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MOLECULAR BIO-ELECTRONICS BIOMATERIALS

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Abstract This report summarizes some of our efforts aimed at utilizing biomaterials – mainly enzymes – as key components in molecular electronics. The research program is concerned merely with the design and construction of molecular logic elements, the action of which relies on changes in the three–dimensional conformation of biological molecules. Within this context, three main topics are considered: (a) Soliton–actuated bio–molecular switching elements, in which a molecular switch is built on an enzyme at a predesigned location, allowing to control (ON and OFF) its catalytic activity; (b) Enzyme–based logic gates (ENLOG's), particularly their basic concepts and the related approaches for experimentally implementing them; and (c) Interaction of enzymes with electroactive materials, the emphasis being on newly synthesized water–soluble conductive polymers.

INTRODUCTION

There is a growing interest in the possibilities to utilize biological molecules in molecular electronics and, particularly, in artificial intelligence systems[1–7]. This activity is fostered by the basic understanding that, in so doing, one may be able to take advantage of the specific characteristics and unique capabilities of these natural molecules. In the present report, our recent achievements along these lines are presented.

RESULTS AND DISCUSSION

Soliton-Actuated Bio-Molecular Switching Elements

This part of the research is aimed at the design of bio-molecular switching elements built of an enzyme and a molecular switch. The functioning of such elements is based on soliton-induced changes in their three-dimensional conformation.

Three dimensional **conformation** is a crucial characteristic of biochemical systems[8,9]. Conformational changes can be analyzed by means of molecular modeling, using molecular mechanics methodology[10–15].

Soliton is a basic concept in the study of conducting polymers[16–18]. Soliton-based molecular switches for molecular electronics were first suggested by F.L. Carter[19–21]. As a result of soliton passage through the conjugated chain, rearrangements of the electronic structure occurs, which in turn interchanges the location of single and double bonds.

Relying on the above principles, we have considered the possibility that bio-molecular switching elements can be designed, for which the three-dimensional **conformation** attained upon passage of soliton is different from the initial one.

Our study[22,23] was first addressed to the design of molecular switches based on soliton-induced changes in their three-dimensional conformation. Such a switch, when attached to an enzyme at appropriate location in the active site area, will allow or prevent the access of substrate. As a result, control of the catalytic activity is achieved, thereby creating a bio-molecular switching element.

The design relies on molecular modeling techniques. The pertinent calculations were performed using simulation procedures available in the MACROMODEL software[24].

An example of the results obtained is presented in Figure 1. The enzyme Lysozyme, for which a molecular switch replaces the residue VAL 110, is shown. The molecular switch, located at the entrance to the active site, is marked in light gray. The left and right structures represent the switching element in the "OPEN" and "CLOSED" states, respectively.

In summary, bio-molecular switching elements based on enzymes and molecular switches were designed, combining the principles of: soliton passage through a conjugated chain; three-dimensional conformation of molecules as a key for their biochemical activity; and molecular modeling design.

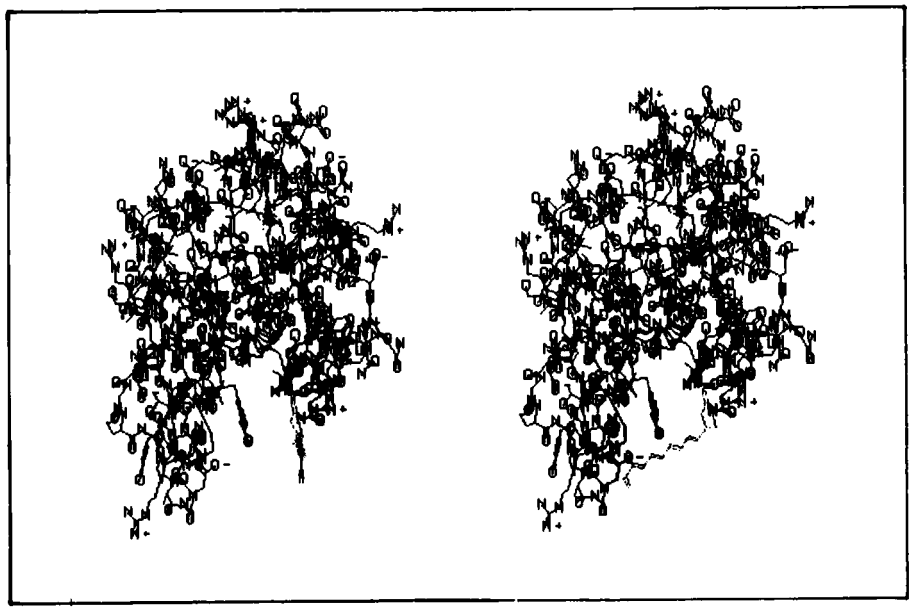

FIGURE 1 A bio-molecular switching element built on the enzyme Lysozyme. The "OPEN" (left side) and "CLOSED" (right side) states are indicated.

Enzyme Based Logic Gates (ENLOG's)

Enzyme based logic gates (ENLOG's) is a new subject, considered in the literature in connection with Molecular Electronics[25-34]. Our research[35,36] involves conceptual studies, as well as related experimental work. In this context, we consider the utilization of enzymes in order to implement logic gates, such as AND, OR, NOT NAND, and NOR. In particular, we concentrate on optically-actuated logic gates.

For illustration, in Figure 2 we describe the behavior of an ENLOG performing the "OR" logic operation. In this figure, panel (A) presents the details of the physical system. Here:

- S_1 and S_2 are two compounds, capable of undergoing reversible cis–trans isomerizations. These processes are independently controllable by optical signals.
- The cis–to–trans and trans–to–cis isomerizations of S_1 are induced by irradiation at λ_1 and λ_2, respectively. Similarly, control of S_2 is achieved by irradiation at λ_3 and λ_4.

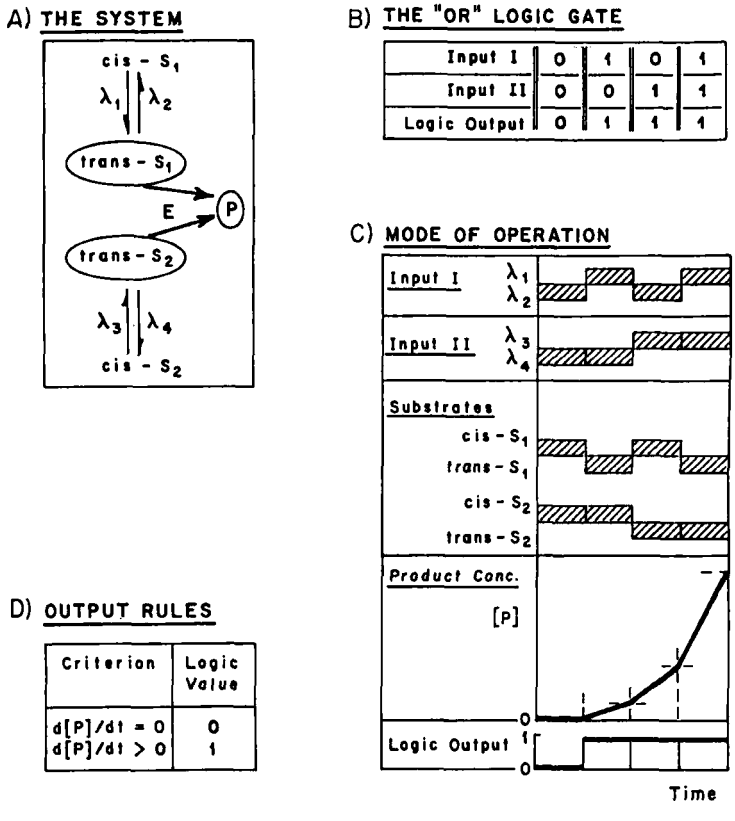

FIGURE 2 The functioning of an ENLOG performing the "OR" logic operation. In panel (C), the symbols (▨) mean that the pertinent input is ON, and the indicated form of the substrate prevails in the system.

- The enzyme E catalyzes the transformation of both S_1 and S_2 into product P, but only when these compounds are in their trans form. The corresponding cis forms of S_1 and S_2 cannot be used by the enzyme and, as such, do not

perform as substrates. Representative examples for such cases are described in the literature[37,38].

Panel (B) presents the function of the "OR" logic gate in terms of the Boolean algebra. The four input sets considered, i.e. the four combination of inputs I and II, are marked (a)–(d). The gate output has the binary value "1" only if at least one of the inputs has the binary value "1". Whenever this condition is not fulfilled, the output is "0".

Panel (C) describes the mode of operation of the gate, under each of the four input sets to be considered. Thus, input set (a) is achieved when both input I and input II are "0". This situation is encountered when signals λ_2 and λ_4 are "ON", causing S_1 and S_2 to assume the cis form, i.e. their completely inactive state. Similarly, input sets (b), (c) and (d) are achieved by using signals λ_1, λ_2, λ_3 and λ_4, as indicated in panels (A) and (C). In all cases, the corresponding system outputs are indicated in panel (C), in terms of the time dependence of product concentration, [P]. The slopes of the corresponding lines, i.e d[P]/dt, represent the reaction rates.

In panel (D), the logic values of the output are now defined. Using these definitions, the logic output of set (a) is "0", while for sets (b), (c) and (d), the corresponding outputs are all "1". These values are shown in the bottom section of panel (C).

It can thus be seen that the ENLOG system described in Figure 1 indeed performs the function of the "OR" logic gate.

As a first step for experimental implementation of the ENLOG concepts presented above, a related system was investigated[35,36]. To this aim, two derivatives of the enzyme Chymotrypsin, carrying different photoreceptor moieties, have been prepared. In these derivatives, the conformational changes are cis–trans isomerizations of key bonds (azo– and ethylenic–type, respectively), and these processes are induced in a controllable manner, by irradiation at appropriate wavelengths. Thus, the input information is transferred into the gate upon illumination of the system, and translated into changes of either the activity (ON or

OFF), or the level of activity (threshold) of the enzyme. These changes can subsequently be processed into logic output.

The Interaction of Enzymes with Electroactive Polymers

This investigation is directed at establishing the background required for building an information transfer system which will operate by addressing electronic flow to and from an enzyme, and will do so by using electroconductive polymers as "molecular wires". To this aim, two novel water-soluble derivatives of polyaniline (PANI) were prepared, and the interaction of these polymers with redox enzymes was investigated. Comparative studies were performed using conductive polymers already described in the literature.

Most of previous research on soluble conductive polymers is concerned with solubility in organic solvents[39–45]. The few reports dealing with water soluble polymers consider derivatives containing ionizable functional groups, such as sulfonate or phenolate[41,46–48]. In our work, we are particularly interested in polymers which, for their water solubility, do not carry additional ionizable groups.

Previous studies have shown that information can be transferred to and from redox enzymes by using redox moieties attached to the protein[49,50], or redox polymers[50,51]. These systems have an intrinsic limitation, originating in the fact that the rate of information transfer depends on the velocity of movement of counter ions to and from the redox center of the enzyme[52]. In order to avoid such limitations, the use of electroconductive polymers may in principle be appropriate.

As part of this study, two water-soluble derivatives of polyaniline, namely poly (3-aminophenylacetic acid) (PAPAA) and poly [3-(2-hydroxyethyl)aminophenylacet- amide] (PAPAEA) have been synthesized. The basic chemical structures of these polymers are shown in Figure 3. PAPAA was obtained by oxidative polymerization of 3-aminophenylacetic acid, using essentially the procedure reported for PANI[53]. The second polymer, PAPAEA, was obtained by attaching ethanolamine to the carboxylic groups of PAPAA, using N, N'-dicyclohexylcarbodiimide as the coupling agent.

The two polymers are soluble in strongly basic aqueous NaOH solutions, and in glycylglycine buffer (0.6 M, pH 8.2). They are also soluble in organic solvents,

such as N–methyl pyrrolidone, N,N–dimethylformamide and dimethyl sulfoxide. In addition, PAPAEA is soluble in methanol and ethanol.

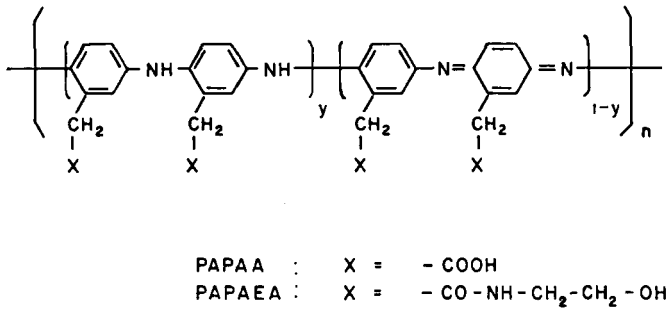

FIGURE 3 The chemical structures of two water–soluble polymers: PAPAA and PAPAEA. For abbreviations, see text.

The interaction between conductive polymers and redox enzymes was studied by quantitatively measuring the ability of polymers to bind the enzymes, and the ability of the bound enzyme to express its biologically–specific activity. Representative results are shown in Figure 4. The data presented were obtained

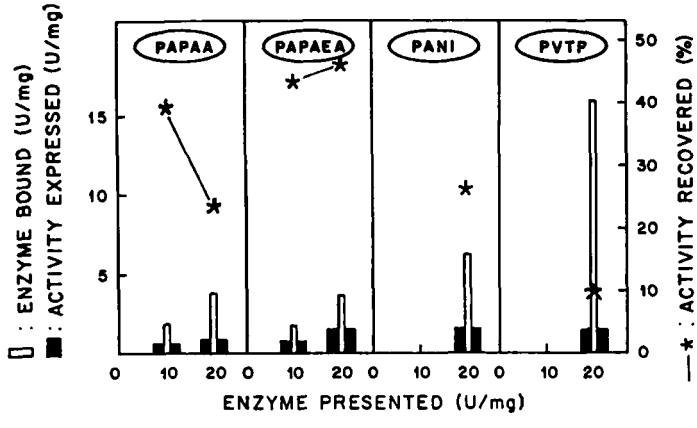

FIGURE 4 Interaction of glucose oxidase with conducting polymers. For abbreviations, see text.

using glucose oxidase (GOX) as test enzyme, and the polymers considered are PAPAA and PAPAEA. For comparison, we have also studied the interaction of GOX with two known polymers, PANI[53] and poly [N,N'-(1,4-divinylbenzene-β,β'-diyl)-4,4'-bipyridinium dibromide] (PVTP)[54], and the pertinent data are also shown in Figure 4. The results obtained indicate that, amongst the polymers investigated, PVTP is the most efficient one for binding GOX, yet the bound enzyme expresses only 10% of its activity. On the other hand, PAPAA and PAPAEA are less efficient at binding the enzyme, yet the bound molecules are rather highly active, expressing up to 50% of their original catalytic activity. Additional experiments were performed with two other enzymes, uricase and xanthine oxidase, and the pertinent data are reported elsewhere[55,56].

The results obtained clearly indicate that the interaction of redox enzymes with conductive polymers is very sensitive to the detailed chemical and physical structure of the latter. Moreover, the newly synthesized polymer, PAPAEA, seems to offer to the enzyme an environment which is rather favorable for it to express its catalytic activity.

CONCLUSIONS

Approaches – both experimental and conceptual – have been developed for the utilization of enzymes as key components in molecular electronics and, particularly, in bio-molecular switching elements and logic gates.

Related to the above, the interaction between redox enzymes and polyaniline derivatives was shown to depend to a significant extent on the detailed chemical structure of the polymers.

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