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Review Article

Molecular Receptors Based on Expanded Porphyrins

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Abstract. Studies on the design and synthesis of receptor molecules capable of selectively binding and transporting substrates (neutral, anionic and cationic) is currently being pursued to develop artificial membranes permeable to the bound species. Expanded porphyrin systems by virtue of increased cavity size and aromatic nature are capable of binding a variety of substrates depending on the nature of the porphyrin and the cavity size. Recently there are a number of reports on the use of expanded porphyrins as molecular receptors for various substrates. Specifically, expanded porphyrins such as sapphyrins and rubyrins in their protonated form bind a variety of anionic and neutral substrates and it has been shown that they act as carriers for transporting different ionic and neutral species. Additionally, expanded porphyrins find their application as MRI contrasting agents and as sensitizers for photodynamic therapy. In this review, an attempt has been made to discuss molecular receptor properties in the solid and solution phases of two expanded porphyrins, sapphyrin and rubyrin which are 22π and 26π electron systems respectively. Furthermore, the synthesis, binding and transport properties of core modified expanded porphyrin systems are also highlighted.

Key words: expanded porphyrins, sapphyrins, rubyrins, core modified porphyrins, molecular receptors, anion transport and anion complexes of porphyrins

List of Abbreviations

AMP	Adenosinemonophosphate
ADP	Adenosinediphosphate
ATP	Adenosinetriphosphate
CMP	Cytosinemonophosphate
DEAE	Diethylaminoethyl
DNA	Deoxy-5′-ribonucleicacid
GMP	Guanosinemonophosphate
5′- GMP	Guanosine-5′-monophosphate

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2′-GMP	Guanosine-2′-monophosphate
HOMO	Highest Occupied Molecular Orbital
H_2TPP	Tetraphenylporphyrin
LUMO	Lowest Unoccupied Molecular Orbital
OEP	Octaethylporphyrin
PDT	Photodynamic therapy
STPP	5,10,15,20-tetraphenyl-21-thiaporphyrin
S_2TPP	5,10,15,20-tetraphenyl-21,23-dithiaporphyrin

1. Introduction

Molecular recognition is an important phenomenon in the biological and environmental area of research [1]. Molecular receptors are host molecules capable of binding or recognizing selectively the guest molecules whose nature varies from neutral to cation and anion. It was long realised that the role of receptors aside from recognizing the substrates, has an additional function and that is transporting them across membranes. Transportation of ions is an indispensable bio-activity [2]. Exploration of its intriguing mechanistic details revealed by experiments performed on model systems is an on going area of current interest. Specifically, nucleotide recognition and transport are of great relevance in the domain of supramolecular chemistry research aimed at designing abiotic molecules to mimic some or part of the functions of the bio-molecules in action [3]. The design and development of such receptors to facilitate recognition and transportation requires considerable effort and in recent years many papers have appeared in this very important area of chemistry. Many different receptors based on cryptands [4], crown ethers [5], calixarenes [6], cyclodextrins [7] and cyclic and polyamines [8] are described in the literature. Macrocycles based on polypyrroles [9] are increasingly being studied because of their rich and diverse chemistry. Expanded porphyrins [9], containing more than four pyrrole rings are hot pursuit multipurpose macrocyles, which can selectively recognize neutral, cationic and anionic substrates under a variety of conditions [10]. Although a few examples of expanded porphyrins have been reported in the past, not much progress was made in their chemistry due to the nonavailability of an easy synthetic method of preparing them in gram quantities. In the early eighties due to the efforts of Sessler and coworkers much progress towards their synthesis was achieved. They not only developed easy synthetic methods, involving a smaller number of steps, for the preparation of expanded porphyrins, but they also exploited their rich and diverse chemistry including anion recognition and transport and they are largely responsible for the accumulation of a wealth of data on receptor chemistry of expanded porphyrins. In this review, we will focus our attention solely on anion binding and the transport properties of receptors based on expanded porphyrins with particular reference to sapphyrins and rubyrins from the early 1990s to the present. Furthermore, the synthesis and anion complexation

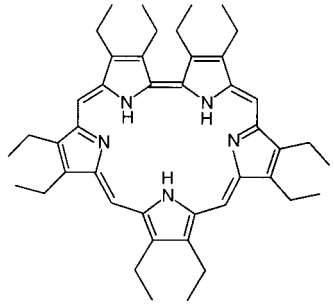
properties of a variety of core modified expanded porphyrins from this laboratory are also discussed. The complexation of cations and neutral substrates with expanded porphyrins has recently been reviewed [10, 11].

2. An Overview of Sapphyrins and Rubyrins

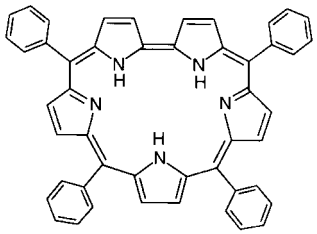
Sapphyrins are basically higher homologous of porphyrins having characteristics typical of porphyrins [12], but at the same time exhibiting some unusual properties. Like porphyrins they have the so called Soret band absorption around 450–515 nm and Q-band absorption in the region of 520–800 nm of the visible region. This long wavelength absorption can be used to design anticancer drugs [13], since the far infra red light is transparent and penetrates deeper into the tissues. Sapphyrins are 22π electron systems and are aromatic having a diatropic ring current as observed in the proton NMR spectra, shifting the outer and the inner protons to down- and up-field respectively. Because, of the larger cavity size than the porphyrins one can expect intriguing chemistry such as chelation of anions, which is not common in the chemistry of porphyrins. Broadly one can classify the sapphyrins into two classes; one is the OEP type where there is an ethyl group on the periphery and free meso positions **1** and the TPP type containing free positions at the β-pyrrole positions and phenyl substitutent in the meso positions of the macrocycle **2**. Both have many similarities and differences arising out of different substitution patterns.

Rubyrins **3** are macrocycles [14] containing six pyrrole rings bridged by four methine groups. They are also aromatic with 26π electrons and by virtue of their larger cavity size two anions of appropriate size can be accommodated. The other most interesting aspect is the accommodation of two metals within the cavity which is not commonly found in the arena of porphyrin literature.

The incorporation of heterocycles other than pyrrole leads to the formation of core modified sapphyrins and rubyrins [15, 16] with varying numbers of pyrroles and heterocycles like furan, thiophene and selenophene. The presence of heteroatoms inside the core of the macrocycle in effect alters its electronic structure as found in the thia, oxa, selena and tellura porphyrins [17]. Not only is there a change in the electronic properties, but the coordination to the metal ion also varies. For example, inclusion of thiophene can have different modes of solicitation to the metal ion such as η^1 to η^5 [18] and it is quite possible that it may stabilize a metal ion in its unusual oxidation state. In the absorption spectra of core modified sapphyrins and rubyrins (thia and selena) the “Soret” and “Q” bands are shifted towards the red region of the spectrum compared to pyrrole only sapphyrins and rubyrin. This has been explained on the basis of the rearrangement of the frontier orbitals [19]. These expanded porphyrins also show a marked affinity for the anions and most of their rich chemistry has yet to be unraveled.



1



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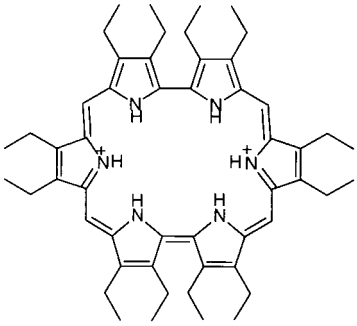

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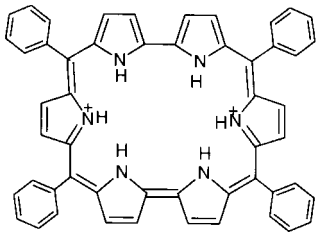


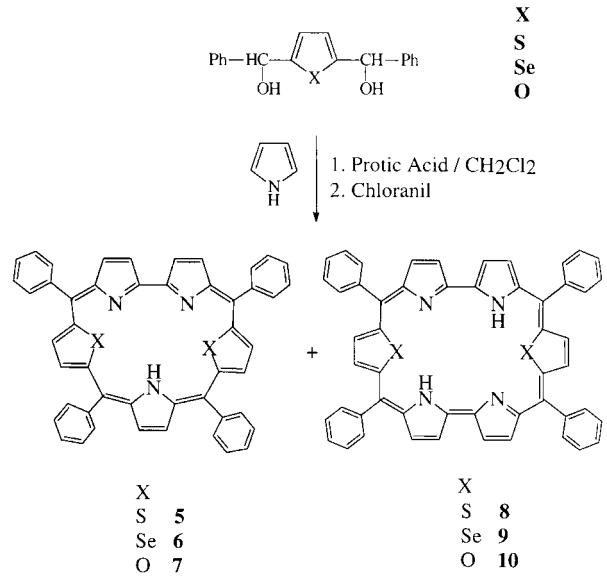
4*

* not yet known

Chart 1.

3. Synthesis

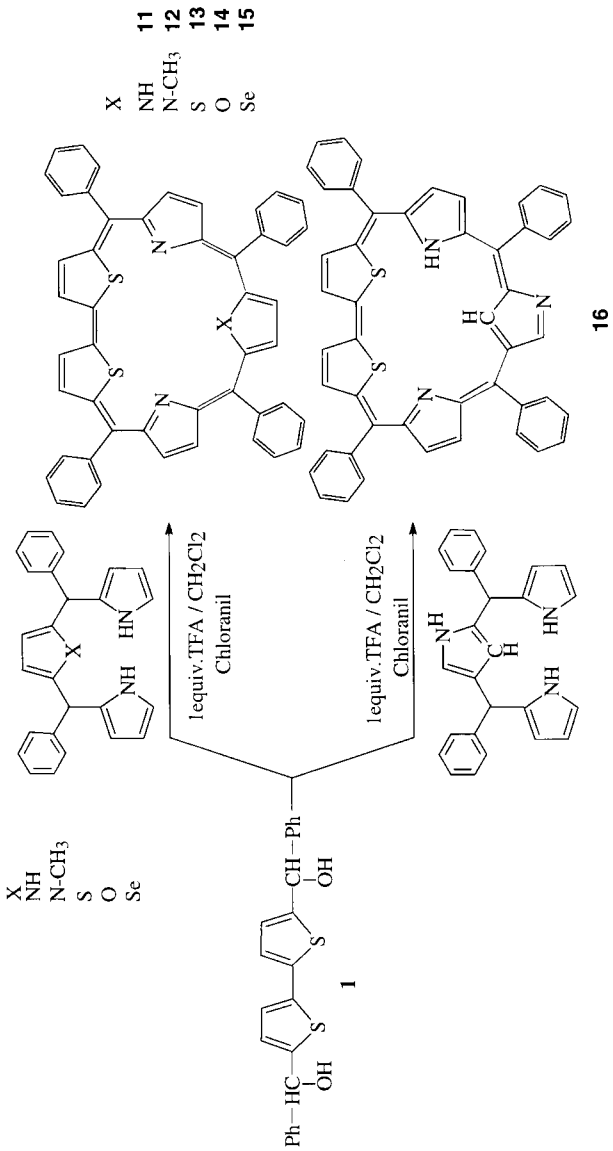
The synthesis of these exotic macrocycles has been made possible by the efforts of Woodward and his coworkers in the early 1960s [20]. However, the synthesis of the target molecule contained numerous steps and was synthetically laborious. It basically involved the acid catalysed MacDonald-type condensation of the diformyl bipyrrole and bis(pyrrolylmethyl)pyrrole diacid. Later Grigg and Johnson [21, 22] reduced the number of steps involved in the synthesis. The preparation of two key precursors, a diacid and a diformyl bipyrrole were later optimized and as a consequence, many different expanded porphyrins were synthesised by Sessler and his coworkers [23–26]. The core modified sapphyrins were also prepared in a similar manner, however all these macrocycles happen to bear ethyl groups on a few or all β-pyrrole carbons with free meso-positions. Expanded porphyrins of the TPP class (meso tetraphenyl sapphyrin **2**) were reported by Grazynski [27], which were isolated as a byproduct of the reactions of pyrrole and benzaldehyde under Rothemund conditions. However, meso substituted core modified expan-



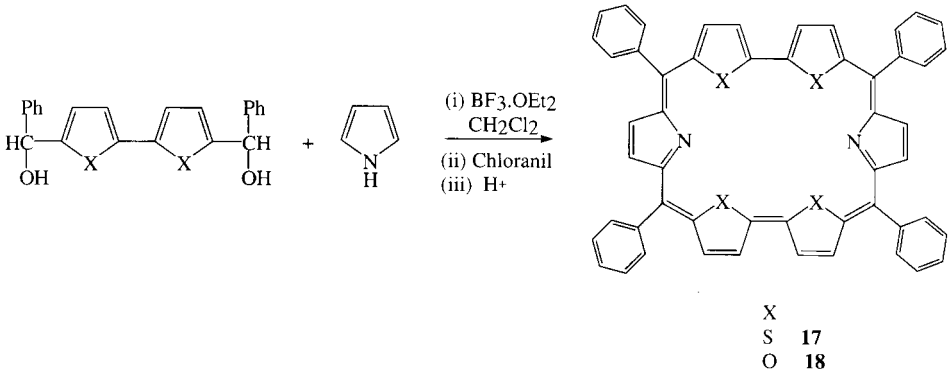
Scheme 1.

ded porphyrins were unknown until the recent synthetic efforts in this laboratory. Many different synthetic protocols (Schemes 1, 2, and 3) have been developed for the synthesis of a plethora of core modified sapphyrins and rubyrins. It has been shown that a simple change in the reaction conditions, for example change of acid catalyst from a Lewis acid to a protic acid in a condensation reaction between the bithiophene diol and tripyrrin, leads to core modified sapphyrins with S_2N_3, Se_2N_3, Se_2N_4, S_2N_4 cores [28]. The product distribution can be varied either by changing the acid catalyst or by increasing the equivalent of a particular acid catalyst (Table I). These macrocycles can also be obtained by one step reaction of modified tripyrrins in dichloromethane in the presence of an acid catalyst except Lewis acids [29]. MacDonald [3 + 2] type condensation of a modified tripyrrin and a diol (bithiophene, bifuran or biselenophene) results in the formation of S_3N_2, Se_3N_2, Se_4N_2, S_4N_2 expanded cores [30–31]. A 4 + 2 condensation of modified terpyrrin containing three heteroatoms and a diol leads to the formation of rubyrin [32].

There is an apparent change in the spectral and electrochemical properties on inclusion of heterocycles other than pyrrole. The Soret-like and Q-bands absorption are red shifted and the quantum of red shifts depend upon the nature and number of heteroatom incorporated into the macrocycle (Figure 1). Upon protonation there is a bathochromic shift of the Soret and Q-bands which is typical of core modified sapphyrins and invariant from β-ethyl substituted expanded porphyrins. The red shift of the absorption bands upon protonation is due to the structural change occurring, by releasing the repulsive interaction between the ortho-hydrogens of the meso phenyl rings and the adjacent pyrrole protons. However, a reversal of trend


X
NH
N-CH3
S
O
Se
1equiv.TFA / CH2Cl2
Chloranil
1equiv.TFA / CH2Cl2
Chloranil
Ph—HC—OH
CH—Ph
OH
1
11
12
13
14
15
16

Scheme 2.



Scheme 3.

Table I. Product distribution of core modified sapphyrins and rubyrins in different acid catalysts

Compound	Isolated yield (%)		
	TFA (1 equiv.)	p-TsOH (1 equiv.)	HBr (1 equiv.)
5	27	6	6
6	12	5	12
7	9	8	10
8	9	9	14
9	18	7	12
10	15	8	10

was observed for meso-phenyl substituted N5 sapphyrin.^{1}H NMR reveals that they are all aromatic having diamagnetic ring current. But, unlike in N5-sapphyrin no dramatic 180° ring flipping of pyrrole opposite to a bipyrrole ring was observed in heteroatom substituted expanded porphyrins. A comparison of the redox potentials with that of β-substituted sapphyrins suggested easier reductions for the meso aryl core modified sapphyrins by about 120–200 mV. The Δ_{redox} calculated from the difference of first oxidation potential and first reduction potential suggest a decrease in the values relative to mesoaryl porphyrins. Thus, the electrochemical and spectral studies point to changes in the energies of the HOMO and LUMO upon hetero atom incorporation into the expanded cores [31].

4. Receptor and Carrier Property

Macropolycyclic synthetic motifs are of special interest for designing artificial receptors, as they possess cavities of proper size for accommodating or encapsulating

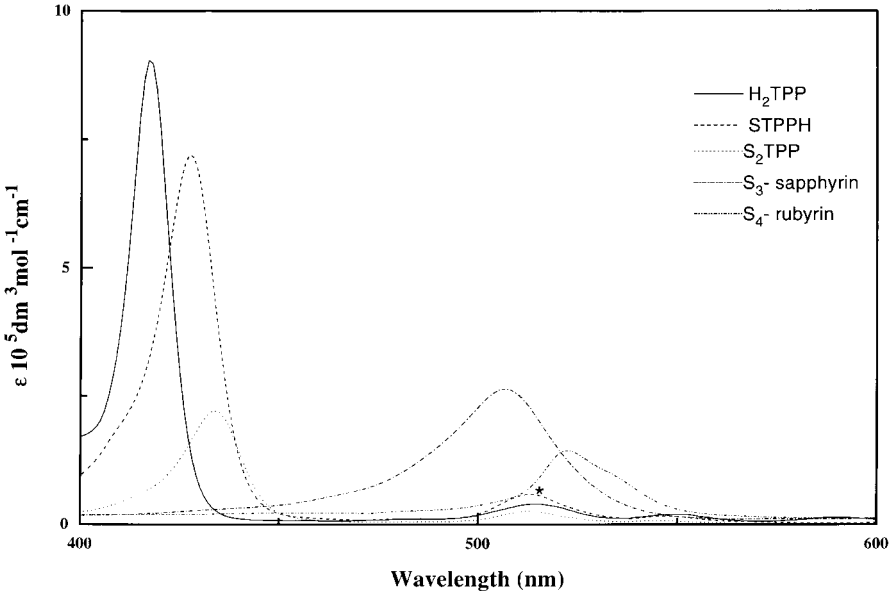


Figure 1. Comparison of absorption spectra of various porphyrins. The asterisk denotes the Q-band absorption of H_2TPP, STPPH and S_2TPP.

a particular ion, which are stable enough to be characterized. The more demanding proposition of having an additional function like transport for a molecular receptor is that the stability of the receptor–ion complex should not prevent it from releasing the host. The search for the right choice of a molecular receptor for an ion will not only throw light on the coordination and structure of the complex but will also help in the design of drug delivery systems. The coordination chemistry of anions is a well established and growing field of current research, which has yielded a great variety of novel structures and properties of both chemical and biological significance [33–36]. Anions have different topologies; spherical (F^-, Cl^-, Br^-, I^-), linear (N_3^-, OCN^-), planar (NO_3^-, RCO_2^-), tetrahedral, (SO_4^{2-}, ClO_4^{2-}, PO_4^{2-}).

4.1. SOLID STATE STRUCTURE:

The receptor property of a molecule relies on the cavity size, the most crucial and deciding factor that often determines the binding and selectivity of anions. It is of consequence because different anions have different sizes and the cavity of the molecular receptor should be large enough to accommodate the anions. In view of this it is understandable that, since porphyrin has a trans-nitrogen distance of only ∼4 Å, its receptor chemistry is not known in the literature. On the other hand expanded porphyrins such as rubyrins and sapphyrins have large cavity size, delivering interesting anionic binding characteristics which are otherwise impossible, via hydrogen bonding interactions. The planar pentapyrrolic skeleton of sapphyrin

possessing aromatic character forces the three N—H bonds to point their positive ends toward the centre of the cavity, of size ∼5.5 Å diameter [37]. Upon protonation two more protons are added to give a total of five symmetric arrays of hydrogen bonding sites that is almost perfectly predisposed for anion encapsulation. It is to be remembered that only the protonated form of sapphyrins serves as a molecular receptor. The high positive charge required for molecular recognition, firstly, is to prevent planar or flat sapphyrins from dimerizing, thus avoiding complications in the analysis and secondly, to neutralize the charge on the guest anion substrates, resulting in a neutral host-guest complex. It also makes the compound soluble in common organic solvents enabling the complexation study of nucleotide bases.

The diprotonated form of sapphyrin has unusual binding affinities for anions which has no precedent in its congener, porphyrin chemistry. This unexpected and quite revealing aspect arises because of the larger core size and symmetric disposition of the protons on the pyrrole nitrogens towards the centre of the molecule. The recognition of halide anions was very selective and experimental evidence suggested that certain anions can be transported across the artificial membranes [38–40]. The solid state structures of diprotonated sapphyrin-fluoride and -chloride complexes (Figure 2) are described in the literature [37]. Both have contrasting coordination patterns in the solid state. The possible modes of binding of anions are depicted in Figure 3. Thus, it is clearly seen that the smaller the anion the better will be the inclusion inside the cavity. The point is that the N to F bond distance is ∼2.7 Å and the diprotonated sapphyrin has the right diameter of about ∼5.5 Å to accommodate fluoride anions inside the core. On the other hand, in the case of the chloride complex the N to Cl bond distance is ∼3.1–3.2 Å which is quite large for this molecule to include it inside its cavity. Coordination wise the chloride ion complex is of type IV (Figure 3), in which the chloride ion is bound via hydrogen bonding well above and below the sapphyrin molecular plane symmetrically. Because of this, displacement of the chloride ion from the mean macrocyclic plane is about 1.88 Å above and 1.77 Å below. The $HF{\cdot}HPF_6$ complex has a N to F bond distance nearly equal to 2.7 Å expected for the N–H$\cdots$F hydrogen bonding interactions and exhibits type II mode in the solid state. It has been deduced that the adaptation of various coordination modes by the macrocycle for different anions is to minimize the effect of unfavourable steric and electronic interactions possible in the coordination complex. Monoprotonated sapphyrins also form complexes with mono anions like chloride [41], azide [25] and benzoic acid [42]. Unlike the chloride complex which has a structure similar to that of the diprotonated sapphyrin, the azide anion was complexed to the sapphyrin via a hydrogen bond in end on fashion through one of the terminal nitrogens, and like the dihydrochloride complex the azide nitrogen is 1.13 Å above the mean plane of the macrocycle. Monoselena sapphyrin [15c], a core modified sapphyrin derivative with one less pyrrole ring, also showed an affinity for binding halide anions, which is manifested in the crystal structure of the selenasapphyrin dihydrochloride adduct (Figure 4). As seen in all aza-sapphyrin the dihydrochloride was held in a symmetrical fashion,

however, only by two hydrogen bonds above and below the macrocyclic plane, with a Cl···Cl distance of ∼5.33 Å. The single crystal structure of the 1 : 1 neutral complex formed between benzoate anion and monoprotonated sapphyrin is shown in Figure 5. In this structure the ligated oxygen atom of the benzoic acid moiety is held at 1.195 Å above the plane of the five pyrrolic nitrogen atoms. A close C—H···N (unprotonated nitrogen) contact distance was noticed (H···N distance ∼2.38 Å). X-ray crystal structural details are available for sapphyrin derivatives **19** and **21** with phosphate anions [43, 44]. The information provided from solid state structures is that the macrocycle is flexible in chelating the phosphate anions. For instance, monobasic bis(phenylphosphate) forms a 2 : 1 complex and monobasic phosphoric acid forms a 1 : 1 complex with the diprotonated sapphyrin derivatives as exemplified in Figures 6 and 7. Diphenyl phosphate also forms a 2 : 1 complex (Figure 8). The crystal structure of 2 : 1 complexes resembles that of the chloride ion complex, in such a way that the phosphate anions are well displaced above and below the mean plane by about 0.83 Å. The oxygen atoms of the phosphate anion are ligated by 2 to 5 hydrogen bonding interactions. The 1 : 1 complex is quite interesting in the sense that only a single oxygen atom of the phosphate moiety is complexed by the diprotonated sapphyrin and is 1.22 Å above the mean sapphyrin plane via five hydrogen atoms and the remaining three oxygen atoms are left free. Rubyrin **3** was reported to form complexes with anionic substrates via hydrogen bonding. The dihydrogenchloride complex of **3** shown in Figure 9 has features similar to sapphyrin-chloride adducts, but the chlorides are held above and below the macrocyclic plane at 1.6 Å, which is less than observed for the sapphyrin-chloride adducts, because of reduction in the intracore N^+H to N^+H electrostatic repulsive interactions within the larger rubyrin cavity.

4.2. SOLUTION PHASE STUDIES

The proof for encapsulated fluoride anion in the solid state was further substantiated from the results of ^{1}H NMR studies [37]. Figure 10 shows the ^{1}H NMR of dihydrochloride, dihydrobromide, dihydrofluoride and mixed hydrofluoride-hexafluorophosphate salts of sapphyrin. The splitting pattern and the chemical shift values differ greatly for fluoride and the rest of the anions. In the case of hydrochloride and hydrobromide salts one observes three singlets with a proton ratio of 2 : 1 : 2 in the range −4.2 to −5.1 ppm, whereas for the fluoride salt three doublets with a 1 : 2 : 2 splitting pattern at −4.6, −5.8, −6.0 ppm was observed. The chemical shift values for fluoride anions are moved further towards the negative region than the chloride and bromide salts. The appearance of doublets has been attributed to the ^{1}H-F coupling, and this kind of interaction was found to be absent in other salts. Further, the chemical shift values were found to be concentration dependent: on increasing the concentration of HF the N-H proton signal shifted substantially towards the negative region which indicated formation of higher aggregates. Thus, the^{1}H NMR study supported the formulation of tight in-plane pairing of fluoride

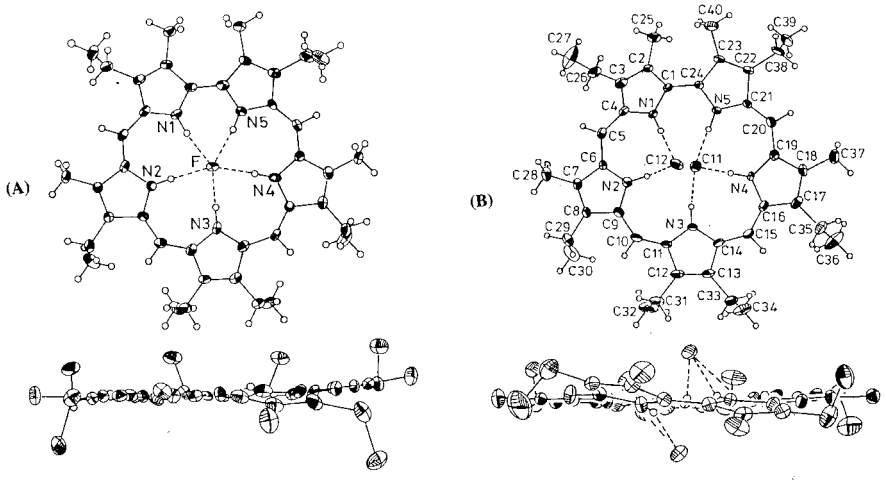


Figure 2. X-ray structures of sapphyrin-fluoride (A) and sapphyrin-chloride (B) complexes showing two views; (top) plane perpendicular to the nitrogen atoms and (bottom) plane through the nitrogen atoms. Reproduced from Reference 37 with permission.

ions in the solid state and it is interesting to realise the fact that the solid state structure was retained in the solution phase as well.

The absorption bands of the dihydrofluoride salt were shifted by about ~10 nm towards blue compared to the dihydrochloride and dihydrofluoride complex. The photophysical properties of these complexes revealed that the quantum yield and lifetimes are dependent on the nature of the counter ion employed and it has been found that the emission bands are strongly quenched in the case of dihydrochloride and dihydrobromide due to the internal heavy atom effect which enhances the nonradiative deactivation of the excited singlet state via a spin-orbit coupling mechanism. An increase in the concentration of the fluoride anions increases the fluorescence intensity and it was partly ascribed to charge neutralization and decreased rate of non-radiative deactivation of the singlet state due to the minimization of the N—H bond vibrational mode by the encapsulated fluoride ion [37]. A similar behaviour was observed for the core modified sapphyrin and rubyrin also. However, there is no solid state structure for a conclusive proof. The fluoride anion binding properties of S_3-sapphyrin and S_4-rubyrin were reported and the binding constant, revealed strong binding for S_3-sapphyrin ($K = 807\ M^{-1}$) relative to S_4-rubyrin ($K = 48\ m^{-1}$) [16]. However, these values are much smaller than those reported for pyrrole only expanded porphyrins. Spectral titrations of anions to a methanolic solution of **17** resulted in different degrees of binding for different anions depending on the nature of the rubyrin (Scheme 4). The binding constants decreased along the series $N_3^- > AMP > F^-$ [30a].

Diprotonated sapphyrins are not only good receptors of fluoride ions, but also efficient carriers across a proton gradient [45]. Translocation of anions can be ex-

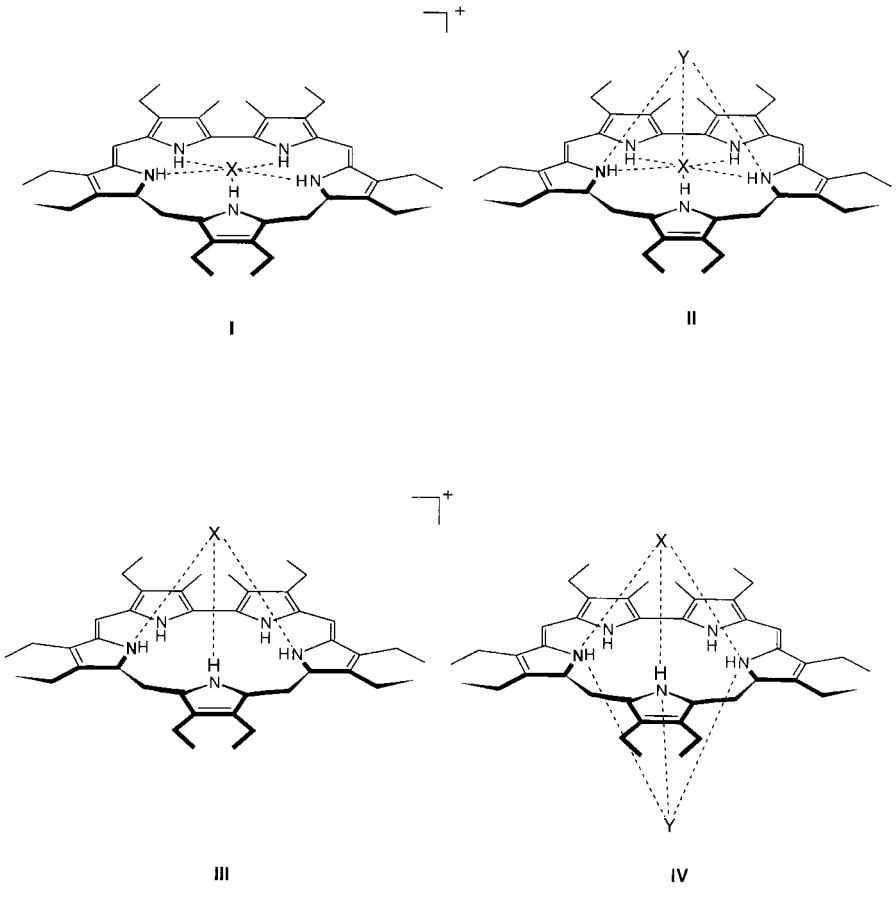


Figure 3. Possible modes of binding of anions with sapphyrins. Reproduced from Reference 37 with permission.

plained on the basis of antiport and symport mechanisms [46]. A system is said to be sym-coupled, if a pair of chemical species reside together in a receptor surface and anti-coupled if they compete with each other. The transport experiment was carried out in a U-tube containing three phases Aq I —CH_2Cl_2— Aq II, a model for a transport of ions across membranes. In the absence of the carrier, only slow uptake of fluoride into Aq II was observed, however addition of carrier enhances the fluoride ion concentration in Aq II phase (Scheme 5). This transport of fluoride anions in line with the symport mechanism and experimental evidence suggested anti-transport was not operating. A controlled pH experiment was performed to determine the optimum pH for an efficient transport and a pH of 3 was found

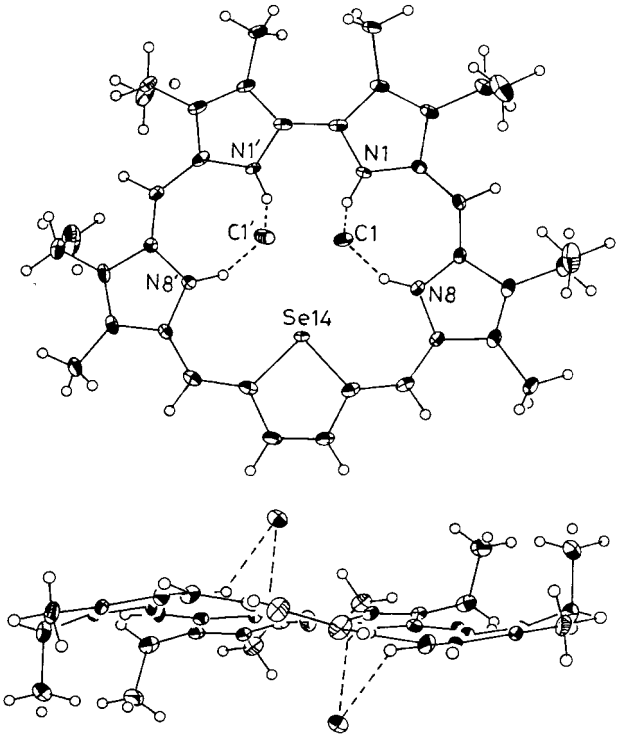


Figure 4. X-ray structure of the selenasapphyrin-chloride complex showing two views; (top) plane perpendicular to the nitrogen atoms and (bottom) plane through the nitrogen atoms. Reproduced from Reference 15c with permission.

to be the right choice. Addition of chloride in these experiments slightly inhibits the transport efficiency indicating a competitive binding of chloride and fluoride with protonated sapphyrins. Considering the extensive experimental evidence, it is highly likely that diprotonated sapphyrins act as an efficient and selective receptor and carrier of fluoride ions which has no parallels in porphyrin chemistry. Transport studies using rubyrin receptors **17** revealed transport of F and AMP with lowered transport rates than those observed for pyrrole only sapphyrins and rubyrins [30a].

Phosphate anions and their derivatives are involved in many crucial biological functions such as energy storage, information processing and gene replication [47, 48]. It has recently been discovered that some forms of phosphate derivatives are active against a wide range of disorders including in certain instances herpes simplex and AIDS [49, 50]. However their potential utility is severely limited to *in vitro*, and not in the *in vivo* use, due to their highly charged nature. To overcome this problem many different synthetic receptors have been designed and modeled to recognize and transport across the membranes. Sapphyrins which are highly effective in recognition and transport of fluoride anions have been found to be efficient receptors and carriers of phosphate anions. Solution phase studies of sap-

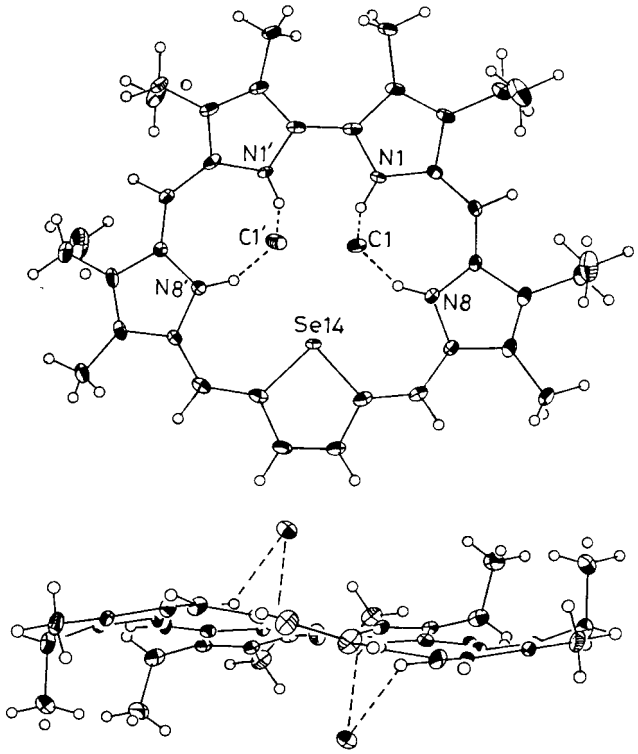
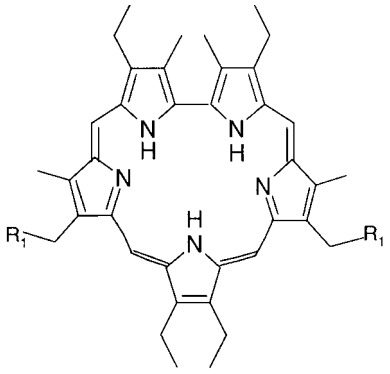


Figure 5. X-ray structure of the 1 : 1 complex of sapphyrin-benzoic acid showing two views; (top) plane perpendicular to the nitrogen atoms and (bottom) plane through the nitrogen atoms. Reproduced from ref. 43 with permission.



$R_1 = CH_2CON(CH_2CH_2OH)_2$ **19**
$= CH_3$ **20**
$= CH_2CH_2OH$ **21**

Chart 2.

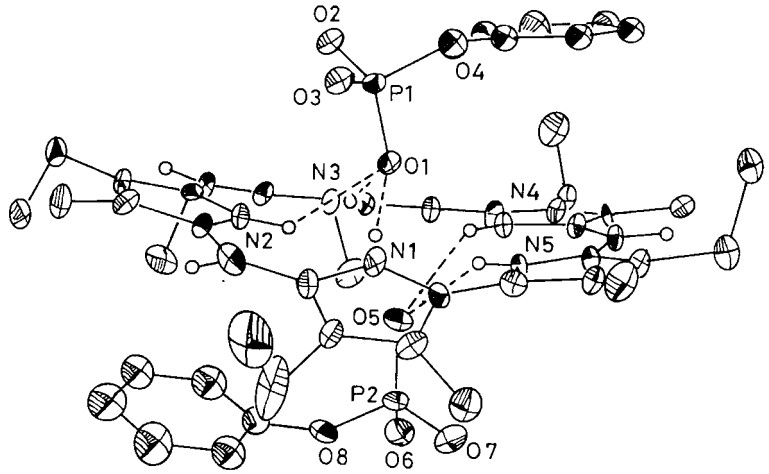


Figure 6. X-ray structure of the 1 : 2 complex of sapphyrin-monobasic bis(phenylphosphate) showing two views; (top) plane perpendicular to the nitrogen atoms and (bottom) plane through the nitrogen atoms. Reproduced from Reference 43 with permission.

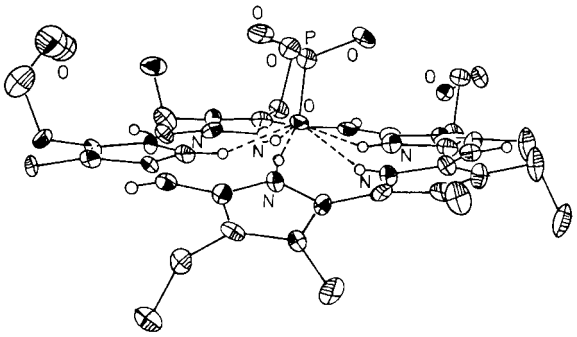


Figure 7. X-ray structure of the sapphyrin-monobasic phosphoric acid 1 : 1 complex. Reproduced from Reference 44 with permission.

phyrin derivatives **19** and **21** supported the formation of the sapphyrin-phosphate complexes. In ^{1}H NMR and ^{31}P NMR the methine proton and phosphorus were shifted more upfield than in their unbound state, suggesting complex formation. Absorption spectroscopy was used to delineate the formation of 1 : 1 from 2 : 1 sapphyrin-phosphate complex by monitoring the number of Q-bands in the visible region. Normally, three Q-bands are displayed by the free-base sapphyrin, however, for the 1 : 1 complex since the symmetry is lower 4 bands are seen and for the 2:1 complex only 2 bands are seen because of increase of symmetry [43, 44].

Sessler and his coworkers have shown that the protonated form of sapphyrins could serve as carriers of nucleotide bases [51]. This is important because the monophosphate derivatives of both 9-(β-D-arabinofuranosyl)adenine (Ara-AMP) and 9-(β-D-xylofuranosyl)guanine (Xylo-GMP) have been shown to have high

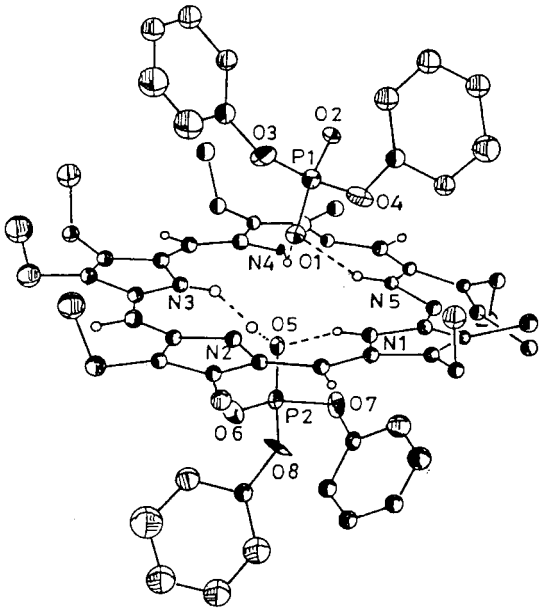


Figure 8. X-ray structure of the sapphyrin-diphenylphosphate 1 : 2 complex. Reproduced from Reference 43 with permission.

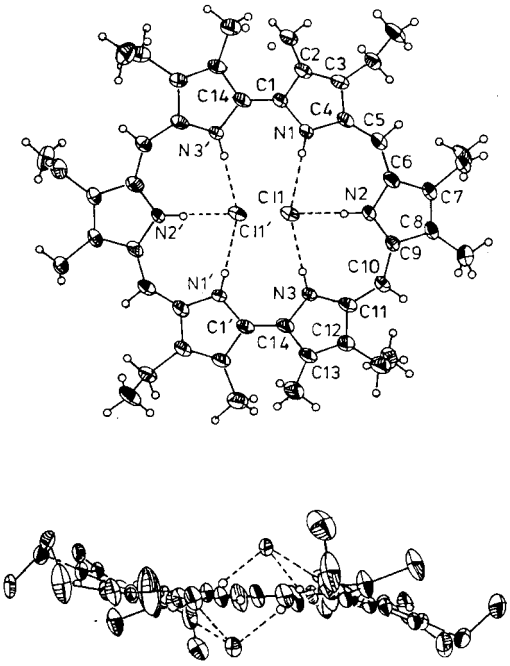


Figure 9. X-ray structure of the rubyrin-chloride complex showing two views; (top) plane perpendicular to the nitrogen atoms and (bottom) plane through the nitrogen atoms. Reproduced from Reference 43 with permission.

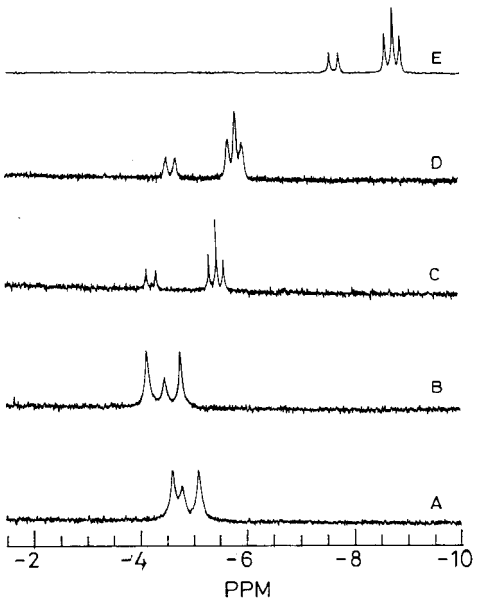
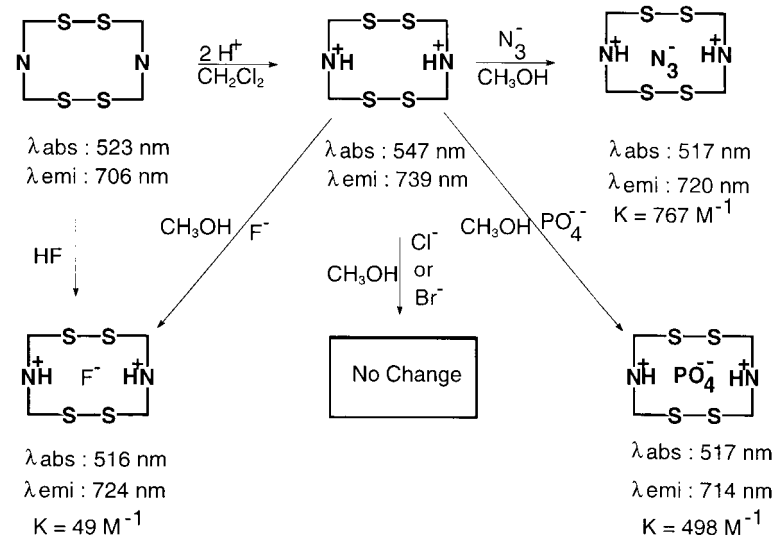
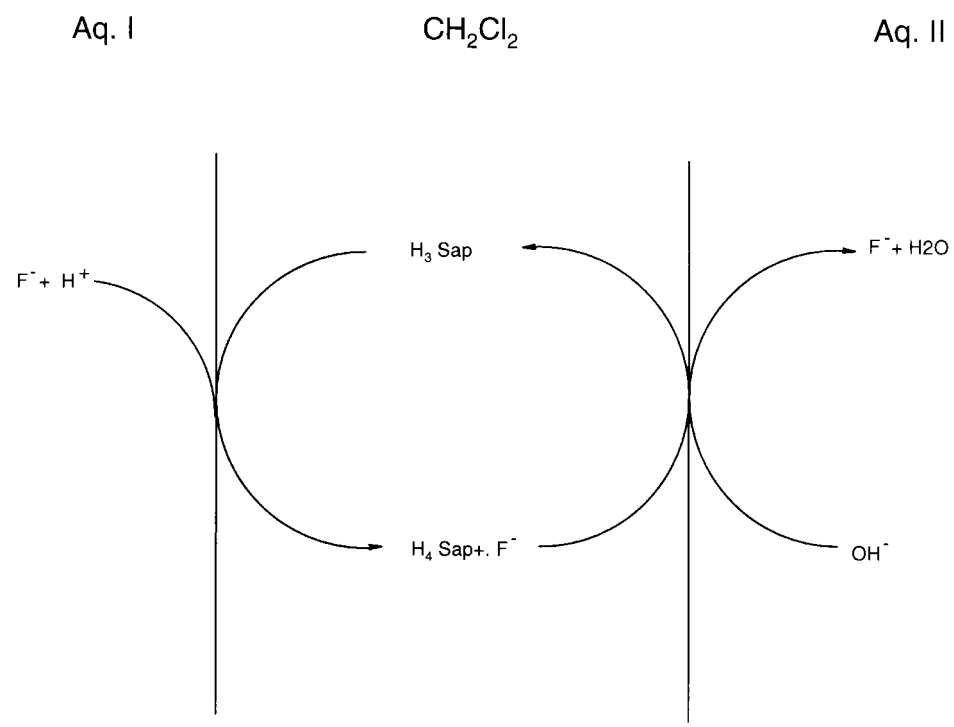


Figure 10. ^{1}H NMR of sapphyrin with various anions in the shielded region of the spectrum. (A) sapphyrin.2HBr, (B) sapphyrin.2HCl, (C) sapphyrin.HF.HPF_6, (D) sapphyrin.2HF (1 mM CD_2Cl_2) and (E) sapphyrin.2HF (30 mM CD_2Cl_2). Reproduced from Reference 37 with permission.



Scheme 4.



Scheme 5.

anti-HSV activity in cell free suspension [52]. The transport of nucleotides was carried out in a U-tube type, Aq I —CH_2Cl_2— Aq II, model membrane system. A pH of 3.5 was determined to be the ideal condition for effective transport across the lipophilic barrier prior to the U-tube experiment. Mononucleotides GMP, AMP and Ara-AMP were efficiently transported across the dichloromethane membrane at this pH. A possible 1 : 1 complex formed between sapphyrin and GMP is shown in Figure 11. Increase of pH or addition of competitive anions such as NaCl or NaF to Aq I leads to long induction periods for nucleotide transport. Peripheral modification of sapphyrins greatly amplifies the transport character, and towards this end cytosine and guanosine **22–25**, were attached via amide bond to the sapphyrin [53]. Cytosine was attached to the receptor sapphyrin for two reasons. First to solubilize the hydrophilic nucleotides in the lipophilic phase, so that transport can take place at neutral pH and second, to have a Watson–Crick type interaction for effective recognition and transport. Mono cytosine-sapphyrin conjugates have high selectivity in the recognition and transport of GMP compared to AMP or CMP. On the other hand guanosine-sapphyrin conjugate recognises and transports CMP selectively, in preference to GMP or AMP. Surprisingly, it was inferred that within the isomer of XMP, the receptors have high selectivity for the 2′-XMP and it was quantified in the case of the cytosine-sapphyrin conjugate. The rates of transport of 2′-GMP were roughly 10 times higher than those observed for 5′-GMP. Molecular modelling

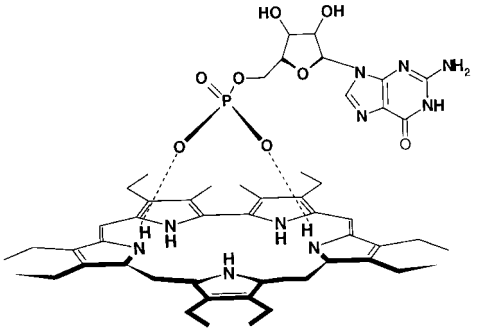


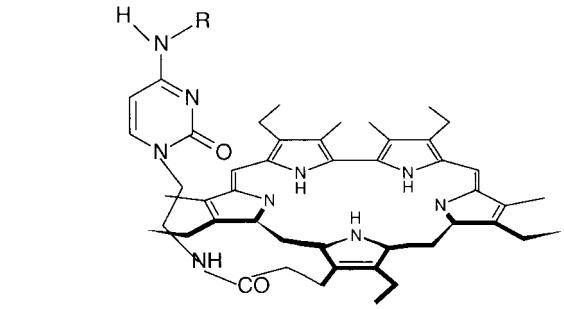
Figure 11. Proposed structure of the complex formed between sapphyrin-GMP. Reproduced from Reference. 51 with permission.

gave some clue to the differences in relative binding affinities. It was speculated that it was due to 5-GMP forming the complex in an unstable *syn* conformation, and 2′-GMP adopting a more stable *anti* conformation [54]. The supramolecule formed on mixing the sapphyrin and mono basic GMP isomers is shown in Figure 12. Linking a second cytosine to the sapphyrin decreases the selectivity in recognising GMP relative to AMP or CMP due to a increase in possible number of hydrogen bonds.

To facilitate recognition of nucleotide di- and tri-phosphates oligosapphyrins were synthesised [55, 56]. The sapphyrin monomers were connected via amide spacer groups. Although, mono- and di-phosphates were effectively transported across the membrane model system trimeric sapphyrins **26** and **28**, but failed to transport the tri-phosphates. On the other hand, tetrameric sapphyrin **29** transports triphosphates easily. In all these cases **26–29** adenosine based nucleotides were found to be more easily transported than those derived from uridine, cytosine or guanosine.

Water soluble sapphyrin derivative **19** was highlighted to form a complex with DNA in a way different from other traditional noncovalent interactions described by intercalation, groove binding and simple electrostatic interaction [43]. The authors verified [57] various experimental evidence to determine that sapphyrin interacts with DNA via phosphate recognition, a theme observed in the solid state structure of the sapphyrin-phosphate complex. In this context, the phosphate recognition by the sapphyrin was exploited for the separation of nucleotides from mixtures, by linking the sapphyrin macrocycle to silicagel. AMP, ADP and ATP were clearly separated from each other on the sapphyrin column but at the same time could not be separated on the DEAE column at neutral pH. Thus, the sapphyrin appended silicagel column was noteworthy in separating the simple nucleotides which is otherwise not possible in the commercially available HPLC columns [58].

Dicarboxylate recognition and transport is also made possible by the versatile sapphyrin platform. Linear and cofacial sapphyrin dimers were reported to display excellent recognition properties for various dicarboxylate anions [42]. In the ab-



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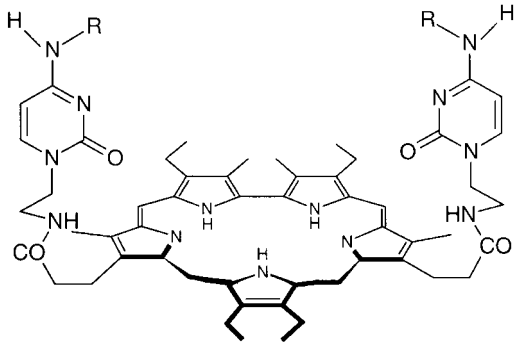

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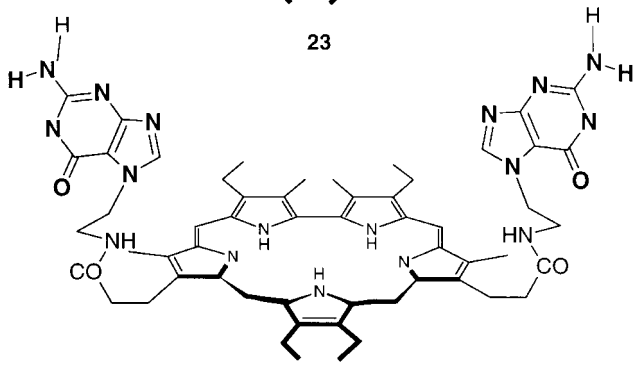

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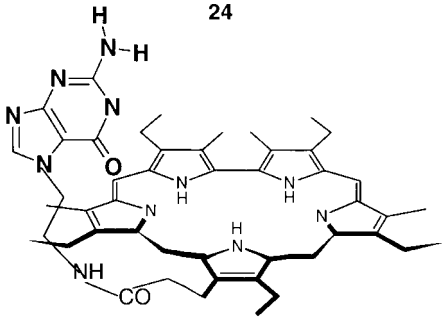

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Chart 3.

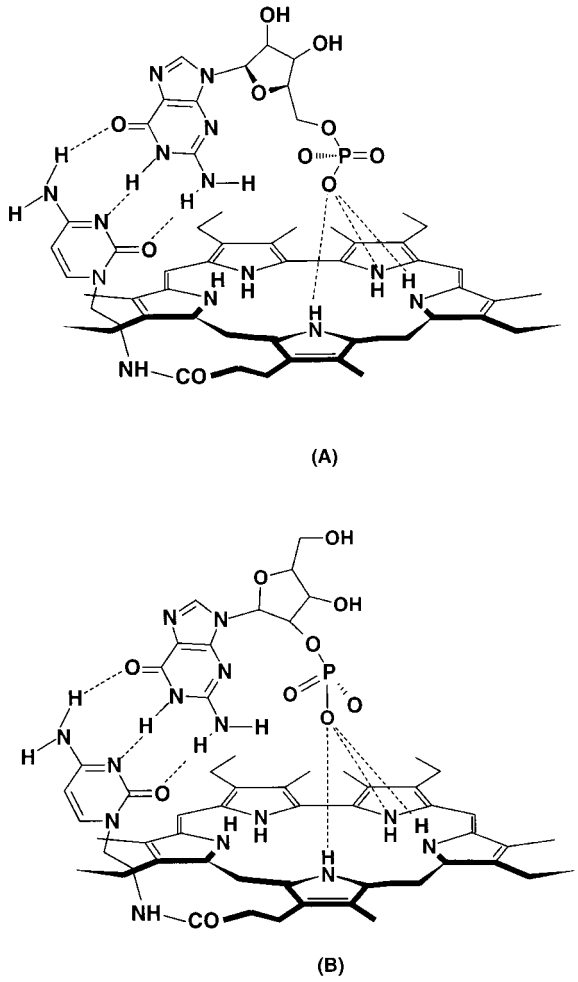
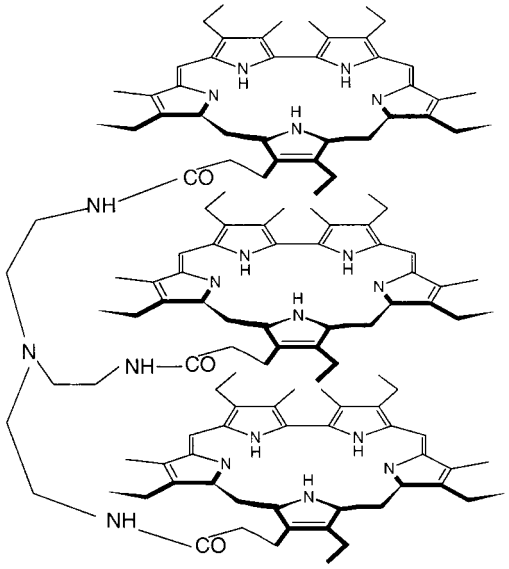


Figure 12. Proposed structure of the complex formed between (A) sapphyrin.5′-GMP in *syn* conformation and (B) sapphyrin.2′-GMP in *anti* conformation. Reproduced from Reference 54 with permission.

sorption spectra of sapphyrin dimer **27** two bands (422 and 441 nm) are seen which are attributable to folded and open conformers. Upon addition of dicarboxylate anions an increase in intensity at 441 nm at the expense of the 421 nm band, was stated to be consistent with a binding model (Scheme 6) wherein the dicarboxylate anion binds inside the cavity of the two sapphyrin subunits in a sandwich fashion. These dimers transport dicarboxylate anions across the artificial membrane with high selectivity, often aromatic substrates were preferred over aliphatic ones and it has been rationalized in terms of π-π interaction or edge bound C—H—N or C—H—π hydrogen bonding interactions involving the aromatic platforms of the sapphyrin receptor and phenyl containing substrates. The presence of this



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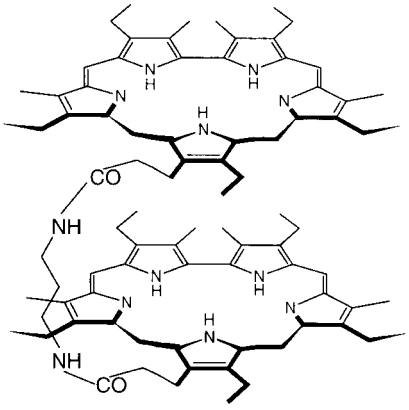

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Chart 4.

type of interaction was confirmed from the solid state structure of the sapphyrin-benzoic acid 1 : 1 complex wherein hydrogen bonding C—H—N contact was seen. The extension of recognition characteristics to chiral dicarboxylates needs chiral containing receptors. Based on this idea chiral containing sapphyrins were made and their selectivity was probed with chiral dicarboxylate species, specifically, *N*-carbobenzyloxy-protected aspartate and glutamate anions. Binding studies re-

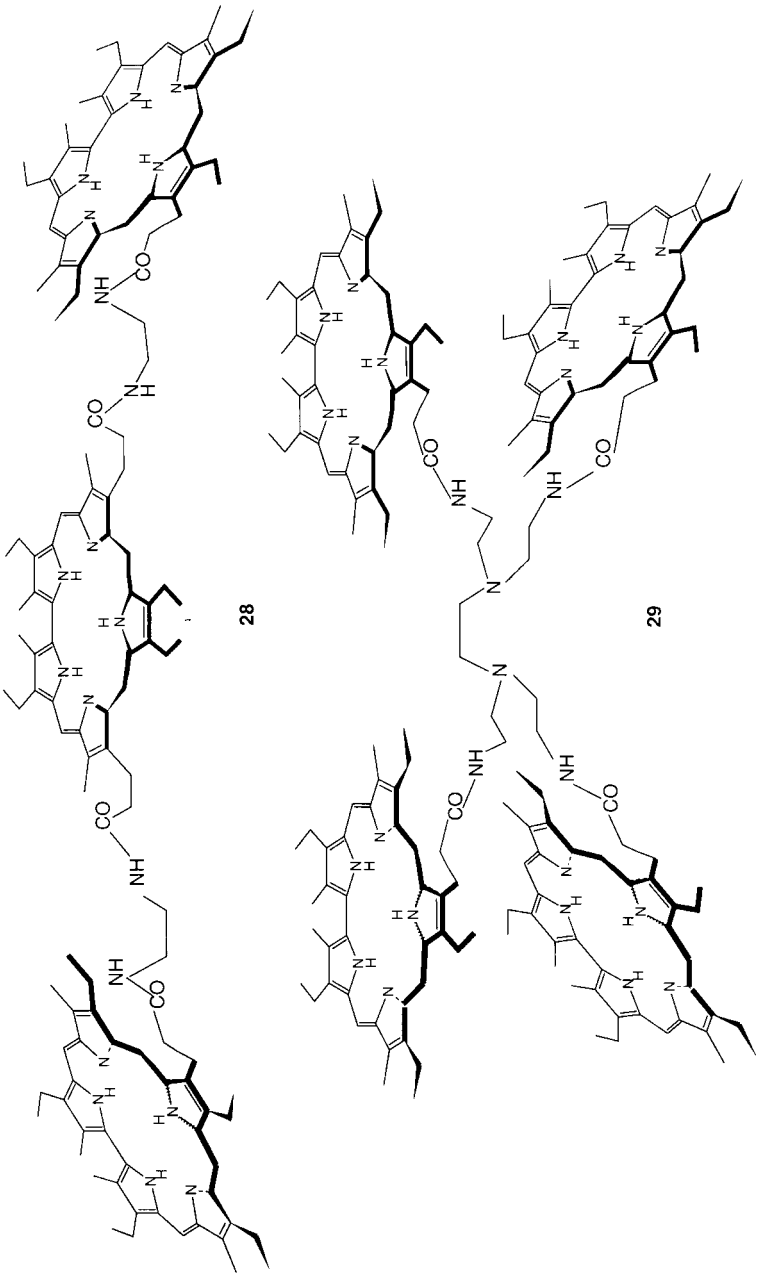
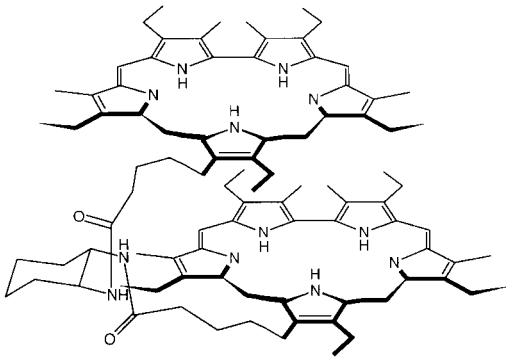


Chart 5.



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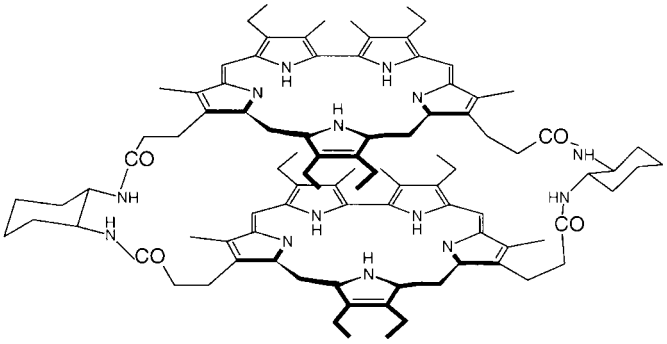

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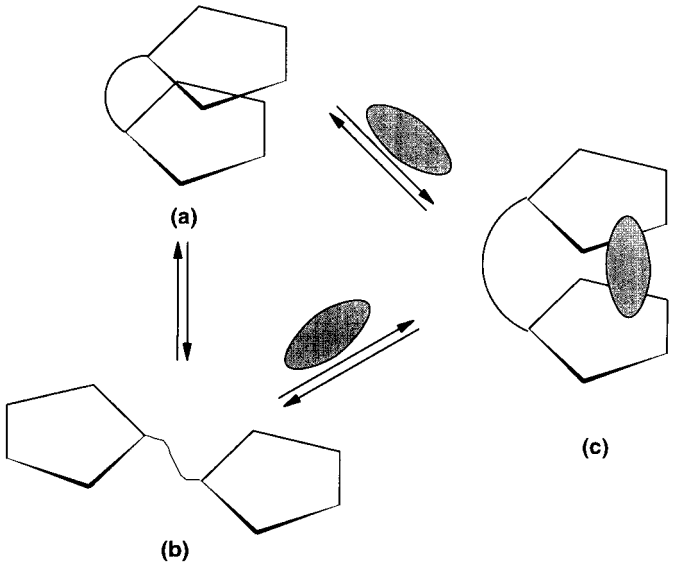
Chart 6.

vealed that chiral sapphyrin dimers **30** and **31** bind both these substrates strongly but, shows selectivity for glutamate over aspartate [57].

Sapphyrin-lasalocid conjugates [59] were found to be efficient receptors and carriers of amino acids such as phenylalanine, tryptophan and tyrosine. Sapphyrin-lasalocid conjugate **32** transports these amino acids at neutral pH and it was shown that L-amino acids are transported with greater efficiency than D-antipodes, however, the binding affinities for these two enantiomers was the same and hence, it was pointed out that not only is the binding of the substrate an essential condition but also the substrate release rates are important in terms of mediating transport efficiency. Among these amino acids, L-phenylalanine was transported four times faster than L-tryptophan and a thousand times faster than L-tyrosine. A proposed mechanism for amino acid transport mediated by the sapphyrin-lasalocid conjugate

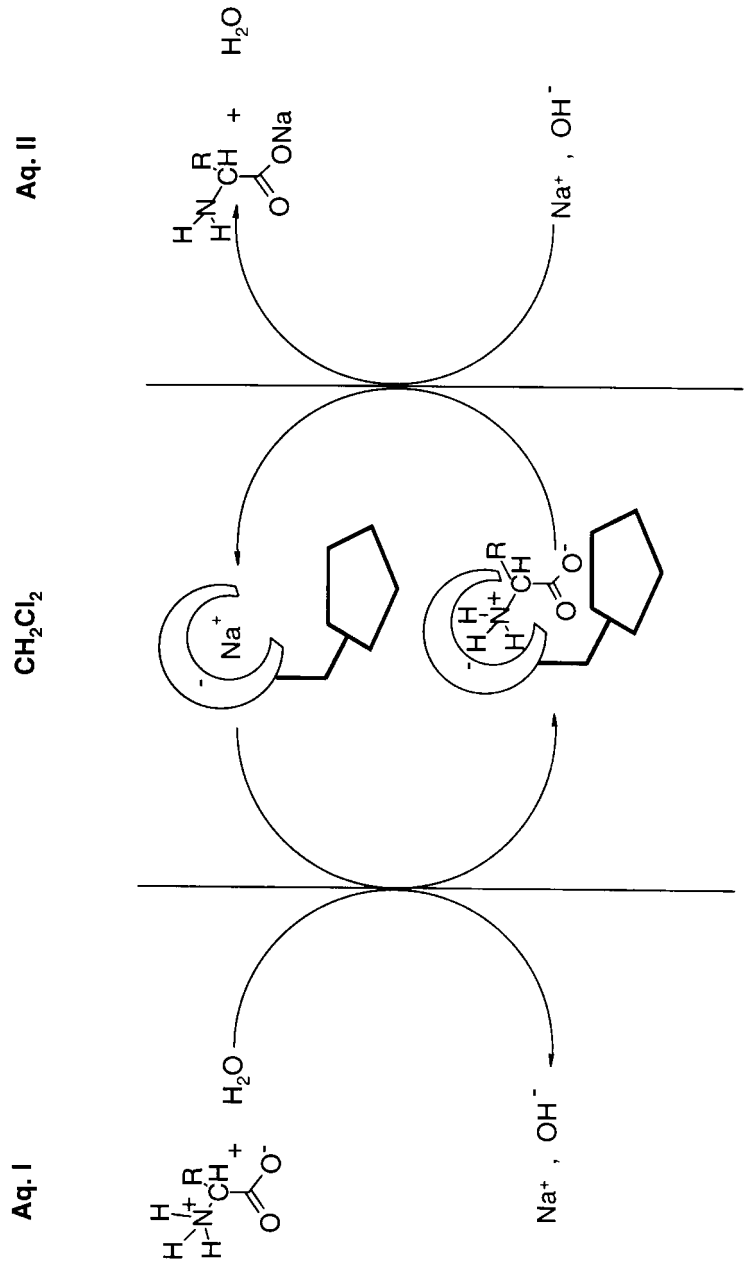


Scheme 6.

is shown in Scheme 7. In order to enhance the carrier ability to transport zwitterionic amino acids the sapphyrin-lasalocid conjugate was attached to phenylalanine residue **33** and **34**. Depending upon the nature of the phenylalanine residue (D or L) the zwitter ionic carrier shows selectivity. For example, if D-phenylalanine residues were present then D-phenylalanine was transported and vice versa.

5. Conclusions

Nature has developed an efficient mechanism by which anions are recognised and transported across membranes for multiple and diverse functions. Mimicking or modelling these processes which are of biologically significance would need versatile synthetic platforms. Understanding the intricate mechanistic details of recognition and transport could eventually lead to the design of drug delivery systems. Thus, expanded porphyrins discussed in this review promise to be one of the potential candidates as an abiotic molecular receptor and carrier of anions. Since, synthesis by itself is the art of making molecules, it may be possible to make an anion specific receptor, as exemplified in the selective transport of fluoride over chloride or bromide anions. Photodynamic therapy (PDT) is another area where the expanded porphyrins like texaphyrin, which is not a subject of this review, promises to be an effective photosensitizer for killing cancer cells. Furthermore, expanded porphyrins can be used to remove radioactive materials like the lanthanide and actinide series of elements from radioactive waste for better environment, as sapphyrin is known to form complexes with larger cations such as uranium. Some of the functions of the metalloproteins and enzymes could be modeled to elucidate the



Scheme 7.

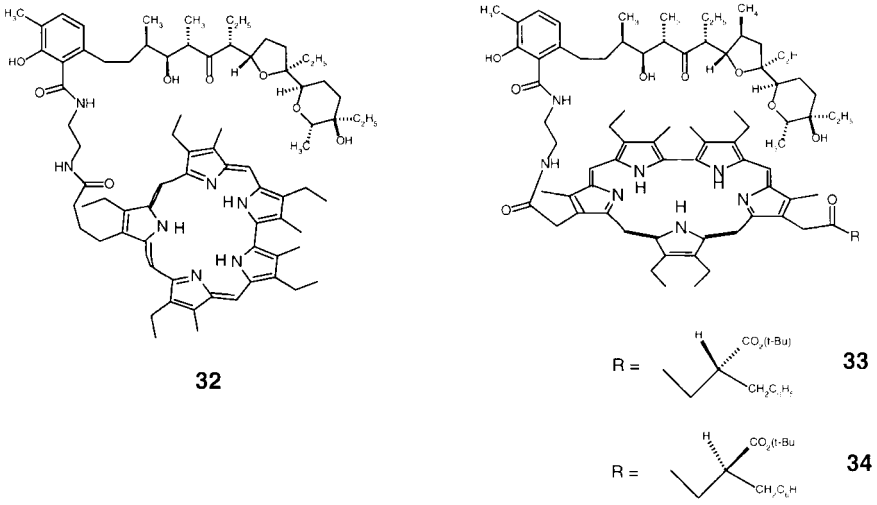


Chart 7.

biosynthetic pathways using expanded porphyrins instead of traditional porphyrins. Finally, one can anticipate that this stimulating field of research would eventually lead to greater understanding of its chemistry and its hidden properties.

Acknowledgments

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