Chapter 3 (Section 3.1.2). Results from studies on the photo-induced electron-transfer between this *bis*-

porphyrin and both a *bis*-pyridine phenyldiimide and a *bis*-pyridine naphthalene diimide guest have also been reported (Figure 1.32).[155,156]

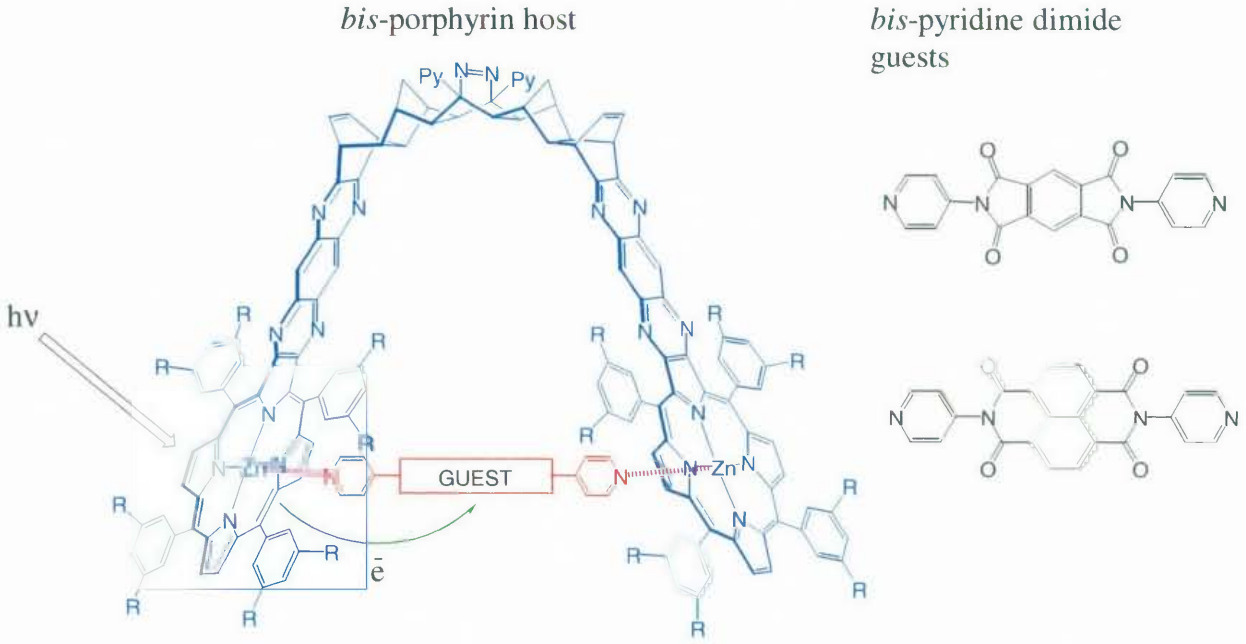


Figure 1.32 Electron transfer between Warrener and Johnston's *bis*-porphyrin host and a non-covalently linked *bis*-pyridine guest.[155,156]

Addition of the diimide *bis*-pyridine guests led to quenching of the porphyrinic luminescence band at 660 nm and this was attributed to a rapid electron-transfer from the porphyrin unit to the diimide guest at a rate of 1.1×10^{10} s^{-1}. It was found that the rates of the forward (charge separation) and reverse (charge recombination) processes were both decreased in comparison to analogous covalently linked systems due to the weaker interaction between the donor and acceptor components. The efficiency of the forward process was still high ($\phi = 90\%$) with a longer lifetime of the resulting charge-separated species by approximately two to three orders of magnitude compared to covalently linked systems. It was proposed that the comparatively longer charge-separation lifetimes of these systems made them appealing as light-energy storage systems.

1.5 COMBINED DESIGN PRINCIPLES OF PORPHYRIN-SPACER-PORPHYRINS (PSPS) AS POTENTIAL MOLECULAR SWITCH OR ARTIFICIAL ENZYME SYSTEMS

The key features required in the design of a molecular switching device have been outlined in some detail so far using instructive examples from a number of different research areas with an emphasis on systems that incorporate porphyrinic sub-units. Research into the mechanisms of energy transduction and electron transfer processes in natural photochemical systems as well as biomimetic and artificial systems have provided a wealth of information, however, the development of practically useful nano-devices remains a challenge. There is currently still a need to focus on the fundamentals of molecular switches at the molecular level before further developments can be made. From the examples discussed, it is clear that an effective molecular switch that relies on a photoinduced electron transfer mechanism is likely to have the following components: (i) a suitable chromophore or donor group (D) or groups, (ii) a suitable acceptor (A) group or, preferably, multiple acceptor groups, (iii) strict geometrical control of the donor and acceptor groups either by use of a rigid, saturated bridging group or an efficient self-assembly procedure via complementary molecular recognition interactions, (iv) a design principle that maximises the quantum yield of the ion-pair (ϕ_{IP}) and the lifetime of the charge-separated species (τ_{IP}), including a large separation distance between D and A or some other mechanism to prevent charge recombination and (v) a reversible transition between two or more stable geometries or chemical states.

It is clear that porphyrins have proven to be invaluable functional building blocks in many of these systems and their presence as key active components in PRCs is not surprising when their long list of useful properties are appreciated. Listed below is a revision of some of the key features and properties of porphyrins that render them ideal molecular-switch building blocks: (i) a large delocalised π-system suitable for efficient electron transfer; (ii) ease of analysis (e.g. NMR and U.V-Vis spectroscopy); (iii) stability at high temperatures and pressures; (iv) solubility; (v) control of excited-state and ground-state electronic properties via peripheral functionalisation, linker geometry, type and position, and variation of metallated state (vi) a mostly planar geometry and (vii) ease of synthesis.

A novel molecular switch design is proposed that combines aspects of the covalently linked D-A systems discussed with those relying on molecular recognition processes. This design has two

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different porphyrin building blocks covalently joined by a rigid saturated spacer. The two porphyrin sub-units are designed to act as molecular-scale electrical 'contacts' and will need to have appropriate redox properties to facilitate photoinduced electron transfer. A third functional group, covalently attached to the centre of the bridging group and projected down inside the cavity of the *bis*-porphyrin, is designed to act as a mobile 'armature' that can transfer an electron from the photo-excited donor porphyrin to the acceptor porphyrin via non-covalent interactions much like those incorporated in supramolecular based devices. The mechanism by which the electron transfer occurs would, presumably, be similar to supramolecular switches such as the porphyrin catenanes of Gunter.[16,72,157]

An advantage of covalently attaching the acceptor group or 'armature' is that it would drastically increase the nominal concentration of the acceptor unit compared with an analogous acceptor group in solution. A disadvantage may be the synthetic effort required to get an ideal overlapping geometry between the porphyrin and acceptor units. The linkage would have to be suitably flexible to attain this overlap which may impact on the speed that electron transfer can occur between one porphyrin unit and the other. The ability of such systems to work effectively can only be guessed at, so experimental results would be instructive in any case.

Computational modelling should help in the design of a suitable armature linkage and the use of a building block strategy would allow a number of different armature groups to be introduced efficiently. As with other porphyrin containing electron or energy transfer devices the ground-state optical characteristics and excited-state properties of the D and A porphyrin units can potentially be tuned by variation of the metallation pattern and/or changing the *meso* or β substituents of the porphyrin building blocks.

The proposed molecular switch is designed to operate via several steps (Figure 1.33). The initial step would involve the excitation of one of the porphyrins (e.g. Zn-porphyrin) through an interaction with light of an appropriate energy to induce excitation.

The central armature group, which is free to interact with either porphyrin sub-unit, is designed to act as a mobile electron acceptor. The electron accepting properties of paraquat and its derivatives are well known and such behaviour has seen them utilised as potent non-selective herbicides. The combination of the redox properties and electrostatic repulsion makes a paraquat derivative an ideal target for the centralised armature unit. After the initial electron transfer there will be an expected electrostatic repulsive force between the porphyrin π-cation radical and the

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reduced paraquat monocation radical. The flexible linker allows the mobile acceptor to move away from the initial transfer contact site and to subsequently interact with the second, otherwise insulated, porphyrin unit (either free-base or transmetallated) thereby transferring an electron to it. In the final state the electrostatic repulsion between the primary porphyrin π-cation radical and the mobile acceptor unit is maintained preventing a back electron transfer reaction to occur. In this way a long-lived ion-pair is produced which could be used for useful chemical work. The basic design of the molecular switch allows for future development by directly attaching the porphyrin acceptor unit to another molecular device such as a molecular wire, an amplifier (e.g. porphyrin array), or another switching unit.

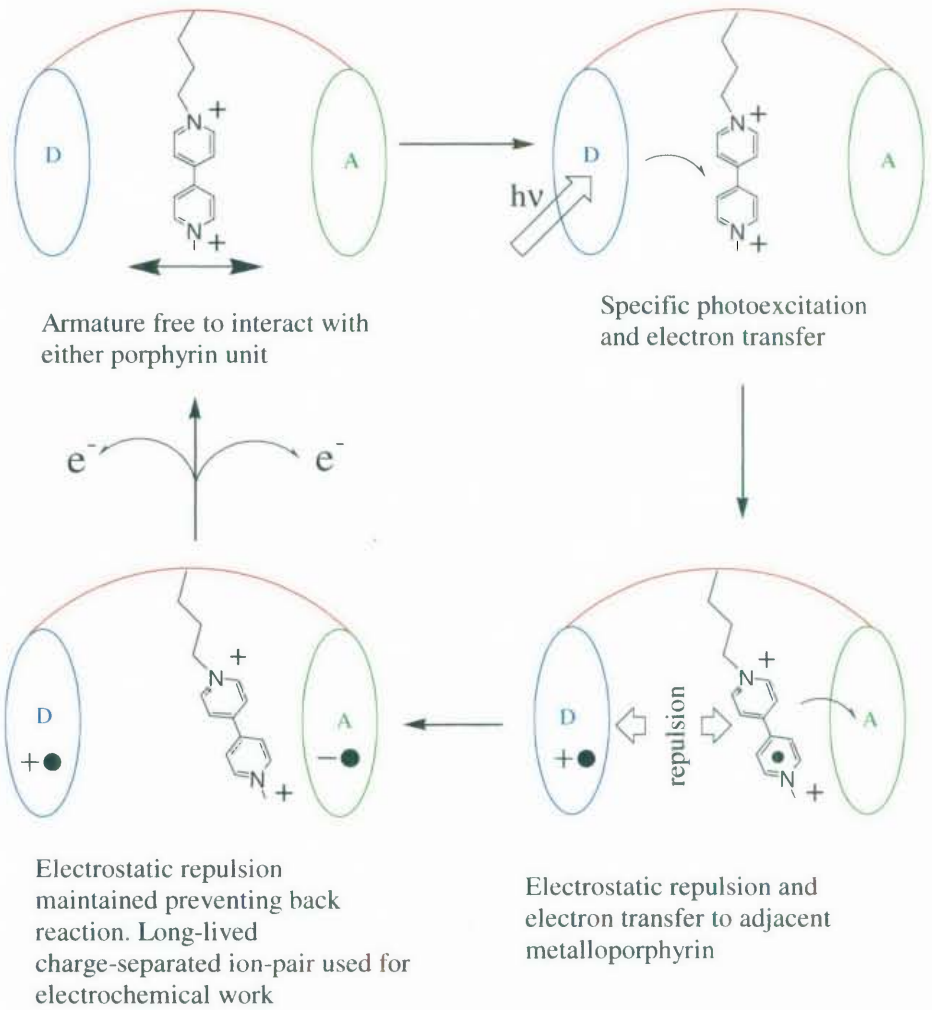

Figure 1.33 Schematic representation of a novel molecular switch and predicted mode of operation.

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The basic design of the Porphyrin-Spacer-Porphyrin (PSP) also lends itself to development as an artificial enzyme. Although the final products of a molecular switch program and an artificial enzyme program will eventually differ, the initial synthetic strategy will be identical. An artificial enzyme would incorporate a third binding group or catalytic group attached to the central spacer instead of the molecular switch armature unit. At a later stage in the PSP development increased guest binding selectivity, through the introduction of a chirally active binding group at the central position, could also be explored. The artificial enzyme prototype will have two identical Zn-porphyrins which will act to position two reactants via coordinate covalent bonding in a similar manner to the Sanders' dimers and trimers (Figure 1.34). The proposed design may be superior to the Sanders' linear dimers, based on entropy cost considerations, due to the annulment of rotational freedom between the porphyrin binding sites although the flexibility of the proposed PSP system will need to be tested. Using a host system where there are just two binding sites for binding either one bidentate or two monodentate ligands should also lead to a simplification of the analysis and more efficient catalytic binding compared with Sanders' cyclic porphyrin trimer host systems in which there is a superfluous porphyrin binding site.

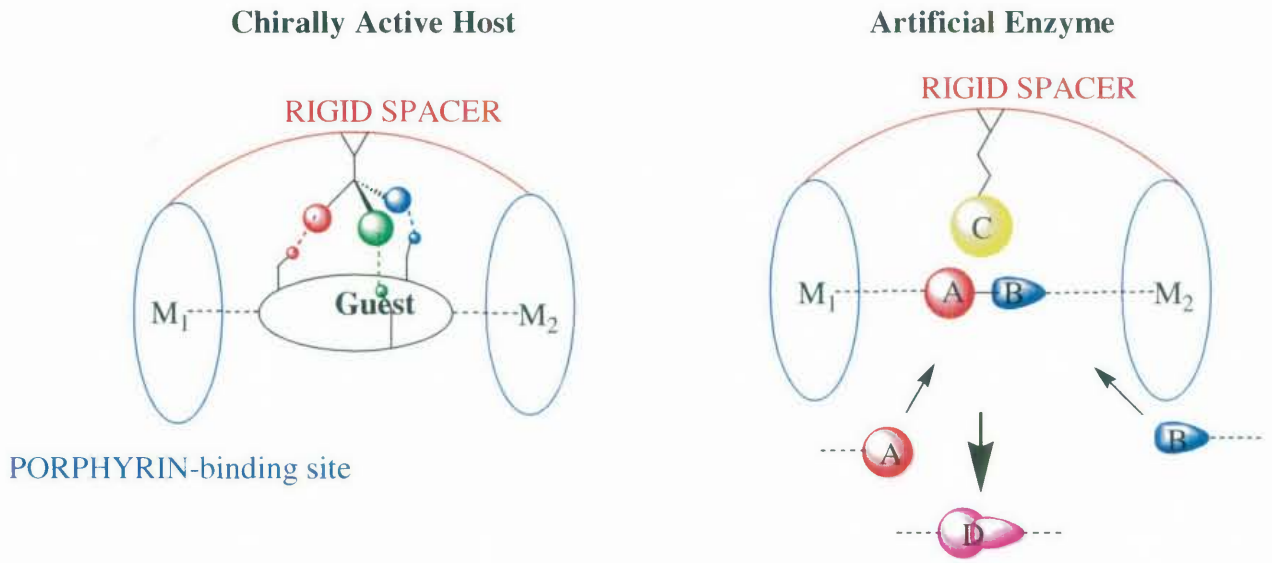

Figure 1.34 Schematic representation of novel chirally active PSP host and PSP artificial enzyme systems and predicted modes of operation. The incorporation of a chiral binding site is expected to affect the selectivity toward and orientation of a complementary guest. A and B are two different monodentate reactants held in close proximity through coordinate covalent bonding to the metalloporphyrins. Introduction of a catalytic group or binding site at C is designed to further enhance catalytic activity and/or substrate selectivity. The final product(s) (D) could be either bidentate (poor turnover) or monodentate (good turnover) depending on the reaction and substrate type. M_1 and M_2 may be identical or different metals.

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The time and effort required to make well-defined multi-component macromolecules using step-by-step covalent bond building strategies is one of the justifications for using self-assembly or template-directed approaches. The development of a convergent and complementary building block strategy has the potential to alleviate this problem to some extent. Instead of synthesising just one system in isolation, an extra degree of design flexibility and control is added by developing a library of complementary molecular building blocks of varying size and geometry and finding general methods of joining them together.

The main aim of this project is to develop a synthetic approach toward prototype porphyrin-spacer-porphyrins (PSPs) that have the potential to be developed as either a molecular switch or an artificial enzyme. The synthetic work has two separate but convergent aspects, namely, the synthesis of suitable Warrener type dual blocks, to act as rigid-spacer molecules, and the synthesis of complementary porphyrin blocks (PBlocks). A detailed account of the synthesis of several rigid-spacer and porphyrin building blocks, with reference to previously developed building blocks, is presented in Chapter 2, including a description of a generalised method for the introduction of central functionalised aryl groups. The subsequent syntheses of two related PSPs are also described in detail. Chapter 3 focuses on the analysis of the final PSPs, including preliminary host-guest UV-Vis binding studies and initial findings on the flexibility of these *bis*-porphyrins from comparative binding studies using two different *bis*-pyridyl porphyrin guests. The experimental work is presented in detail in Chapter 4.

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