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MACROCYCLIC RECEPTOR MOLECULES: ASPECTS OF CHEMICAL REACTIVITY. INVESTIGATIONS INTO MOLECULAR CATALYSIS AND TRANSPORT PROCESSES.

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Abstract - Macropolycyclic receptor molecules form supramolecular structures by selective binding of suitable substrates. In addition to recognition, such supermolecules may perform two other functions, molecular catalysis and membrane transport if appropriate reactive sites or structural units are introduced into the receptor. A chiral macrocyclic receptor which binds primary ammonium salts has been modified so as to perform reactions on the bound substrate. Accelerated hydrogen transfer occurs inside the receptor-substrate complex between a derivative bearing dihydropyridine groups and bound pyridinium salts. Another derivative fitted with (*L*)-cysteinyl residues displays enhanced rates of intracomplex thiolysis of p-nitrophenyl esters of amino-acids and dipeptides; the reactions show marked structural selectivity; high chiral recognition is also observed for enantiomeric dipeptides esters. Various aspects of transport processes are discussed. Amino-acid transport may be pumped by acid-base reactions. Macrobicyclic cryptands function either as selective receptors or carriers for alkali cations. The transport rates depend on the carrier, the cation and the anion. They are discussed in terms of complexation and phase distribution properties. Simple structural modifications of cryptands allow the conversion of receptors into carriers. The anion of the transported salt also affects markedly the rates. The results provide guidelines for carrier design. Finally, electron transport systems using redox carriers are described; the following processes have been realized: electron/anion antiport, electron/cation symport (in presence of a selective cation carrier) and electron transport driven by visible light irradiation.

The design of receptor molecules, the binding of substrates via intermolecular interactions, the properties of the resulting "supermolecule", constitute a *chemistry of the intermolecular bond* (Ref. 1-3). Like a covalent bond, it has an energy and a geometry, a stability and a reactivity. Thus, receptor-substrate association may be considered as a form of chemical reactivity involving reactions which result in the breaking and formation of intermolecular bonds, just as molecular reactions break and make covalent bonds. The study of such *supramolecular reactivity* covers the structure, the shape, the stereochemistry of the receptor-substrate association, its stability and selectivity, its rates of formation and dissociation, the modification of the individual properties of its components within the complex, as well as the intracomplex reactions.

A supermolecule may thus display several functions:

- *recognition* of the substrate among a collection of species;
- *molecular catalysis* by reaction of catalytic sites borne by the receptor with the bound substrate(s);

- *transport* of the substrate across a membrane, if the receptor bears groups which enable the receptor-substrate pair to dissolve into it.
- Higher forms of molecular organization and function, *cooperativity and regulation*, might also be brought about in *multi-site* receptor molecules via simultaneous or sequential (cascade) binding of several substrates which interact with each other.

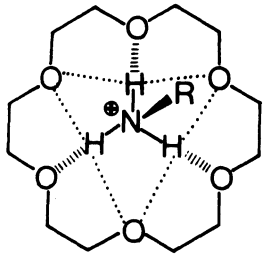
As pointed out earlier (Ref. 1-3), *macropolycyclic molecules* possess structural features which make them ideal candidates for the design of receptors, catalysts and carriers. Indeed the multiple bridges present in such molecules provide ideal means of delineating the *size* and *shape* of the receptor cavity, of maintaining appropriate *conformations* to fit the *intermolecular stereochemistry* of the binding interactions, of introducing reactive sites in the desired *location* and *orientation*, etc.

Cryptate complexes result from the inclusion of a substrate into a macropolycyclic cavity. Their stability and selectivity, their kinetic and thermodynamic properties etc. are all aspects of the chemical reactivity associated with the receptor-substrate combination. Macrobicyclic and macrotricyclic receptors and their cryptates have been described and reviewed in earlier reports (Ref. 1-3 and references therein). In the present account, the discussion of molecular receptor design will be limited to a brief summary of the results on the binding of ammonium salts by functionalized chiral macrocycles. Thereafter we shall describe our work towards the *design of macrocyclic molecular catalysts* and of *selective carrier molecules*, two areas which represent major aspects of molecular reactivity and function: catalysis and transport.

Cryptate formation may also markedly affect the properties of the complexed species (e.g. modification of pK_a's, of redox potentials, etc.) or of its counterion (e.g. anion activation); such effects on chemical reactivity will not be discussed here; they have been reviewed earlier (Ref. 2 and references therein)

MACROCYCLIC RECEPTOR MOLECULES

Macrocyclic polyethers or aza-polyethers of the "18-crown-6" type form complexes with primary ammonium salts $R\text{-}NH_3^+$ by inclusion of the anchor group $-NH_3^+$ into the central circular cavity of the ring (Ref. 4-8). The binding is essentially electrostatic in nature. Since the charge is located on the three hydrogens of the $-NH_3^+$ group (Ref. 9-11), its interaction with the ring oxygens may be described as involving a double bonding pattern: a first array of three linear $N\text{—}H^+\cdots O$ hydrogen bonds (see the crystal structure of the 18-crown-6, NH_4Br complex, Ref. 8a) and a second array of six electrostatic interactions which may be considered to form weaker, bent hydrogen bonds, as pictured in structure 1. This and other bonding schemes (for instance with the $-NH_3^+$ group rotated by 30° in structure 1; see however Ref. 8a) are being explored theoretically (10b).



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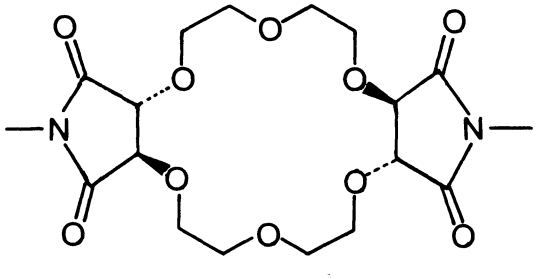

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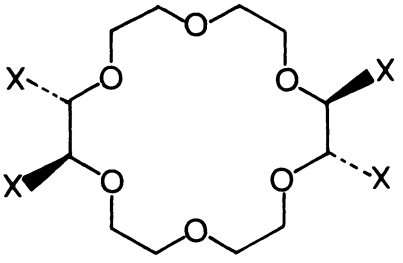
The complexation ability of 18-crown-6 type ligands has been the basis of a wide exploration of modified structures. Chiral derivatives (Ref. 5, 6), especially those containing a binaphthyl group as chiral unit inserted into the macrocycles (Ref. 5), have been shown to resolve racemic ammonium salts. However the presence of aromatic units, like benzo and binaphthyl groups, markedly decreases the complexation ability of the parent structure (Ref. 4, 12).

Our own work employed as basic unit the chiral macrocycle 2 (Ref. 13) which has three attractive features: it retains the structure of the parent macrocycle, all oxygen sites being aliphatic ethers; it bears four functions which may be used for further structural modifications; it is chiral and of known absolute configuration.



2 X = $CONMe_2$

4 X = $CONBu_2$

5 X = $CONH-CH_2-CH_2-N$ (CONHBu)

7 X = $CONH-(L)-CH(CH_2SH)-COOMe$

Attachment at positions X of various groups which may interact with the bound ammonium substrate allows a modulation of the *receptor* properties of such macrocycles and opens ways to the design of molecular *catalysts* if the units X contain reactive functions. A number of derivatives of the basic structure have been prepared in which groups X contain charges, lipophilic fragments, amino-acid residues etc. Their complexation properties towards ammonium cations will only be briefly summarized here (see ref. 3, 7, 14)*.

Very pronounced *central discrimination* is observed between primary $R-NH_3^+$ and more highly substituted ammonium salts since only the former group is able to bind to the macrocycle following scheme 1, whereas binding of the latter is sterically hindered.

Lateral discrimination manifests itself in modifications of the stability constants of the ammonium complexes as a function of the groups attached to the positions X of the macrocycle. Effects resulting from electrostatic, hydrophobic and charge-transfer type interactions have been observed depending on the nature of the groups X and of the substrate. Very stable complexes may be obtained, for instance when X=carboxylate or tryptophanate in 2. Electrostatic cation-anion interactions contribute strongly both to stability and selectivity by lateral effects, whereas the macrocyclic cavity markedly affects the binding selectivity via steric factors.

A striking example of the effect of *conformation* and *intermolecular stereochemistry* on complexation ability is given by compound 3. Closing the fused imide rings severely

* Idealized axial type orientations have been pictured throughout for the X groups in compounds 2, 4, 5, 6, 7 (see also Fig. 1, 2, 5), but equatorial orientations may also occur; in view of the crystal structure of the [18-crown-6, NH_4^+] complex (Ref. 8a) two vicinal X groups may be quasi-axial and the other two quasi-equatorial in the same molecule; these points will be discussed elsewhere (Ref. 14).

distorts the conformation of the macrocycle which therefore does not provide anymore the arrangement of intermolecular interactions required by simultaneous binding to the oxygen sites. Whereas the stability constant of the complex of K^+ with 2 is about 30 000, it is <10 with 3! (in methanol/water 95/5; Ref. 13). The same holds for the binding of ammonium salts. Weakening of binding by ring distorsion may also contribute to the lowering of stability constants in the binaphthyl-crowns (Ref. 12; see also the crystal structure of a complex, Ref. 8b). Idealized representation of the conformations of the macrocycles 2 and 3 are shown in Figure 1.

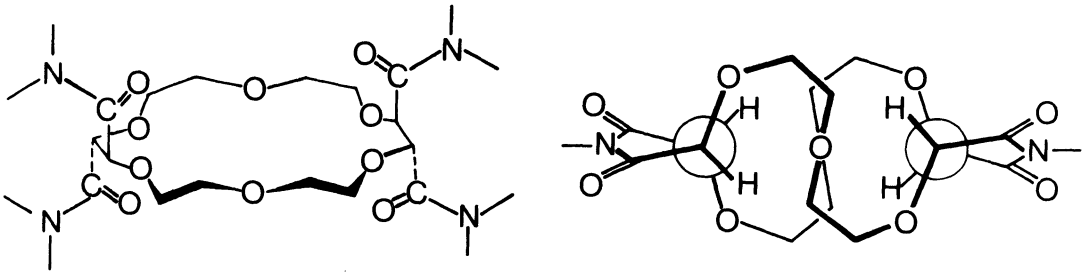


Fig. 1 Idealized conformations of macrocycles 2 (left) and 3 (right)

A more detailed description of the complexation properties of macrocyclic receptors derived from 2 will be given elsewhere (Ref. 14). Lipophilic derivatives like 4 may be used as efficient and selective carriers for membrane transport experiments.

MOLECULAR CATALYSIS. RATE ENHANCEMENT, STRUCTURAL AND CHIRAL RECOGNITION IN COMPLEXES OF REACTIVE MACROCYCLIC RECEPTOR MOLECULES.

The design of highly efficient and selective molecular catalysts may provide model systems revealing the factors responsible for enzyme catalysis, as well as new types of chemical reagents for use in mechanistic studies and in synthetic applications. Such artificial systems present in principle the advantage that their properties may be tuned to a given set of requirements by appropriate structural modifications.

A molecular catalyst should possess the following set of properties:

- selective substrate binding,
- fast and selective reaction with the bound substrate,
- regeneration of the reactive site after reaction,
- fast rates of association and dissociation of the substrate and product,
- high turnover, i.e. high stability to the reaction conditions.

Macropolycyclic systems are of special interest for the design of synthetic molecular catalysts since they may be constructed so as to provide both a receptor site for substrate binding and a reactive site for transformation of the bound substrate.

The ability of cyclodextrins to complex lipophilic substrates lead to the preparation of a variety of derivatives which react with the bound molecule and display rate enhancement and structural selectivity (Ref. 15). Synthetic macrocycles containing a hydrophobic cavity and bearing a reactive site have been studied (Ref. 16). More recently, the development of macropolycyclic receptors capable of binding polar substrates opened another way to the design of molecular catalysts. Thus, functionalized macrocyclic polyethers have been shown to display substantially enhanced rates of thiolysis of bound amino-ester salts (Ref. 17, 18) and of hydrogen transfer from a 1,4-dihydropyridine contained in the macrocycle to a sulphonium salt substrate (Ref. 19). Our own work has been directed towards the use of the

macrocycle 2 as a basic system for studies directed towards molecular catalysis. Two types of reactions have been investigated first: hydrogen transfer and trans-acylation.

Hydrogen Transfer from a Dihydropyridine Macrocyclic Receptor to Bound Pyridinium Substrates (Ref. 20).

Reductions by 1,4-dihydropyridine type reagents are reactions of great biological interest and present intricate mechanistic problems. A number of model studies have been reported in which intermolecular hydrogen transfer occurs. Our own interest focuses on realizing hydrogen transfer between a 1,4-dihydropyridine (DHP) unit and a pyridinium ion (P^+) inside a synthetic receptor-substrate complex. Intermolecular models for DHP to P^+ H-transfer have been reported in the literature (see for instance ref. 21, 22). Starting from the macrocycle 2, compound 5 bearing four DHP units was synthesized. It contains a receptor site and four reactive groups: it may thus bind appropriate substrates bearing $-NH_3^+$ anchor functions and reduce them by H-transfer. Indeed the pyridinium salts (S_1) and (S_2) were found to bind to 5. A schematic representation of the supramolecular structure [(S_2), 5], 6, resulting from binding of substrate (S_2) to receptor 5 is shown in Figure 2; the exact conformations of the side chains and of (S_2) in the complex are not known at present.

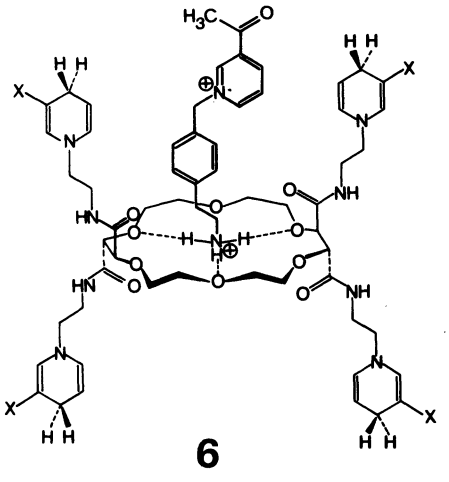


Fig. 2 Schematic representation of the complex of receptor 5 with substrate (S_2) (X=CONHBu).

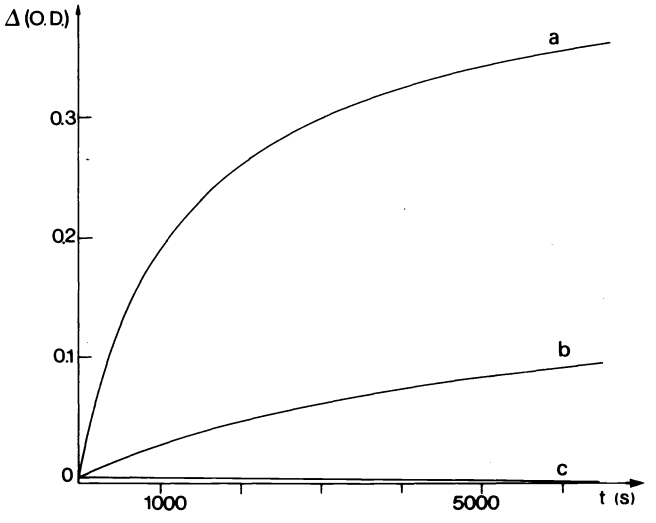
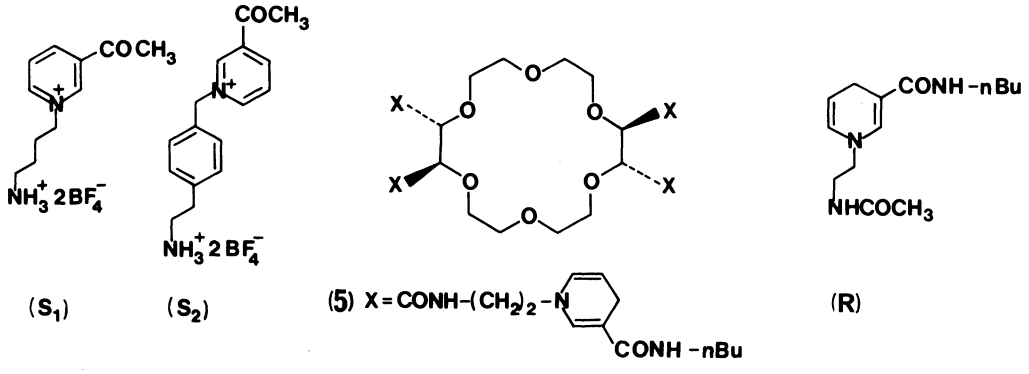


Fig. 3 Time dependence of the absorption at 400nm for 5 + (S_2) (curve a); in presence of excess KBr (curve b); in presence of excess $^+H_3NCH_2CH_2NH_3^+$ (curve c); in acetonitrile at 23°.

When substrates (S_1) and (S_2) are added to 5, changes occur in the electronic spectrum of the mixture; they correspond to the reduction of (S_1) and (S_2) to their 1,4-dihydro derivatives. Figure 3 shows the changes in optical density observed as the reaction proceeds. The rate constants obtained by analysis of the kinetic data are presented in Figure 4. The reaction between 5 and (S_1) or (S_2) is first order, implying that it is *intramolecular* and occurs in a *preformed complex*. When excess K^+ is added the intracomplex reaction is inhibited; the process becomes intermolecular with second order kinetics and its rate decreases, getting comparable to that found for reduction of (S_1) by reagent (R) (Fig. 4).



	$S_1 + 5$	$S_2 + 5$	S_1 OR $S_2 + 5 + K^+$	S_1 OR $S_2 + 5 + NH_3^+(CH_2)_4NH_3^+$	$S_1 + R$
k_1 (s^{-1})	$1.2\ 10^{-4}$	$2.5\ 10^{-4}$	-	-	-
k_2 ($M^{-1}s^{-1}$)	-	-	$1.2\ 10^{-2}$	$< 10^{-4}$	$1.2\ 10^{-2}$

Fig. 4 Rate Constants for Dihydropyridine to Pyridinium Hydrogen Transfer (Solvent CH_3CN; 25°C).

This results from the displacement of the substrate from the receptor site by the more strongly complexed K^+ cation. Even stronger inhibition is observed when the diammonium salt $H_3N^+(CH_2)_4NH_3^+$ is added, probably because of combined displacement and electrostatic effects. Like in the case of pyridine nucleotide coenzymes, a subsequent reaction would be required for regenerating the DHP units of 5 after reaction.

Rate Enhancement, Structural and Chiral Recognition in Thiolysis of Substrates Bound to a Reactive Macrocyclic Receptor (Ref. 23).

The tetrakis-(*L*)- cysteinyl methyl ester receptor molecule 7, synthesized from 2, should be able to react with active esters in a transacylation reaction releasing the alcohol fragment, as also observed with other crown ethers bearing thiol groups (Ref. 17, 18). Primary ammonium salt- active ester substrates of type H_3N^+-R-COOPNP (PNP: para-nitrophenyl) are expected to bind to and to react with 7, releasing para-nitrophenol and forming an internally complexed -S-acyl-Catalyst derivative. The process is illustrated in Figure 5 for the glycyl-glycine-OPNP substrate.

Reagent 7 indeed complexes the salts of a variety of primary amino-esters. When NH_3^+-R-COOPNP substrates are added to 7, *large rate accelerations* for p-nitrophenol release are observed, up to acceleration factors of about 1900 or 15000 (in different conditions) for the complex [Gly-Gly-OPNP, 7] with respect to (7) + (*L*)-Pro-Gly-OPNP (Figure 6). The latter substance, being a bulky secondary ammonium salt is at best only weakly complexed by 7 and may serve as a satisfactory reference compound.

An analysis of the reaction of 7 with Gly-Gly-OPNP shows *saturation kinetics* which change to second order kinetics when excess KBr is added for inhibiting the intracomplex reaction by displacement of the substrate.

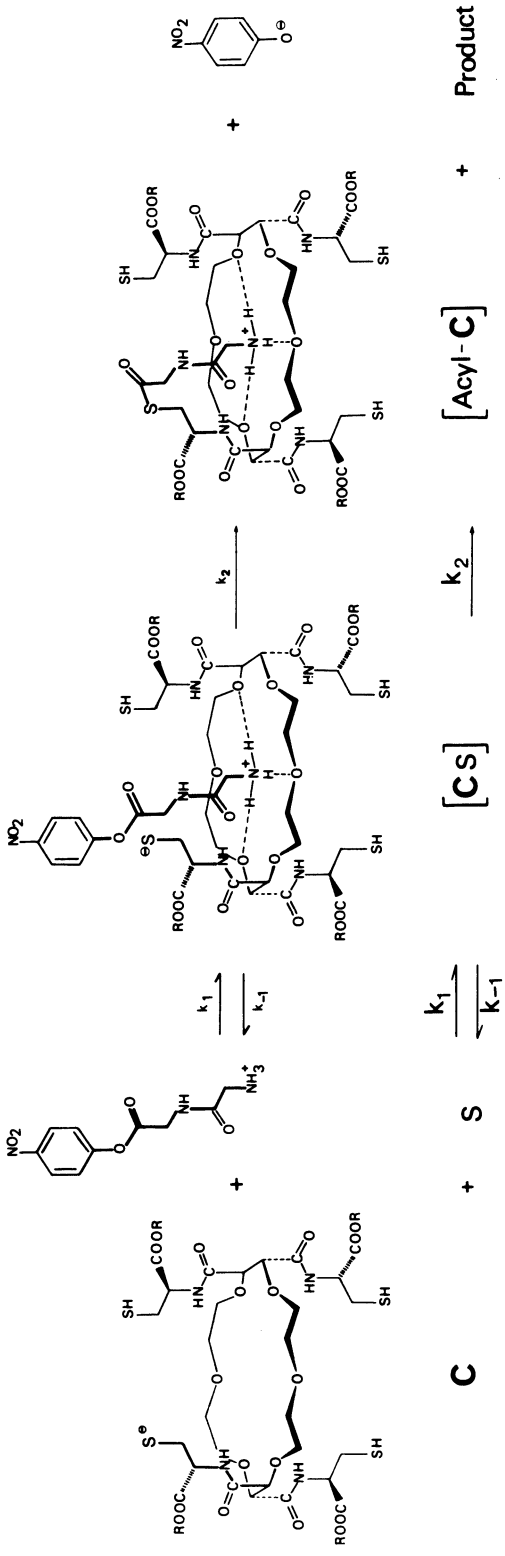


Fig. 5 Complexation and thiolysis of glycyl-glycine-p-nitrophenyl ester by the reactive receptor molecule 7.

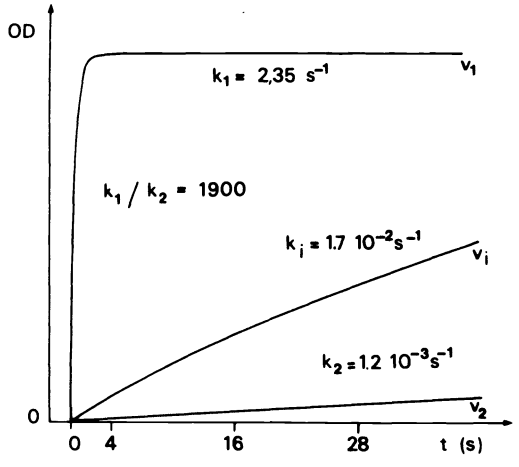


Fig. 6 Enhanced rates of intramolecular thiolysis; v_1: 7 + Gly-Gly-OPNP; v_i: same as v_1 with inhibition by KBr; v_2: 7 + (*L*)-Pro-Gly-OPNP (rates corrected for reaction with buffer).

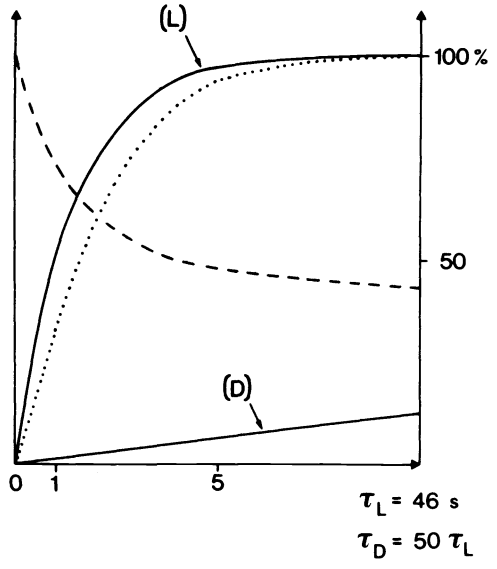


Fig. 7 Chiral recognition in the thiolysis of enantiomeric dipeptide ammonium esters; OD (—): observed changes in optical density for *p*-nitrophenol release from Gly-(*L*)-Phe-OPNP (L) and from Gly-(*D*)-Phe-OPNP (D); (---): percentage of remaining unreacted ester starting from racemic (*DL*) ester; (....): percent enantiomeric excess in remaining (*D*) ester starting from racemic (*DL*) ester computed from the (L) and (D) curves); the abscissa unit is the half-life τ_L (=46s) of the reaction (L).

The rate acceleration factors display appreciable *structural selectivity* among the various amino-esters used. The best substrates are dipeptide esters, especially Gly-Gly-OPNP which reacts with compound 7 much faster than the esters of α, β or γ-amino-acids.

Finally, *high chiral recognition* is found for the reaction of 7 with the enantiomeric dipeptide esters Gly(*L*)-Phe-OPNP and Gly-(*D*)-Phe-OPNP, the former reacting 50 to 90 times faster depending on the medium (Figure 7). A rate factor of 8 was observed for thiolysis of enantiomeric substrates by a chiral binaphthyl crown reagent (Ref. 17). Subsequent rapid deacylation of the acyl-catalyst derivative (Figure 4) formed in the above reactions will be required for reagents like 7 to be true catalysts.

In conclusion, the reactive receptor molecules 5 and 7 display a number of properties which a molecular catalyst should possess, i.e. properties of an abiotic enzyme model: selective substrate binding, intracomplex reaction with rate acceleration, inhibition by unreactive species which compete for the binding site, structural selectivity and chiral recognition towards the substrates. More precisely designed receptors and catalysts may be developed ; other reactive groups may be introduced allowing other types of reactions to be studied. The development of molecular catalysts represents a wide open field of research which has bearing on a variety of both chemical and biological processes.

TRANSPORT PROCESSES AND CARRIER DESIGN

Research in transport through membranes has been actively pursued in the physico-chemical and above all in the biological fields. Comparatively little work has come from organic chemistry although there are numerous aspects in which it might make important contributions to this broad field overlapping many scientific areas.

Among the different transport mechanisms, *facilitated diffusion* or *carrier mediated transport* consists in the transfer of a substrate accross a membrane phase with the assistance of a carrier molecule. It involves four main steps as schematically represented in Figure 8a:

- formation of a carrier-substrate complex at one interface;
- diffusion of the complex through the membrane;
- release of the substrate at the other interface;
- back diffusion of the free carrier.

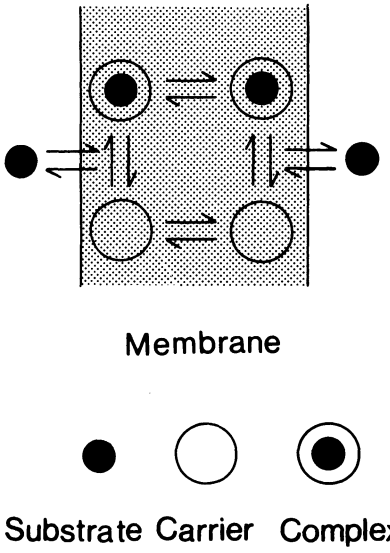


Fig. 8a Mechanism of carrier mediated transport of a substrate through a membrane.

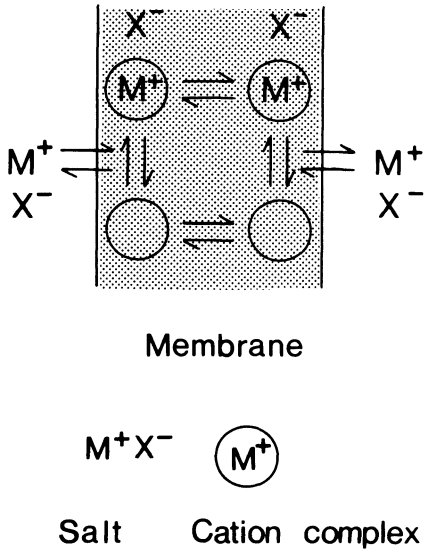


Fig. 8b Transport of an ion pair mediated by a cation carrier

This process presents several analogies with molecular catalysis, the carrier being a *transport catalyst*, which strongly increases the rate of passage of the substrate as compared to free diffusion and shows enzyme- like saturation kinetics as well as competition or inhibition phenomena etc. In addition coupling of the transport of substrate S_1 with transport of a second species S_2 in the same (symport) or in opposite (antiport) direction may also occur.

The central role in facilitated diffusion is played by the *carrier*. Thus, organic chemistry may contribute notably to the study of transport phenomena via the *design and synthesis of carrier molecules* aimed at accomplishing the efficient and selective transport of a given substrate. Such studies may result in a deeper insight into transport mechanisms, in the development of selective carriers for use in pharmacology (drug absorption etc.), in analytical chemistry or in separation science (analysis of mixtures, separation of racemates, recovery of minerals, recycling) etc.

Our work has been concerned with three main topics: the setting up of transport processes in artificial organic systems; the carrier properties of macropolycyclic molecules and the design of new carriers; the transport of electrons and its coupling to light; the demonstration of electron/substrate symport and antiport processes.

The second topic, which is more closely related to the subject of the present account will be discussed in more detail than the others. Our studies have been conducted with two types of artificial membranes: the so-called "liquid membranes" which are simply a layer of organic solvent (light, like toluene; or heavy, like chloroform) separating two aqueous phases; or supported membranes, i.e. cellulose nitrate filters impregnated with a suitable water immiscible solvent (diphenyl ether, for instance). The carrier is dissolved in the membrane and the passage of substrate(s) from one aqueous phase to the other and into the membrane, is studied.

Organic Transport Systems. Transport of Aminoacids.

Using lipophilic cationic or anionic surfactant type molecules as simple carriers, amino-acids, dipeptides, acetylcholine etc. may be transported against inorganic ions. Transport of amino-acids against their concentration gradient, pumped by protonation and deprotonation reactions, has been realized following the processes represented in Figure 9 (Ref. 24).

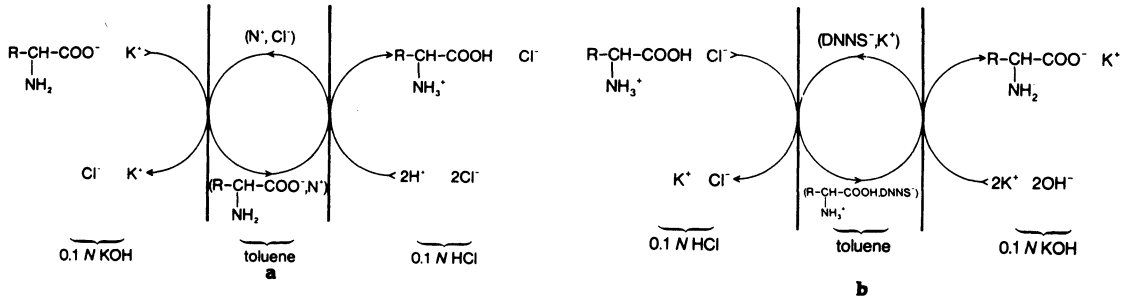


Fig. 9 Transport of amino acids through a toluene barrier: (a) from basic to acid aqueous phases using a positively charged carrier (N^+, tricapryl-methylammonium chloride, Aliquat 336); (b) from acid to basic aqueous phases using a negatively charged carrier ($DNNS^-$, dinonylnaphthalenesulfonate).

The rates of passage follow the lipophilicity sequence of the amino-acids; the dipeptide (*L*)-Phe-Gly is nevertheless carried about 30% faster than Gly-(*L*)-Phe. A gradient of an inorganic salt may also be used to pump organic substrates.

In these studies the process itself was of interest more than the very simple carrier used; the question of carrier design has been considered especially for cation transport.

Carrier Design. The Transport of Metal Cations by Macrobicyclic Cryptand Carriers.

Macrobicyclic cation receptor molecules forming *cryptate* inclusion complexes may also function as *ionophores*, selective cation carriers. One of the original motivations of our work on cryptates was the design of ligands which might be either cation receptors or carriers depending on their structure (Ref. 1).

The factors influencing selective cation transport may be divided into internal ones arising from the carrier and external ones due to the medium. In a diffusion controlled process the rates will depend on the thermodynamic equilibria at the interfaces, i.e. on the relative extraction efficiency towards different cations.

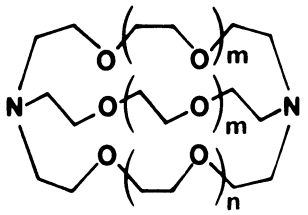
The *carrier factors* require ligands displaying high selectivity of complexation with sufficient stabilities, which are flexible enough to allow fast cation exchange at the interfaces; the outer surface must be lipophilic so that the complex be soluble in membrane media; the ligand should not be too large so as to diffuse rapidly. Thus, in addition to the properties of a cation receptor, a selective carrier requires lipophilicity and a compromise between thermodynamics (stability) and kinetics (exchange rates) of complexation.

The *external factors* comprise the nature of the membrane and of any other external species, which may participate in the process. Both may strongly influence the transport rates via the phase distribution equilibria and diffusion rates. When a neutral ligand is employed to carry an *ion pair* by complexing either the cation or the anion, the remaining uncomplexed external member of the pair may affect the rates simply by modifying the phase distribution of the substrate.

Thus, cation transport by a neutral ligand occurs via facilitated diffusion of an *ion pair* $[M^+, \text{Carrier}]X^-$ (Figure 8b), where the *external anion* X^- is expected to strongly influence the amount of salt extracted into the membrane. Natural macrocyclic or acyclic molecules (like valinomycin, enniatin, monensin etc.) as well as synthetic polyether macrocycles have been extensively used as cation carriers (Ref. 25, 26). We have mainly been studying the carrier properties of the macrobicyclic ligands shown below.

Synthetic carriers, which may in principle be modified at will, offer the possibility to monitor the transport process via the structure of the ligand and analyze the effect of various structural units on the thermodynamic and kinetic parameters which determine transport rates and selectivity.

Because of their wide range of stability constants and exchange rates (see Ref. 1, 2, 27, 28) cryptates cover the whole range of properties from cation receptors to cation carriers.



[2.2.2]	m=n=1
[3.2.2]	m=1, n=2
[3.3.3]	m=n=2
$[2.2.C_8]$	m=1, third bridge = $-(CH_2)_8-$
$[2.2.2, C_{10}]$	m=n=1; $C_{10}H_{21}$ chain on one of the central CH_2 groups

The *transport rates* are found to depend strongly on the carrier, the cation and the anion* and present marked cation selectivities. They are *not* proportional to the complex stability nor to extraction efficiency (Ref. 29, 30). Thus [2.2.2] has a transport sequence $K^+ < Na^+ << Cs^+$ (Figure 10) opposite to the stability sequence of the complexes $Cs^+ << Na^+ < K^+$ (Ref. 27).

* For comparison purposes, usually the anion is picrate and the organic liquid "membrane" phase is a chloroform layer, unless indicated otherwise.

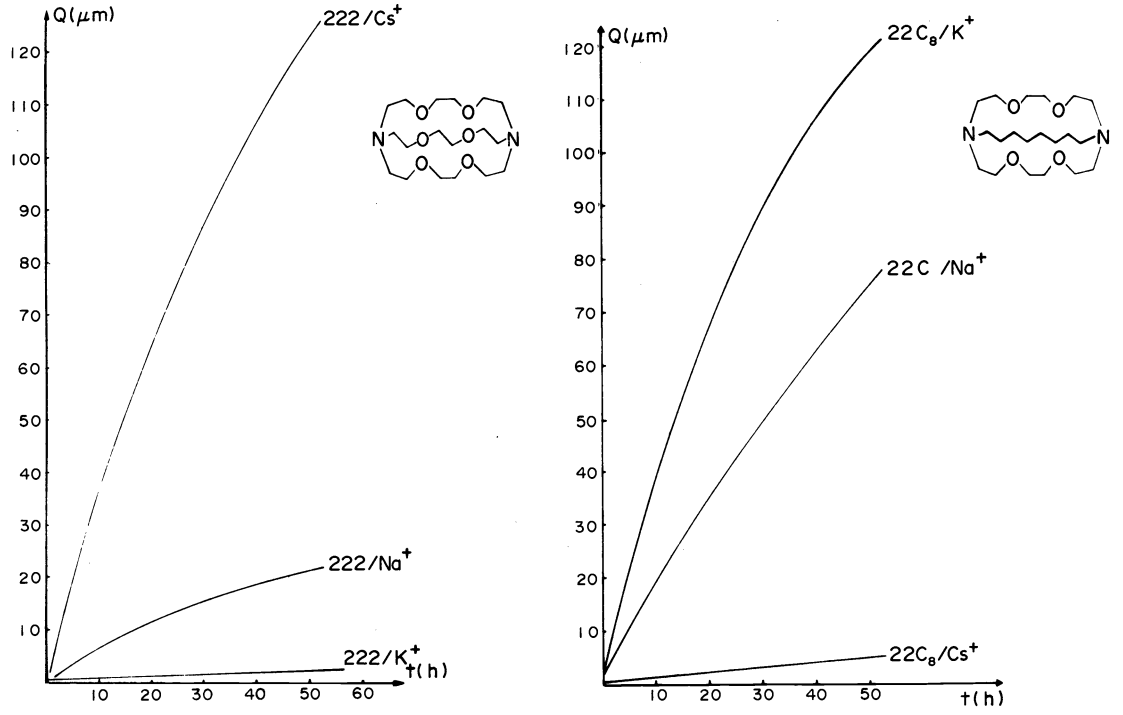
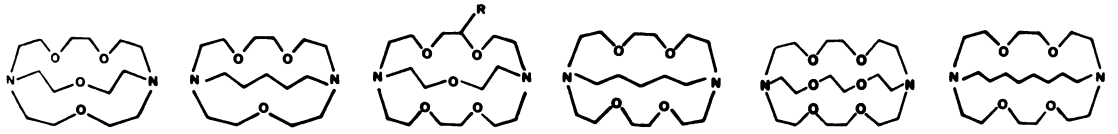


Fig. 10 Quantity of cation picrate transported Q (in micromoles) as a function of time (in hours) by cryptands [2.2.2] (left) and [2.2.C_8] (right).

Similarly [3.2.2] has opposite complexation $Na^+ < K^+$, Cs^+ and transport Cs^+, $K^+ < Na^+$ selectivities, whereas [3.3.3] has $Na^+ < K^+$, Cs^+ for both complexation and transport selectivities. The origin of these differences in receptor and carrier behavior lies in the extent of carrier saturation. The most stable cryptates, like [$K^+ \subset$ 2.2.2] have slow cation dissociation rates (Ref. 2, 28, 31) and extract very efficiently the picrate salt of their preferred cations; as a result the carrier is saturated or close to saturation and there is little free carrier present for back diffusion. This is the case for [2.2.2] and [3.2.2] which complex too well the cations Na^+, K^+ and K^+, Cs^+ respectively; in contrast [$Cs^+ \subset$ 2.2.2] and [$Na^+ \subset$ 3.2.2] have lower stabilities which are suitable for lower carrier filling and fast transport. The comparison of [3.2.2] and [3.3.3] is also instructive; their transport selectivities result from opposite factors: the Cs^+, $K^+ < Na^+$ sequence of [3.2.2] arises from too efficient complexation and extraction of Cs^+ and K^+ whereas the $Na^+ < Cs^+$, K^+ sequence of [3.3.3] is due to an unsufficient stability and extraction of the Na^+ cation. The empirical result is that, under the conditions of the experiment, those cryptate complexes which display a formation constant of about 10^5 in methanol solution, have *optimum stability* for efficient transport (Ref. 29).

The *transformation of a cation receptor into a cation carrier* may be achieved by simple structural changes. The idea is to retain the cation complexation selectivity of a cryptand by keeping the size of the intramolecular cavity about constant but to decrease the stability constants so as to decrease the extraction efficiency and to increase the exchange rates. This may be accomplished by replacing one of two oxygen binding sites by non-binding CH_2 groups. The results of such modifications are shown in Figures 10 and 11 (Ref. 30).

Receptor	Cation	Transport Rate (μM/H)	Transport Rate (μM/H)	Acceleration Factor	Cation	Carrier
[2.1.1]	$\boxed{Li^+}$	0.05	1.0	20	$\boxed{Li^+}$	[2.1.C_5]
	Na^+	0.6	1.8	3	$\boxed{Na^+}$	
	Ca^{2+}	0.1	0.2	2	Ca^{2+}	
[2.2.1]	Li^+	3.5	0.03	0.01	Li^+	[2.2.C_5]
[2.2.1]C_{10}	$\boxed{Na^+}$	0.25	3.5	14	$\boxed{Na^+}$	
	Ca^{2+}	0.4	0.08	0.2	Ca^{2+}	
[2.2.2]	Na^+	0.6	1.6	3	Na^+	[2.2.C_8]
	$\boxed{K^+}$	0.03	3.6	120	$\boxed{K^+}$	
	Cs^+	2.9	0.07	0.02	Cs^+	



[211] [21C_5] [221] (R=H) [221C_{10}] (R=$C_{10}H_{21}$) [22C_5] [222] [22C_8]

Fig. 11 Structural modifications for converting cation receptors (left) into cation carriers (right). The underlined cations are those transported preferentially; those inscribed in a square are preferentially complexed (left), preferentially complexed and carried (right).

[2.1.1], [2.2.1] and [2.2.2] are respectively Li^+, Na^+ and K^+ receptors but transport these cations very inefficiently. In contrast, [2.1.C_5], [2.2.C_5] and [2.2.C_8] are respectively Li^+, Na^+ and K^+ carriers. The change due to such a slight modification is striking.

The opposite behaviour of receptors and carriers may serve to characterize them as illustrated in Figure 12. For a selective receptor like [2.2.2] the most efficiently bound cation is the most slowly transported one; for a selective carrier like [2.2.C_8] the most efficiently bound cation is also the fastest transported; the *slope of a plot of (transport rates) versus (stability constants) is negative for a receptor and positive for a carrier molecule*. By this definition, [3.3.2] is a receptor and [3.3.3] a carrier.

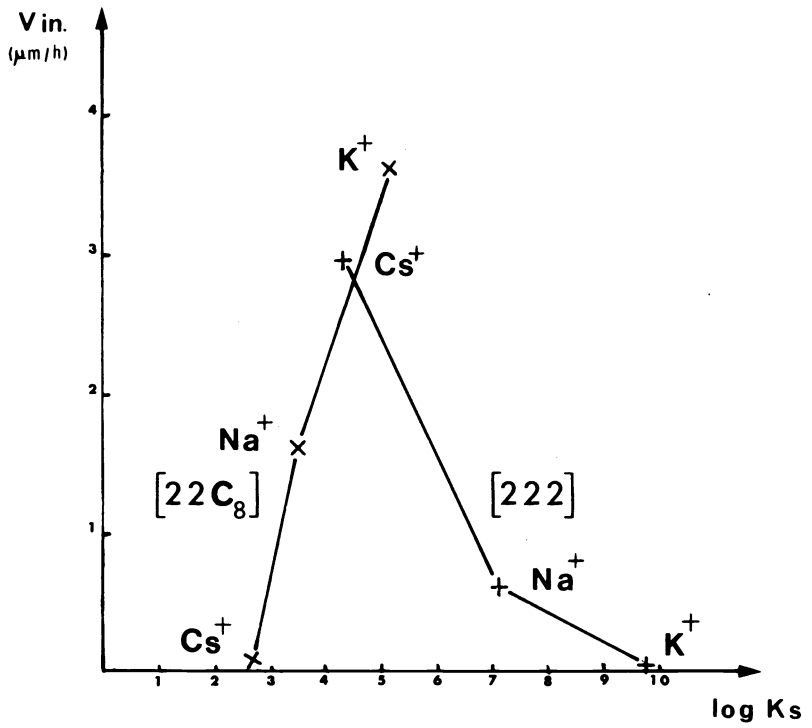
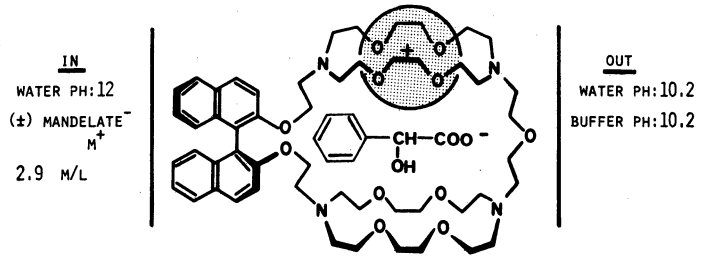


Fig. 12 Plot of initial transport rates (V in. in micromoles per hour) of cation picrates as a function of the logarithm of the stability constants log K_s (in aqueous methanol 95/5, Ref. 27).

As already noted the nature of *the anion* should strongly affect transport rates by simply modifying the extractability of the salt; the amount extracted will decrease with increasing hydration energy of the anion. The weakly solvated picrate anion favours distribution into the membrane and even ligands which form complexes of much lower stability than the cryptates, like the crown macrocyclic polyethers, transport efficiently the picrates of their preferred cations (Ref. 25, 26, 32). However with the more common and strongly solvated anion chloride, the high stability of the cryptates becomes of much interest since it still allows high transport rates to be achieved. Indeed the lipophilic carrier [2.2.2, C_{10}] is able to extract 25% KCl in a chloroform layer in contact with 0.025M KCl; appreciable KCl transport is observed (about 1 µmole/h), whereas potassium picrate saturates the carrier [2.2.2] and blocks transport (Ref. 2, 30). In contrast, dibenzo-18-crown-6 carries only very slowly (< 0.01 µmoles/h) in similar conditions (Ref. 30; see also Ref.33).

Of special interest is the case of *cascade processes* where the ability to complex a cation allows the extraction of an anion and its attraction into a cavity by ion pairing. This has been observed with an optically active macrotricycle (Ref. 34): complexation of an alkali cation by one of the macrocyclic subunits leads to extraction of the mandelate anion which is expected to penetrate at least partially into the central molecular cavity by ion pair formation. Cation dependent, weak *resolution* of racemic mandelate counter-anion has been observed in a transport system using the macrotricycle as ion pair carrier. (Figure 13, Ref. 35). Chiroselective transport of racemic mandelate by an optically active acyclic ammonium salt (Ref. 36) and of racemic ammonium salts by chiral binaphthyl-crowns have also been reported (Ref. 37).



CATION	Na^+	K^+	Cs^+
TRANSPORT RATE M/LH $\cdot 10^3$	0.6	1.4	0.6
$[\alpha]_D$ IN	0 ± 0.5°	+0.5 ± 0.1°	-0.1 ± 0.05°
$[\alpha]_D$ OUT	-0.7 ± 0.4°	-11.5 ± 0.5°	-1.8 ± 0.8°
OPTICAL PURITY OUT	0 %	10 %	1.5 %

Fig. 13 Cation-dependent chiroselective transport of racemic mandelate anion by a chiral macrotricyclic carrier.

The lipophilic receptor 4 may be used for selective extraction and transport of *primary ammonium* salts in marked preference to more highly substituted oned. *Anion transport* may also be envisaged. The development of selective anion receptors like the anion cryptates (Ref. 38), opens the way to the design of selective *anion carriers*.

Fine tuning of the structure of the ligand in accord with the nature of the counterion and of the membrane should allow the design of carriers for a given substrate in a given set of conditions, i.e. selective carriers for a desired goal from regulation of cation or anion levels and transport in organisms to recovery, separation and depollution in industrial and environmental applications. Because of the shuttle type mechanism of carrier mediated transport, carriers act as catalysts for substrate transfer (turnover substrate/ligand >> 1), as compared to simple two phase extractions where the quantity extracted is equal or smaller to the quantity of extractant.

Carrier Mediated Electron Transport. Coupling to Irradiation with Visible Light and to Substrate Transport.

Electron transport may be achieved by using membrane soluble carriers which are able to undergo redox reactions. The quinone/hydroquinone and thiol/disulfide pairs are suitable candidates for such processes. Quinone type carriers are involved in mitochondrial and photosynthetic electron transport; they perform the cotransport of two electrons and two protons through their reduced hydroquinone form. Artificial systems of this kind have been set up and shown to perform the coupled electron/proton transport (Ref. 39, 40).

Light-driven electron transport may be realized by photochemical generation of a reducing species which may itself transfer electrons through the interface to a quinone carrier dissolved in the membrane. We have set up such a system, as pictured in Figure 14.

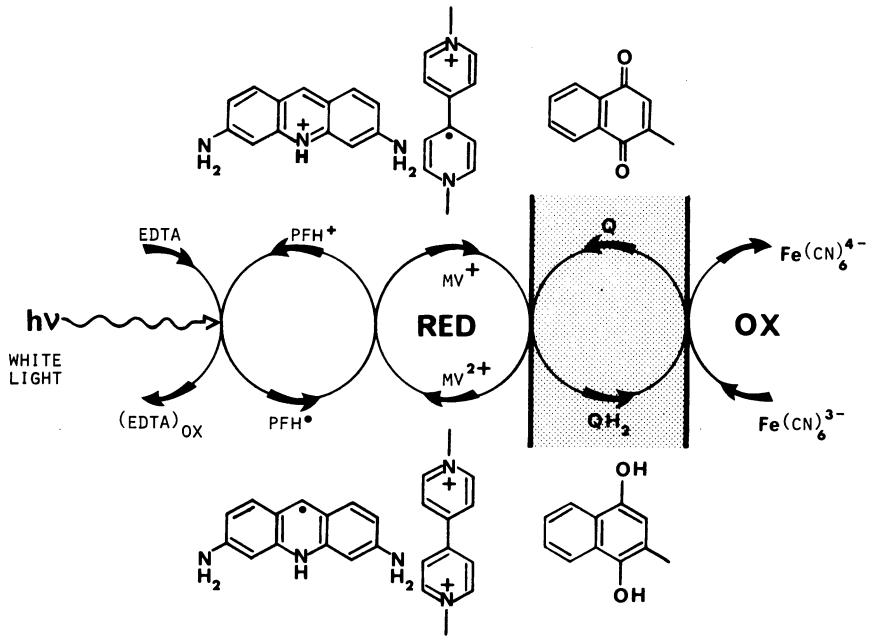


Fig. 14 Diagrammatic representation of the light coupled symport of electrons and protons accross a membrane. The reducing species in the RED aqueous phase at left is the radical cation MV^{+} produced via proflavine (PF)-sensitised photoreduction of methyl viologen MV^{2+} by the electron donor EDTA. The membrane contains vitamin K_3 as carrier molecule and the oxidising agent in OX is ferricyanide.

Visible light irradiation of the RED side produces the blue MV^{+} cation which reduces Vitamin K_3 in the membrane; on the other side of the membrane the electrons are transferred to ferricyanide which regenerates the quinone carrier. More details are found in Ref. 38.

Recent work was directed towards the *coupling of electron transport to symport or antiport of a cation or an anion*, thus realizing *active transport*, against the concentration gradient of the cotransported species.

Two such systems have been designed. One involves *electron/anion antiport*: a flow of electrons (mediated by a ferrocene/ferricinium ion couple) in one direction drives the uphill transport of picrate anions in the opposite direction (Ref. 40).

The second is a *multi-carrier process* for *electron/cation symport*: electron transport mediated by an electron carrier (a nickel-bis(dithiolene) complex) drives the selective transport of potassium cations mediated by a cation carrier (the macrocyclic polyether, dicyclohexyl-18-crown-6). This process involves *two carriers* (i.e. two catalysts), a *redox pump*, a *selection* process via the ligand, and *regulation*, since the transport rate is markedly affected by the nature of the cation/ligand pair (Ref. 40).

Systems of the type described here were of interest to us also for other reasons. In addition to representing model transport processes, they may lead to photochemical cells and batteries for energy storage. Furthermore, an electron transfer membrane may also be of use in a *photochemical water splitting system* where the membrane would separate the oxidative component producing oxygen from the reductive component generating hydrogen. In such a set-up the carrier would serve to transport the electrons coming from water oxidation to the second half-cell. Such a hypothetical system is schematically illustrated in Figure 15.

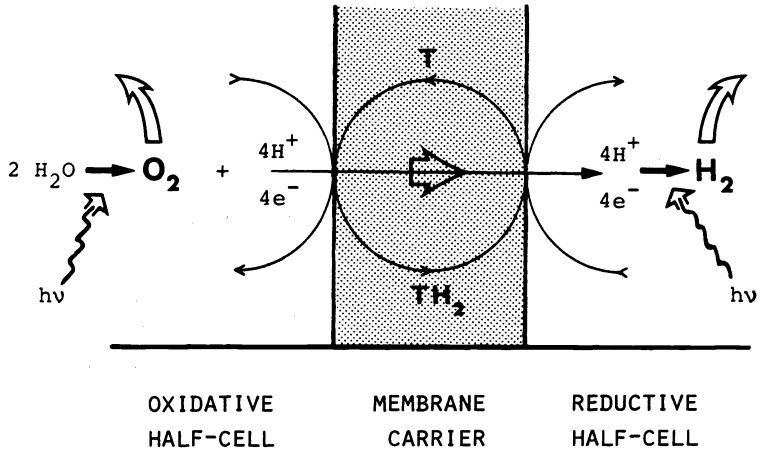


Fig. 15 Schematic illustration of the use of electron carriers in a hypothetical, membrane-separated, photochemical water-splitting system.

We have recently described a model system for the catalytic generation of hydrogen from water under visible light irradiation, using an organic molecule as electron source, water as proton source and metal complexes as photosensitizers and catalysts. A detailed account of this work will be found elsewhere (Ref. 40). It illustrates another aspect of catalysis, *photocatalysis*, in which light absorption by a suitable species is used to drive a chemical reaction with regeneration of the absorber at the end of the processes. The next steps would reside in coupling the hydrogen production process to an electron carrier in a membrane and to realize the oxidative component of the system, so that water be both the proton and the electron source.

CONCLUSION

The present account provides an overview of various aspects of our work on the *functional properties* of supramolecular systems, emphasizing investigations towards molecular catalysis and transport processes rather than receptor properties. It seems clear that in addition to further progress in receptor chemistry, developments in the design of molecular catalysts and carriers should also benefit greatly from the architectural and functional "plasticity" of macropolycyclic molecules.

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