

Molecular devices: Caroviologens as an approach to molecular wires—synthesis and incorporation into vesicle membranes

(carotenoids/bispyridinium polyenes/electron channel)

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ABSTRACT Molecular wires, which would allow electron flow to take place between different components, are important elements in the design of molecular devices. An approach to such species would be molecules possessing an electron-conducting conjugated chain, terminal electroactive polar groups, and a length sufficient to span a lipid membrane. To this end, bispyridinium polyenes of different lengths have been synthesized and their incorporation into the bilayer membrane of sodium dihexadecyl phosphate vesicles has been studied. Since they combine the features of carotenoids and of viologens, they may be termed caroviologens. Vesicles containing the caroviologen whose length approximately corresponds to the thickness of the sodium dihexadecyl phosphate bilayer display temperature-dependent changes of its absorption spectrum reflecting the gel → liquid-crystal phase transition of the membrane. The data agree with a structural model in which the caroviologens of sufficient length span the bilayer membrane, the pyridinium sites being close to the negatively charged outer and inner surfaces of the sodium dihexadecyl phosphate vesicles and the polyene chain crossing the lipid interior of the membrane. These membranes may now be tested in processes in which the caroviologen would function as a continuous, transmembrane electron channel—i.e., as a molecular wire. Various further developments may be envisaged along these lines.

Molecular devices may be defined as structurally organized and functionally integrated chemical systems built into supramolecular architectures. The development of such devices requires the design of molecular components performing a given function (e.g., photoactive, electroactive, ionoactive, thermoactive, or chemoactive) and suitable for assembly into an organized array. A major requirement is that these components and the devices that they build up should perform their function(s) at the *molecular and supramolecular* (1) levels, as distinct from the level of the bulk material.

Components and devices such as molecular wires, resistors, switches, rectifiers, diodes, photosensitive elements, etc., might be assembled into ultramicrocircuits to yield systems performing functions of storage, processing, and transfer of signals and information by means of various mediators (electrons, protons, photons, metal cations, anions, molecules) with coupling and regulation.

Advantage may be taken of the three-dimensional information storage and read-out capacity of molecules (as operating in molecular recognition processes) (1), of the diversity of *chemical* species that may act as mediators and effectors (selective molecular reagents, catalysts, carriers, and channels), and of polymolecular organization (molecular layers, membranes, vesicles, mesomorphic phases, solid state). Thus, an intriguing,

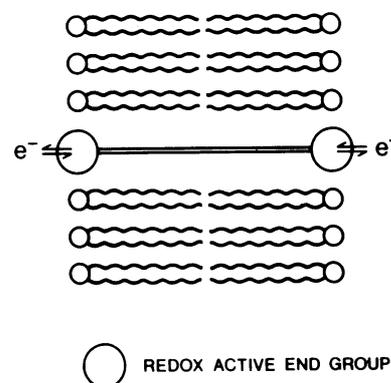


FIG. 1. Schematic representation of a molecular wire as transmembrane electron channel.

although rather futuristic, field of chemistry may develop, which may be termed “*chemionics*”—the design and operation of components, devices, circuitry, and systems for signal and information treatment at the molecular level (1–3).

Molecular *electronic* devices and “*molecular electronics*” are increasingly attracting attention (refs. 4 and 5 and references listed therein); molecular rectifiers and transistors have been envisaged (6–8) and the molecular photodiode features of charge-transfer excited states in organic molecules and metal complexes may be noted (see, for instance, refs. 9 and 10). More generally, molecular *ionic* devices may as well handle inorganic and organic ions (defining “*molecular ionic*”) and operate by performing highly selective recognition, reaction, and transport processes (1, 11).

Among the basic components of such systems, a unit of fundamental importance is a connector or junction allowing electron flow to take place between different parts of the system—i.e., a *molecular wire*.

In attempts toward the actual realization of molecular components, we have investigated *inter alia* an approach to a molecular wire under the requirement that it satisfy three criteria: (i) contain an electron-conducting chain; (ii) possess terminal electroactive and polar groups for reversible electron exchange; (iii) be long enough to span a typical molecular supporting element like a monolayer or a bilayer membrane (Fig. 1).

We describe here the synthesis, some properties, and results of incorporation into bilayer membranes of compounds 1^{2+} and 2^{2+} , members of a class of molecules displaying such basic characteristics: vinylogous derivatives of methylviologen, which combine the features of the carotenoids and of the viologens and may therefore be termed *caroviologens*. They possess the electroactive and hydrosoluble pyridinium groups of the viologens for electron exchange (12, 13) as well as long conjugated polyene chains for electron conduction and membrane spanning. Two other

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analogues, a shorter bis(4-pyridinium) molecule, 6^{2+} , and one containing a central benzene ring, 10^{2+} , have also been studied for comparison purposes.

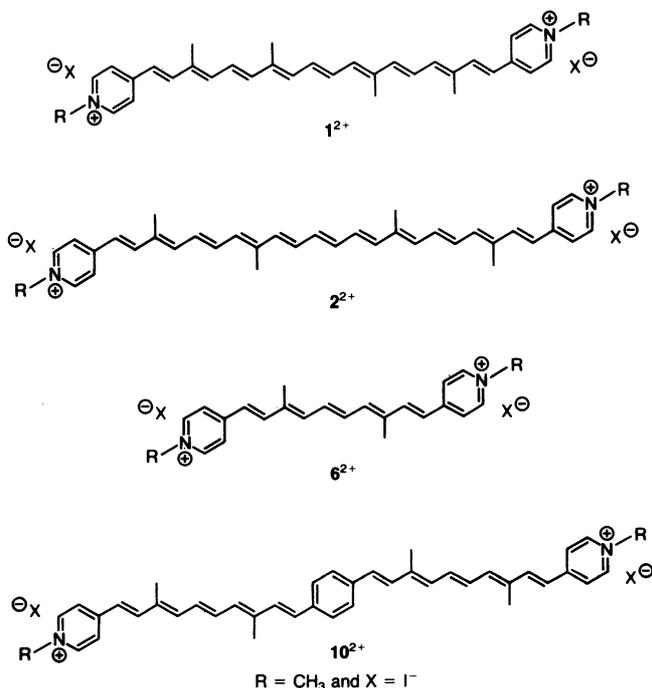
MATERIALS AND METHODS

Chemicals. All chemicals used were high-purity commercial reagents. The dialdehydes **4** and **5** were gifts from Hoffmann-La Roche.

Synthesis of the Bis(4-pyridinium) Polyenes 1^{2+} , 2^{2+} , 6^{2+} and 10^{2+} . The bis(4-pyridine) polyenes **1**, **2**, **6**, and **10** were synthesized by way of double Wittig-Horner condensation following the reaction sequence shown in Fig. 2. Double Wittig reactions have been used extensively in carotenoid synthesis (14). Lithiation of 4-methylpyridine with BuLi followed by reaction with ClPPh₂ and subsequent oxidation with O₂ gave the phosphine oxide **3** (mp, 212°C; 70% yield). The phosphonates **8** (15, 16) and **9** (17) were obtained in 90% and 76% yield, respectively, by heating the corresponding dibromides with triethylphosphite.

Condensation of 2.3 eq of **3** with 1 eq of crocetin dialdehyde **4** using NaH in tetrahydrofuran (in the presence of 18-crown-6 or cryptand[2.2.2] for solubilization) gave compound **1** [cryst. ethanol; mp, 210°C; 50% yield; λ_{\max} , nm (ϵ): 452 (93,000), 478 (126,000), 510 (108,000), ethanol]. The same reaction applied to **5** gave compound **6** [cryst. ethanol; mp, 220°C; 70% yield; λ_{\max} , nm (ϵ): 390 (65,000), 409 (90,000), 434 (85,000), ethanol]. The monoaldehyde **7** was obtained as was **6** but by using only 1 eq of **3** and no solubilization catalyst; it was separated from **5** and **6** by chromatography on alumina [mp, 93°C; 40–60% yield; λ_{\max} , nm (ϵ): 375 (60,000), 393 (55,000), ethanol].

Double condensation of **7** with **8** or with **9** in tetrahydrofuran in the presence of NaH and 18-crown-6 gave **2** or **10**, respectively, which were purified by chromatography on alumina under argon and not by recrystallization to avoid decomposition: **2**, 45% yield, λ_{\max} , nm: 472, 500, 534, (CH₂Cl₂); **10**, 40% yield, λ_{\max} , nm: 450, 470, 496, (CH₂-Cl₂).



(Compounds **1**, **2**, **6**, and **10** are the corresponding bispyridine polyenes.)

The bis(4-pyridinium) polyenes 1^{2+} , 2^{2+} , 6^{2+} , and 10^{2+} were obtained in about 90% yield by treating the corresponding bispyridine with methyl iodide in nitromethane (**1**), dichloromethane (**2**, **10**), or acetonitrile (**6**); λ_{\max} , nm (ϵ): 1^{2+} , 554 (82,000); 2^{2+} , 564 (97,000); 6^{2+} , 466–486 (66,000); 10^{2+} , 527 (107,000) (ethanol). The bis(2-pyridine) and bis(3-pyridine) analogues of **1** and their bis(*N*-methylpyridinium) derivatives have been reported (18). Most of the reactions and purifications were conducted under argon, avoiding direct light to minimize decomposition. The molecular weights of **1**, **2**, **6**, and **10** were confirmed by mass spectroscopy. Their structures and purity as well as those of 1^{2+} , 2^{2+} , 6^{2+} , and 10^{2+} were checked by analysis of their 200-MHz and 400-MHz proton NMR spectra. The microanalyses always showed the presence of water, which was very difficult to remove completely but was also found in the NMR spectra.

Vesicle Preparation and Substrate Incorporation Experiments. Large sodium dihexadecyl phosphate vesicles were prepared by the vaporization method of Deamer and Bangham (19) adapted to sodium dihexadecyl phosphate by Carmona-Ribeiro *et al.* (20). Substrate incorporation has been performed with 1^{2+} , 2^{2+} , 6^{2+} , and 10^{2+} . In a typical experiment, a warm chloroform solution (1 ml) of the bispyridinium polyene 2^{2+} or 1^{2+} (0.18 mg, 3.3×10^{-4} mmol) containing sodium dihexadecyl phosphate (9.1 mg, 0.016 mmol) was injected at a rate of 0.1 ml/min into 4 ml of water thermostated at 70°C. One-milliliter aliquots of the dispersion obtained were filtered on a Sephadex G-25 M (Pharmacia PD-10) column and the absorption spectra of the fractions eluted at the void volume were recorded on a spectrometer. The vesicles were observable with a phase-contrast optical microscope, on electron micrographs, and by light scattering (mean diameter, 0.35 μ m).

RESULTS AND DISCUSSION

Properties of the Bis(4-pyridinium) Polyenes 1^{2+} , 2^{2+} , 6^{2+} , and 10^{2+} . The bis(4-pyridinium) polyenes 1^{2+} , 2^{2+} , 6^{2+} , and 10^{2+} have been synthesized as described above (see also Fig. 2).

Structural features. An all-*trans* configuration was confirmed for all compounds by detailed analysis of their 200-MHz or 400-MHz proton NMR spectra as well as by the absence of *cis* bands in their UV-visible spectra (21). Based on the length of canthaxanthin (≈ 29 Å) in the crystal (22), the lengths of the present molecules with fully extended chains may be estimated to about 29 Å, 34 Å, 19 Å, and 36 Å from *N* to *N'* in **1**, **2**, **6**, and **10**, respectively.

Visible spectra and aggregation. On *N,N'*-dimethylation the visible absorption band of all bispyridine polyenes shifted to longer wavelength by about 50–60 nm and lost its three-peak fine structure characteristic of carotenoids. Furthermore, the spectrum of 2^{2+} in aqueous solutions progressively underwent a large blue shift (from 540 to 430 nm) at room temperature; the initial spectrum was restored on heating to 70°C. Such solvent- and temperature-dependent behavior is known for natural carotenoids, and the blue shift has been assigned to formation, in aqueous solvents, of aggregates (23–25) that may dissociate on heating.

Electrochemical properties. Cyclic voltammetry measurements in dry dimethyl sulfoxide/0.1 M NBu₄BF₄ gave for all four bispyridinium compounds a reversible or quasireversible dielectronic reduction at -0.58, -0.60, -0.61, and -0.82 V vs. SCE for 1^{2+} , 2^{2+} , 6^{2+} , and 10^{2+} , respectively. The reduction of 1^{2+} was irreversible in aqueous solution. The parent compound, methylviologen itself, undergoes mono-electronic reduction at -0.68 V vs. SCE (12, 13). Carotenoids of natural origin such as astacene possess terminal α -hydroxydienone groups and may also have structural and redox features of interest for the present purpose.

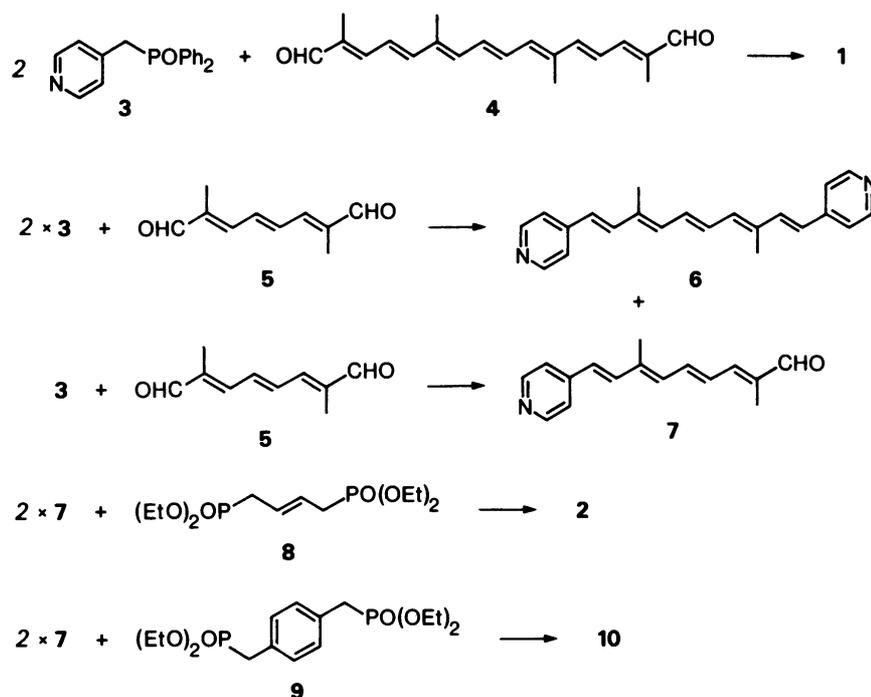


FIG. 2. Synthetic schemes for preparation of the bispyridine polyenes 1, 2, 6, and 10.

The dielectronic reduction and the irreversibility in water might cause problems in electron-transfer experiments with compounds such as 1^{2+} , 2^{2+} , and 10^{2+} , depending on whether or not fast rates of transfer and the membrane phase circumvent these potential difficulties.

Incorporation of Bispyridinium Polyenes (Caroviologens) into Vesicle Membranes. The bispyridinium compounds synthesized above present structural and physical properties compatible with the requirements for designing molecular wires. Since they possess charged terminal groups separated by a long lipophilic polyene chain they should be suitable for incorporation into lipid membranes, in particular of vesicles, and be able to span the membrane if the chain is long enough to allow the polar head groups to reach into the polar regions on each side of a bilayer or of a monolayer membrane (26). Thus, carotenoids bearing hydroxyl groups at both ends may act as membrane reinforcers by spanning the bilayer (27, 28).

When vesicles were prepared by coinjection of sodium dihexadecyl phosphate and of 1^{2+} or 2^{2+} as described above,

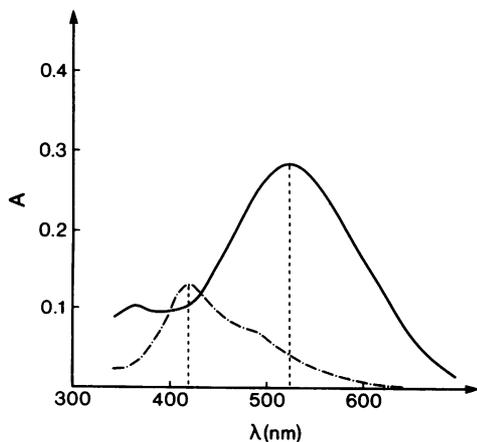


FIG. 3. Electronic absorption spectra of caroviologen 2^{2+} incorporated in sodium dihexadecyl phosphate vesicles at 23°C (---) and at 72°C (—) with compensation by a vesicle suspension; spectra were recorded after filtration on Sephadex with a Perkin-Elmer 554 spectrometer.

gel filtration of the dispersion obtained led to *coelution of all (>95%) the substrate and the vesicles*. The eluate with 2^{2+} presented an absorption at 420–460 nm, which was transformed into a 520- to 530-nm band on heating to about 75°C (Fig. 3). The former should correspond to aggregates of 2^{2+} and the latter to the monomer, in line with the behavior of the natural carotenoid zeaxanthin in phospholipid dispersions (29). Complete coelution was shown in the case of 1^{2+} by the optical density in the eluate and the absence of any remaining discernible color on the gel column or in the later eluate fractions. This indicates that the substrate is associated with the vesicle membranes and is not contained in the interior aqueous phase. The remaining question is whether it is located either *in* the membrane or *on* the exterior and interior surfaces of the vesicles.

Information can be obtained from the temperature dependence of the visible spectrum of the vesicles containing 2^{2+} (Fig. 3). On raising the temperature, the ratio A_{520}/A_{420} or A_{528}/A_{460} (two separate experiments) of the absorbances at 520 and 420 nm or at 528 and 460 nm increased sharply (Fig. 4). These changes correspond to a phase transition with critical temperatures T_c of 57°C and 62°C, respectively (average, $59.5 \pm 2.5^\circ\text{C}$). A study of the temperature dependence of the ESR spectra of a spin-labeled long-chain quaternary ammonium salt (30) contained in the bilayer gave $T_c = 58 \pm 2.5^\circ\text{C}$. These results agree fairly well with the value $T_c = 60^\circ\text{C}$ found for the gel \rightarrow liquid-crystal transition of sodium dihexadecyl phosphate vesicles by the variation of the absorbance at 400 nm with temperature (Fig. 4). The results for the vesicles incorporating 2^{2+} indicate that the additive (i) undergoes an aggregate \rightarrow monomer transformation *together* with the phase change of the membrane and (ii) perturbs only slightly the phase properties of the surfactant. Similar observations have been made for zeaxanthin in phospholipid phase (29). In the same way as with 2^{2+} , compound 1^{2+} in the vesicles exhibited an aggregate \rightarrow monomer transformation together with the gel liquid-crystal transition at $57.5 \pm 2^\circ\text{C}$ (variation of A_{522}/A_{392} with temperature); a less marked transition was observed in A_{484}/A_{400} for 10^{2+} at 60°C. Compounds 1^{2+} , 2^{2+} , and 10^{2+} did not show these temperature-dependent changes when not contained in vesicles. All of these observations speak in favor of the

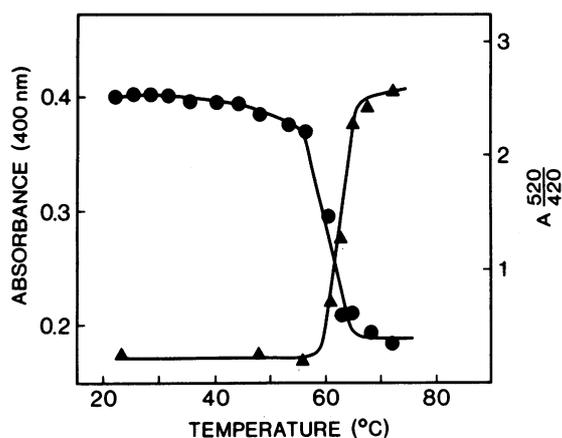


FIG. 4. Temperature dependence of the absorbance of sodium dihexadecyl phosphate vesicles at 400 nm (\bullet) and of the ratio A_{520}/A_{420} of the absorbance at 520 and 420 nm (\blacktriangle) of sodium dihexadecyl phosphate vesicles incorporating the caroviologen 2^{2+} , with compensation by a vesicle suspension.

incorporation of 2^{2+} , 1^{2+} , and 10^{2+} into the sodium dihexadecyl phosphate vesicle membrane. This conclusion is supported by three other series of results: (i) when a sodium dihexadecyl phosphate vesicle suspension was incubated with 2^{2+} for 12 hr, coelution on gel filtration and the spectral transition at 58°C were both observed as for the vesicles prepared by coinjection of 2^{2+} and the lipid; (ii) when dipalmitoyllecithin was used as lipid, 2^{2+} was eluted both with the vesicles and alone; in addition there was no change in A_{520}/A_{420} corresponding to the value $T_c = 41^\circ\text{C}$ known for dipalmitoyllecithin membranes (31), meaning that 2^{2+} was distributed essentially in water, probably as a result of the lower surface charge density of the membrane (32); (iii) when the much shorter bispyridinium polyene 6^{2+} was used instead of 2^{2+} it was found that (a) the visible absorption was about the same in ethanol and in water (470 nm) and did not change on heating; (b) in sodium dihexadecyl phosphate vesicle preparations, 6^{2+} was eluted both with the vesicles and alone; (c) 6^{2+} had an absorption maximum at 570 nm in the vesicles, which underwent a shift to 480 nm, on heating, displaying a transition at $T_c = 70^\circ\text{C}$; this may be due to release of 6^{2+} from the liquid-crystalline phase of the lipid into the aqueous phase.

Results reported recently in the literature also agree with the present picture: methylviologen MV^{2+} itself associates

strongly with sodium dihexadecyl phosphate vesicles (33) and diffuses through the membrane above 30°C (34); lipophilic derivatives of MV^{2+} dissolve in membranes and may act as transmembrane electron carriers (35, 36); long, terminal aliphatic diquatery ammonium cations may span anionic vesicle membranes (37).

Taken together, the available data support a process involving association of the bispyridinium polyenes with the negatively charged surfaces of sodium dihexadecyl phosphate vesicles, followed by diffusion and equilibration toward a transmembrane orientation.

Structural Model of Caroviologens Incorporated in Vesicle Membranes. The results and the discussion above agree with a structural representation in which caroviologens of sufficient length span the lipid bilayer membrane, the pyridinium sites being close to the negatively charged outer and inner surfaces of the sodium dihexadecyl phosphate vesicles and the polyene chain crossing the lipidic interior of the membrane.

With the hydrocarbon chains in their fully extended all-*trans* form, the thickness of the sodium dihexadecyl phosphate bilayer may be estimated to about 43 \AA , which is longer than the caroviologen 2^{2+} . However, because of the occurrence of *gauche* conformations along the chains, the actual bilayer may be substantially thinner, and for instance a thickness of $34\text{--}35 \text{ \AA}$ has been found for the hydrocarbon region of dipalmitoyllecithin bilayers that contain similar hydrocarbon chains (38). Consequently, the thickness of sodium dihexadecyl phosphate bilayers may be estimated to be about the same—i.e., around 35 \AA , which is comparable or only slightly more than the length of caroviologen 2^{2+} (see above). In addition, inclusion of shorter chain amphiphiles should decrease bilayer thickness by increasing the defects in the all-*trans* arrangement of the longer chains (39). A schematic representation of the resulting picture of 2^{2+} in sodium dihexadecyl phosphate bilayers is shown in Fig. 5. Using thinner membranes, such as monolayers (26), or longer caroviologens should allow one to explore the compatibility between the dimensions of the included substrate and the membranes.

CONCLUSION

The results reported here delineate the first two stages in the design of a functional molecular wire: (i) synthesis of a suitable substrate molecule and (ii) incorporation into a molecular support, such as a bilayer membrane. The next

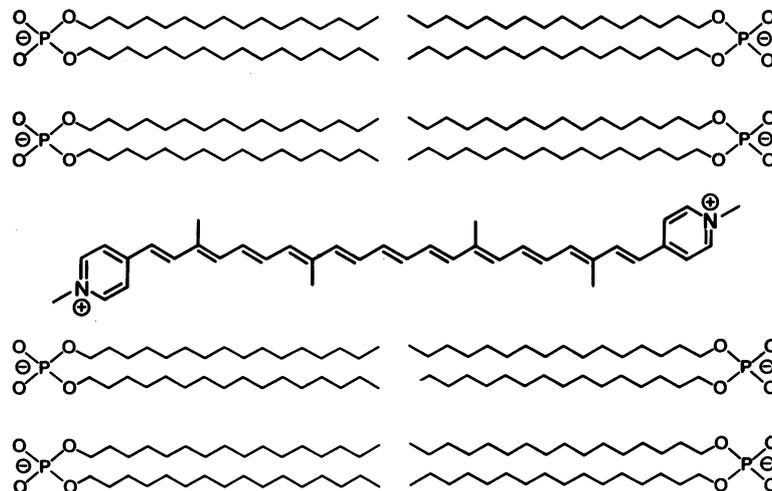


FIG. 5. Schematic representation of the transmembrane incorporation of the caroviologen 2^{2+} into sodium dihexadecyl phosphate vesicles; the lipids, represented in their all-*trans* conformation, have been somewhat reduced in length to take into account factors that decrease membrane thickness.

stage is to investigate its ability to conduct electrons, for instance, by accepting electrons from a reductant phase and delivering them to an oxidant phase across a membrane barrier. It has been suggested that natural carotenoids or polyisoprene chains might be involved in electron conduction (40–42). With respect to electron transport by means of redoxactive mobile carrier molecules (11, 43, 44), the caroviologens would represent *membrane-spanning electron channels*, such as the carriers and channels for metal cations (11, 43). They portray a first approach to molecular wires and may not be the optimal structures; in particular, other terminal redox groups, such as quinones, may be considered. Further developments involve the coupling with photoactive groups to yield photoresponsive electron channels and charge-separation devices by means of photoinduced electron transfer; such elements would also be of much interest for studies in artificial photosynthesis (45–47). Push-pull carotenoids (bearing a donor on one end and an acceptor on the other end of the molecule) could present interesting electronic and (nonlinear) optical properties. Finally, by seeking other supports [such as polymerized (48, 49) or mesomorphic (50) assemblies] as well as other components, one might be able to assemble molecular devices into circuitry and more complex systems capable ultimately of processing information (1–5, 51–53).

Such perspectives in molecular and supramolecular design and engineering lie, of course, in the long range (53), but along the way they could yield numerous spin-offs and they do represent ultimate goals toward which work may already be planned and realized.

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