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Artificial Enzyme Catalysis Controlled and Driven by Light

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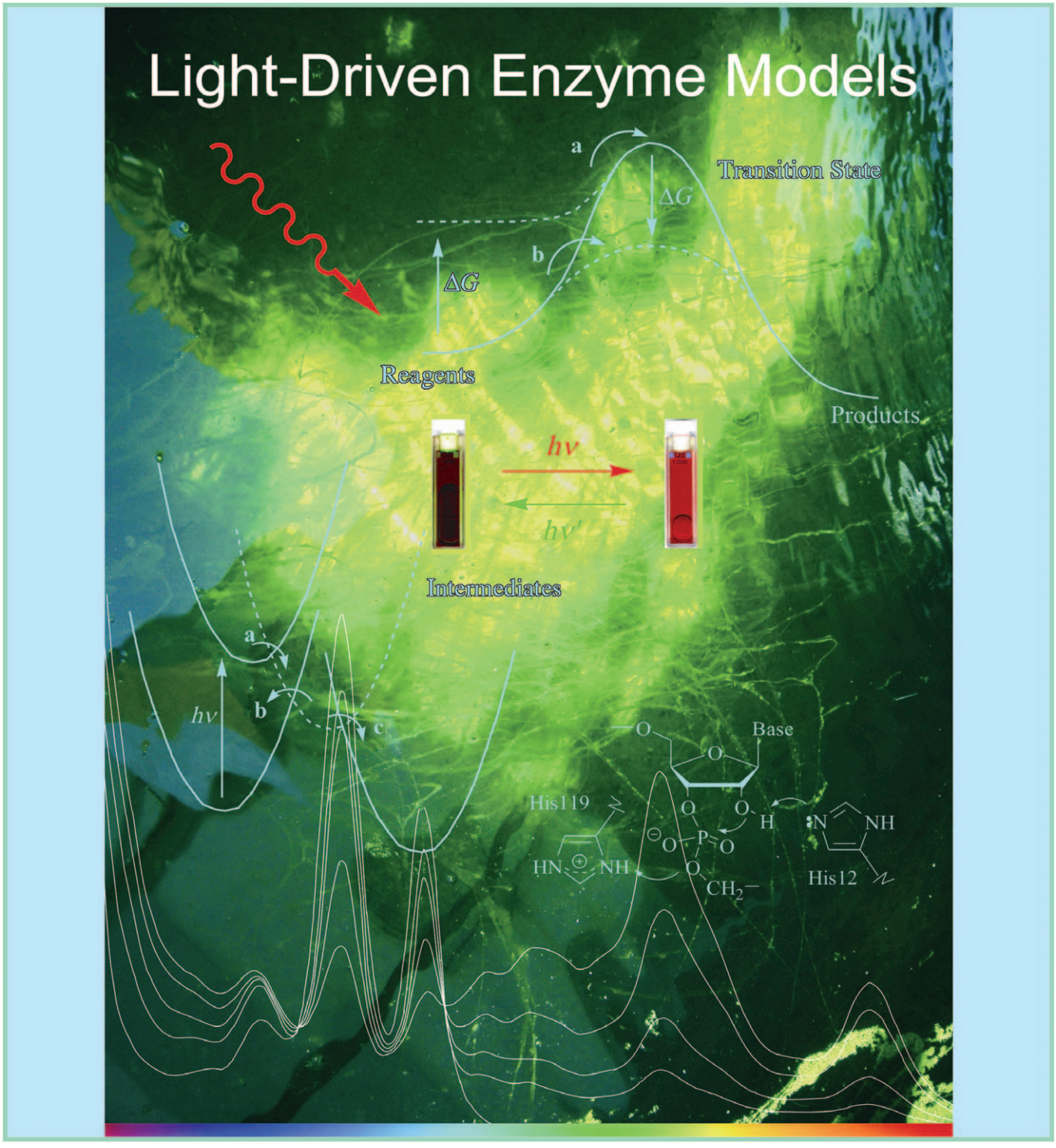

Abstract: Bio-inspired chemistry based on photoresponsive molecules is a rapidly developing new strategy to mimic the function of various biological systems. The interaction of electromagnetic radiation with molecular systems is ideally suited for the control and powering of dynamic processes at the speed of light. Besides typical applications in artificial photosynthesis, many other aspects, such as the catalytic turnover of substrates or the controlled release or uptake of small bioactive molecules, are readily verified with light-driven model systems. The potential of this novel approach in biomimetic chemistry is briefly explored in this concept article.

Keywords: artificial photosynthesis · bioinorganic chemistry · coordination chemistry · enzyme catalysis · photochemistry

Introduction

Over the last decades enormous progress has been made in the elucidation of both structural details and mechanistic aspects of metalloenzymes and other biocatalysts.[1] These important insights can now be systematically exploited and certainly will have a significant impact on the rational synthesis of artificial bio-inspired systems in the near future. The search for laboratory procedures designed to imitate natural chemical processes (e.g., photosynthesis) and the development of new compounds that are able to mimic biological materials in their structures or functions (e.g., biocatalysis) have been defined as the major goals of biomimetic chemistry.[2]

From a chemical point of view, and also in terms of potential practical applications based on biomimetic systems, the construction of robust and synthetically less demanding low-molecular-weight analogues of protein active sites is a highly desirable goal. However, an important disadvantage of such small-molecule-based biocatalyst model compounds is that they are usually not able to simulate the environmental effects and dynamic structural constraints imposed by the natural protein matrix in the course of catalytic turnover.[3] Successful examples of artificial systems with satisfactory biomimetic performance are therefore still very rare in the field. As will be outlined here, this intrinsic problem of synthetic catalyst systems designed to mimic enzyme chemistry can be elegantly solved by the involvement of photochemical key steps. This strategy, however, requires skipping the limitations suggested by the assumption that any artificial system should try to closely duplicate the *structural* features of the native catalytic center to be copied. Instead of this, following the design principles of bionics,[4] the challenge is to learn as much as possible from the evolved features of biological materials or processes, and to keep at the same time as much resemblance to the natural system as necessary in order to achieve an efficient *functional* analogue. This powerful new approach to biomimetic and bio-inspired chemistry opens the door for the application of a much broader variety of synthetic building blocks than can be found in natural systems, in which the limited availability of the chemical elements has significantly constrained the capacity of evolution.

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From Photons to Bionics: Some Basic Design Strategies

A photon is at the same time a quantum of energy and a bit of information.[5] Both aspects can be exploited for the construction of functional model systems mimicking the overall performance of natural systems. This section will briefly describe and summarize some of the main advantages of using photoresponsive molecular components for the modeling of biocatalytic and bioregulatory properties.

Thermodynamic aspects of photoactivation: The absorption of light leads to an activation of the irradiated compound. For a short time existing in the excited state, a molecule reaches an energy level which is situated considerably above that of the corresponding ground-state species. From an energetic point of view, ultraviolet- or visible-light irradiation is usually sufficient to pass the typical activation barriers of most chemical transformations. Thus, it is not surprising that many reactions, which are thermodynamically or kinetically inaccessible in the ground state, can occur with high efficiency from electronically excited states. This general feature makes photochemical activation under ambient conditions an ideal strategy for the functional modeling of difficult or energetically demanding chemical transformations that are otherwise restricted to the expertise of biocatalysis. It is important to be aware, however, that photochemical reactions are not merely light-accelerated thermal processes. The excited-state species formed in the primary steps of photolysis should be considered as modified chemical compounds with a new set of molecular properties. For a successful design of suitable model systems, it is of fundamental importance to keep in mind that the population of excited states of different orbital types can result in quite different reactivity patterns. Therefore, photoproducts may occur that are not obtained at all in thermochemical pathways. Of course, this last feature may turn out to be one of the decisive benefits of the approach.

Clearly, the most important type of chemical reaction, which not only relies on the general advantages of photoactivation, but even critically depends on light absorption as a central driving force, is found in the context of photosynthesis. The laws of thermodynamics impose certain limitations on the efficiency of all energetically uphill photochemical processes. This aspect is of great importance for the development of artificial systems that mimic natural photosynthesis in the conversion and storage of solar energy.[6] In principle, any chemical process that occurs with an overall free-energy storage in chemical bonds could be useful for the purpose of photochemical energy conversion. A representative selection of endoergic substrate transformations that have been proposed as potential targets for the artificial photosynthetic generation of fuel products is summarized in Table 1.

Table 1. Photosynthetic transformations and their thermodynamics[a]

Catalyzed net reaction	n e$^-$	$\Delta G°$ [kJ mol^{-1}]	$\Delta G°$ [eV][b]	λ_t [nm]
$2H_2O \rightarrow H_2 + H_2O_2$	2	355	1.84	674
$CO_2 + CH_4 \rightarrow CH_3OH + CO$	2	142	0.74	1676
$2H_2O \rightarrow 2H_2 + O_2$	4	475	1.23	1008
$CO_2 + H_2O \rightarrow CH_2O + O_2$	4	506	1.31	950
$N_2 + 3H_2O \rightarrow 2NH_3 + 3/2\,O_2$	6	677	1.17	1060
$CO_2 + 2H_2O \rightarrow CH_3OH + 3/2\,O_2$	6	701	1.21	1025
$CO_2 + 2H_2O \rightarrow CH_4 + 2O_2$	8	818	1.06	1170

[a] Partially adopted from references [7–9]. [b] Calculated per electron transferred.

The theoretical efficiency limits for such energy-storing photoreactions arise as an inherent consequence of the quantum nature of the conversion process. Only light with a wavelength shorter than that of the threshold value λ_t is able to drive these reactions at all. The optical properties and lowest excited state levels of suitable dye-sensitizers (or the band-gap energies of other types of absorbers involved) must, of course, satisfy this basic requirement. Furthermore, under polychromatic irradiation such as the absorption of direct solar light, a theoretical optimum exists for the photoenergy conversion process. The maximum value of the thermodynamic conversion efficiency is directly related to the band-gap energy of the photosystem and it increases considerably with an increasing approximation of the real absorber characteristics to the limiting threshold wavelength.[10] As can be seen from the data listed in Table 1, several potential fuel production processes would (under optimized conditions) only require photons of rather low-energy content per electron transferred. A second important design principle for the construction of both natural and artificial photosynthetic devices is therefore given by the demand for an efficient long-wavelength sensitization extending as far as possible into the red or near infrared region of the electromagnetic spectrum. One of the major current challenges in the field of photochemical conversion and storage of solar energy, including artificial photosynthetic devices, is the search for novel photosensitizer molecules that are able to fulfill these requirements .[6] A representative example for modeling the spectroscopic features of photosynthetic light-harvesting pigments with robust synthetic coordination compounds is shown in Figure 1.

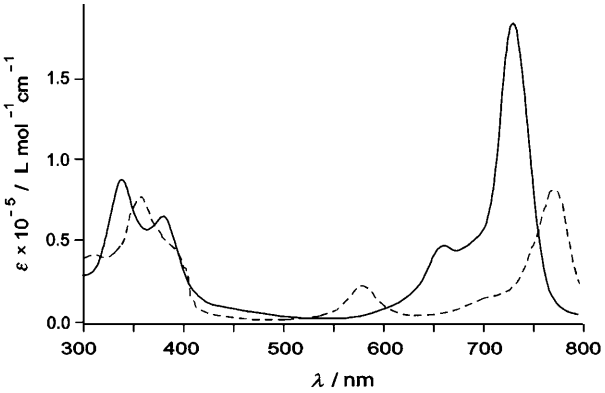


Figure 1. Comparison of typical native and artificial photosynthetic chromophores: Bacteriochlorophyll *a* extracted from antenna-complexes of purple bacteria (-----[11]) and the synthetic metallo-phthalocyanine-complex [(Pc)Sb]F (——[12]).

Acceleration of spin-forbidden processes: Whenever chemical bonds are formed or broken, the valence electrons of the participating species get redistributed. Many substrate transformations of coordination compounds or metallobiomolecules involve a change in spin along their reaction coordinates. For example, the binding of O_2 to certain transition-metal centers is formally a spin-forbidden reaction. In the context of bioinorganic and biomimetic dioxygen activation involving binuclear copper sites, the important mechanistic role of intersystem crossing (ISC) between singlet and triplet states has recently been pointed out.[13] Sometimes, such a spin change can open access to a lower energy pathway through reaction intermediates with a different number of unpaired electrons. If this is the case, the occurrence of intersystem crossing may allow a formally spin-forbidden chemical reaction to proceed even faster than a corresponding process in which the spin is conserved. This interesting phenomenon, which has been termed spin acceleration,[14] is schematically illustrated in Figure 2.

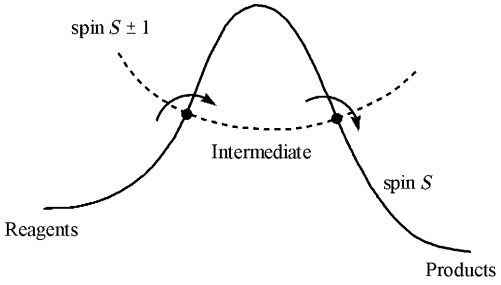


Figure 2. Qualitative energy profile for a spin-accelerated chemical reaction.[14]

Besides significant influences on the rate of a chemical reaction, the participation of spin inversion in the mechanistic key step of a substrate transformation can lead to dramatic effects on the resulting stereoselectivity of the process. A spin-dependent branching of different reactivity patterns seems to be quite common in the field of metal-complex-assisted redox catalysis. This puzzling mechanistic effect of intersystem crossing has been rationalized with the concept of a so-called two-state reactivity of single oxidants.[15] Several recent theoretical and experimental studies have emphasized the important role of spin-state crossing and competing reaction channels with different spin characteristics for the tuning of asymmetric catalysis and the control of regioselective reactivity of metal-based redox centers.[16–19]

In biological systems, the switching between states with a different number of unpaired electrons, for example, low- and high-spin transition-metal centers, is a very common strategy for the control of both catalytic activity and substrate affinity. In an enzyme, these effects are usually induced by reversible changes of the protein conformation around the active site. On the other hand, it is known that the phenomenon of spin crossover in metal complexes is readily achieved by light absorption,[20] and that intersystem crossing is one of the most fundamental processes in the excited-state deactivation cascade of molecules and supramolecular assemblies.[5,21–24] In the absence of a protein matrix, functional biomimetic model systems based on photoreactive compounds may therefore rely on the very convenient possibility of directly influencing the spin state at a substrate binding site. Since many highly desirable features, such as the stereoselectivity of chemical reactions, can evidently be channeled by appropriate spin control, it seems worthwhile to include the properties of excited-state potential-energy surfaces in the considerations of rational catalyst design. Especially, a more detailed theoretical knowledge of factors influencing the probability for potential surface crossing will become a helpful tool to fine-tune the targeted reactivity of new photocatalysts. For example, short-range interactions, such as spin–orbit coupling, due to the presence of heavy atoms could be applied to change the intersystem crossing rates into the desired direction or to diminish spin-related barriers. In this context, it is interesting to note that spin multiplicity is also a key factor in determining the lifetime of photogenerated radical pairs in electron-transfer reactions,[25] and that heavy-atom-induced spin catalysis has already been successfully exploited for the study and modification of metalloenzyme radical reactivity.[26]

Destabilization and structural changes: Ligand-based strain and steric effects can strongly influence the efficiency and selectivity of metal-complex-catalyzed reactions.[27] For biological substrate transformations, the structure and conformational dynamics of the enzyme has clearly been identifed as the origin of catalytic activity.[28] Besides the possibility of tunneling through activation barriers,[29] the enormous rate enhancements observed in enzymatic reactions usually require a minimization of the energy difference between the starting materials and the transition state involved in the catalytic reaction pathway. In general, the reduction of the corresponding activation energy may be achieved by a stabilization of the transition state or by raising the free energy of the ground state (Figure 3).

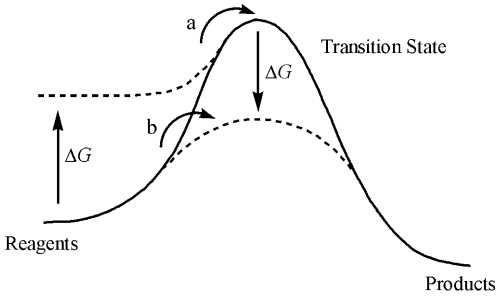


Figure 3. Catalysis of chemical reactions a) by ground-state destabilization, or b) by transition-state stabilization.

It is the synergy of both complementary strategies that leads to the remarkable rate accelerations of biocatalytic processes.[28] This concept, related to the rack-, entatic-state, and induced-fit approaches,[30–33] involves a destabilization of the substrate when it interacts with the active site of an enzyme. Three different types of strain factors may contribute to an increased free energy of ground-state materials in a substrate–catalyst complex (pathway a in Figure 3).

When molecules are pre-organized to adopt a structure resembling that of the transition state, the necessary restriction of conformational flexibility reduces the entropy and thus raises the ground-state free energy of the system.[34–36] Besides such entropic contributions, which are due to mobility restriction, a second important rate-accelerating factor is related to chemical strain effects that may occur upon substrate binding. Especially the activation of molecules by twisting and stretching of bonds appears to play an important role in catalysis by some enzymes.[37–39] Ligand-based constraints around metal sites have also been shown to influence the redox potentials and electron-transfer kinetics of coordination compounds in agreement with the entatic-state hypothesis.[40] The third potential contribution of protein structure to ground-state destabilization and catalytic substrate activation is of electronic nature. Binding of the substrate and its approximation to polarizing groups may lead to a significant electron redistribution that allows the selective activation of certain regions of the molecule.[41–43] The ability to direct a trajectory that maximizes favorable electronic structural changes and to control the optimal orientation of reacting orbitals seems to play a major role in the catalytic power of enzymes.[44]

Photochemical activation, unlike thermal activation in the form of heat, is always a very selective process. Light absorption and the formation of excited-state molecules creates new chemical species with modified properties, including shape, bond structure, and electronic distribution. With the choice of appropriate photosensitive precursors, it there-

fore becomes possible to mimic the crucial chemical and electronic strain factors discussed above in the context of enzymatic reactions. For this purpose, the conformational changes and orbital-steering effects of the protein environment must be successfully replaced by an artificial light-sensitive substrate-activation site. Several aspects of inorganic and supramolecular photochemistry can be exploited to simulate the ground-state destabilization and transition-state approximation along a biocatalytic reaction pathway with low-molecular-weight coordination compounds. For example, the twisting or stretching of bonds may be achieved photochemically by the involvement of antibonding orbitals. Such distortions usually cause a Stokes shift between absorption and emission spectra.[5] The magnitude of this shift can serve as a simple and direct experimental measure for the degree of the desired structural rearrangements between ground- and excited-state species. Furthermore, light-induced changes in orbital degeneracy can be exploited to modify, quench, or enforce molecular distortions according to the Jahn–Teller effect.[45] In metal complexes, the basic factors influencing the site of selective labilization of coordinated ligands are quite well understood and can be predicted by appropriate theoretical models.[46,47] Finally, the population of excited states with charge-transfer (CT) character may be used to control the electron-density distribution in a substrate molecule or the electrostatic interactions around a substrate binding site. The solvatochromic behavior of such systems can be easily studied, in order to evaluate the degree of charge transfer and to calibrate the fine-tuning of electronic strain effects by variations of substituent patterns or ligand types.[48]

In principle, the chemical reaction rates of systems involving an activation barrier can also be directly controlled by mode-selective vibrational excitation, and even the branching between different product formation channels may be influenced by exciting certain vibrational modes.[49] In summary, all of these general considerations make electronic strain and structural distortions involving the formation of excited state species a very attractive route for driving and controlling biomimetic catalytic processes.

General acid–base catalysis and proton transfer: The existence of living systems requires a sufficient stability of their molecular components under physiological conditions (mainly aqueous solutions near neutral pH). At the same time, there must be controlled mechanisms for accelerating the transformation of biomolecular building blocks in the course of metabolic processes. The conversion of neutral organic molecules into their charged conjugate acid or base forms may lead to an enormous increase in reactivity. Thus, it is no surprise that the most common type of biocatalytic reactions is proton transfer.[50,51] Almost every enzymatic reaction includes one or more proton-coupled steps, and hydrogen-bonding interactions frequently contribute to transition-state stabilization (pathway b in Figure 3). For example, the heterolytic cleavage of stable C–H bonds through proton transfer is the first mechanistic step in many biocatalytic systems. Elimination reactions, carboxylations, phosphoryl-transfer reactions, and a variety of other important substrate transformation processes involve the deprotonation of carbon centers under mild conditions.[52] Proton transfer also plays a fundamental role in the field of bioenergetics.[53]

Many biocatalytic systems employ transition-state proton bridging and intramolecular proton-transfer steps (general acid–base catalysis) as part of their strategy to accelerate substrate conversion reactions.[55] A representative example of acid–base biocatalysis with functional histidine residues around the substrate binding site is illustrated in Figure 4 for RNase A, a typical hydrolytic enzyme.[54]

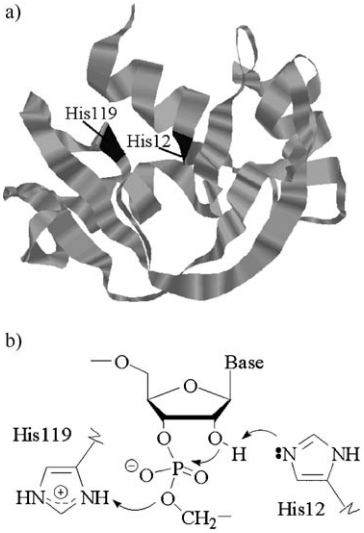


Figure 4. a) Ribbon diagram of the three-dimensional structure of ribonuclease A (data from PDB accession code 1RNW) and location of the amino acid residues His12 and His119 most important for general acid–base catalysis in the substrate binding pocket. b) Mechanism of phosphate ester cleavage of substrate RNA involving proton transfer between the imidazole groups of two histidine residues. The side chain of His12 acts as a base that abstracts a proton from the 2′-oxygen of a substrate molecule and thereby facilitates nucleophilic attack at the phosphorus atom. His 119 acts as an acid that protonates the 5″-oxygen and accelerates its displacement.[54]

The important functional role of amino acid residues in enzymatic catalysis involving proton-transfer reactions can be readily simulated with photochemical methods. It has been recognized decades ago, that the acid–base properties of certain molecules are drastically modified in their excited states,[56] and appropriate methods have been developed for the estimation of the corresponding changes in acidity or basicity upon light absorption.[57] Typical examples are characterized by pK_a value variations of 4–6 units, which is in the range of the transition-state effects observed in hydrolytic enzyme catalysis.[58,59] For the rational design of artificial-light-dependent systems, several excellent accounts of photoinduced acidity constant changes of organic molecules are available in the literature.[60–62] In the field of inorganic photochemistry, such systematic investigations are still rare.

Nevertheless, it is quite clear that metal complexes with acid–base sites on the ligand periphery also exhibit immense changes in their nucleophilic character and their acid–base properties upon excitation.[63] The bonds most frequently encountered in the context of excited state proton transfer reactions include O–H, N–H, and C–H, but the net transfer of hydrogen atoms may also involve sulfur and phosphorus sites with implications for the reactivity of biologically active substances.[64,65] It should be mentioned here, that in recent years there has been significant progress in theoretical models for describing the dynamics of proton-transfer processes.[66–68] This information may also serve as a valuable guideline for the construction of novel biomimetic systems that rely on photochemically controlled general acid–base catalysis. Several basic aspects of homogeneous proton-transfer photocatalysis have already been discussed for reactions involving aromatic organic molecules.[69] The corresponding photoreactivity of coordination compounds and supramolecular systems will certainly offer interesting contributions to the emerging field of biomimetic photocatalysis in the near future.

Catalysis of multielectron-transfer reactions: Light absorption modifies the redox potentials of chemical compounds. Because of the additional free-energy content, an excited state species is always both a stronger oxidant and a stronger reductant than the corresponding ground-state molecule. This general feature makes photoreactions ideally suited for studying electron-transfer processes including bioinorganic and biomimetic redox chemistry. In many cases in which changes in shape, size, or solvation are negligible, the excited-state oxidation or reduction strength of a system is directly related to the ground-state standard potentials of the redox couples. The photochemically enhanced redox reactivity may then be estimated in sufficient accuracy from electrochemical data and the one-electron potentials corresponding to the spectroscopic energy levels of the excited states populated.[5,70] Several compilations of the relevant data are available in the literature; this facilitates the selection of an appropriate photosensitizer for a certain redox process.[71–74] While many excellent reviews and specialized books have been published covering the various aspects of photoinduced electron-transfer (PET) reactions,[75–82] there are still some important unresolved problems concerning the overall efficiency of biomimetic electron-transfer processes and the redox-energy coupling in electron-transfer chains of artificial photosynthetic systems. This section will therefore focus on some of the fundamental concepts to catalyze electron-transfer reactions,[83,84] and to avoid undesired back-electron-transfer processes by coupling primary charge-separation steps to a pairwise or multiple exchange of electrons in order to promote the formation of permanent redox products.[7]

A very powerful method to accelerate the rate-limiting steps of photoinduced electron-transfer reactions is the introduction of additional molecular components that are able to stabilize one or more of the primary redox products by complexation. Several metal ions, such as alkaline-earth or rare-earth cations, which are not directly involved in electron transfer but can coordinate to the radical intermediates formed, have been shown to act as efficient catalysts in this context.[84] Besides the general possibility of catalytic acceleration of the initial electron-transfer steps, a further important design strategy for biomimetic model systems can be derived from the natural engineering principles of oxidoreductase systems. It has been outlined that in proteins the geometrical arrangement and especially the proximity of redox cofactors involved in electron-transfer chains is of crucial importance for an optimized function based on rapid electron tunneling.[85] Similar considerations for the spacing of redox centers (typically 14 Å or less) should be taken into account for the construction of low-molecular-weight biomimetic model systems, supramolecular assemblies, or coordination polymers with a specific redox function.

By far the most critical and difficult challenge in biomimetic redox systems, however, remains the successful coupling of single-electron-transfer reactivity to suitable follow-up steps, which facilitate permanent chemical transformations that require an overall exchange of multiple redox equivalents. As already outlined in Table 1, the oxidation or reduction of many biological substrates leads to changes in oxidation state by two or more units. The net transfer of more than one redox equivalent in chemical reactions usually involves mechanistic pathways that are intrinsically more complex than those of single electron-transfer processes. Typically, the coupling of chemical follow-up steps is accompanied by larger bond and shape reorganizations in molecules.

In this context, photochemical activation involving charge transfer excited states and light-triggered structural variations due to Jahn–Teller effects can be applied to induce suitable bond variations and distortions around a substrate binding site. Such a light-induced generation of reactive intermediates, which are already approaching a product-like geometry, can significantly support the occurrence of nearly activationless secondary electron-transfer steps. This strategy is also very helpful to channel a certain two-electron redox process predominantly into one direction and to suppress chemical back reactions by the presence of a sufficiently large activation energy barrier for the formation of the corresponding one-electron reaction intermediates in the absence of light (Figure 5).

Accumulation and transfer of multiple redox equivalents around a substrate binding site requires the supply of a reaction platform with at least two sufficiently stable oxidation states separated by more than one unit. Several different approaches toward multielectron-transfer photoreactivity may be successful. One of the basic strategies followed in both natural and artificial systems includes the cooperative action of two or more redox active metal centers in close proximity to the substrate. The participation of coordinated organic ligands acting as electron shuttles or intermediate redox reservoirs enables the same function in mononuclear metal complexes. Another important strategy is related to the possibility of photoinduced atom or group transfer, which also

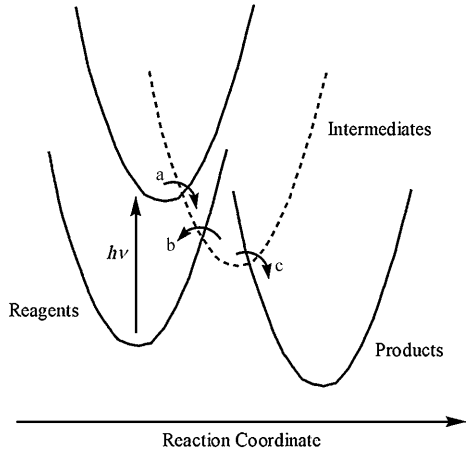
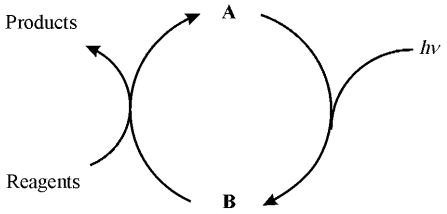


Figure 5. Schematic potential energy diagram for a stepwise photoinduced two-electron transfer process (adapted from reference [7]). The primary electron transfer (a) from the excited-state energy surface results in an intermediate charge separated state (dashed curve). Deactivation of the equilibrated intermediate state occurs by one of the competing processes of either back-electron transfer to the ground-state reagents (b), or by a second electron-transfer step (c) leading to the formation of permanent photoredox products.



Scheme 1. Simplified scheme illustrating the basic principle of photocatalytic reactions that require at least one photon per product molecule formed. Substrate conversion is catalytic with respect to the ground state species **A**, which is not consumed in the reaction. The reversible generation of **B** requires the absorption of light quanta in every single turnover of the process. **B** may represent an excited state of **A** (photosensitized reaction) or a photoproduct resulting from substrate or catalyst irradiation.

results in a net exchange of more than one redox equivalent with the substrate. The construction of potential multielectron transfer (MET) photosensitizers following combinations of these basic concepts has already been described in the literature.[86] In this context, a very promising new development in the field of multielectron photochemistry is the exploitation of two-electron mixed-valence systems.[87]

Signaling and regulation mechanisms: A frequently neglected, but nevertheless very crucial, advantage of photochemical approaches toward biomimetic model compounds is the convenient triggering and control of reactivity by light absorption. It is known that the metabolic functions of living organisms are maintained by a complex network of regulation mechanisms. Typically, enzymatic catalysis may be controlled by a variety of processes including allosteric interactions, stimulation and inhibition by control proteins, proteolytic activation, redox transformations, or reversible covalent bond modifications, such as phosphorylation and dephosphorylation.[88–90] Besides the natural principle of complete recycling of resources, the application of such efficient mechanisms for switching and controlling reactivity is a highly desirable goal for future biomimetic or green chemical-process engineering.

For this purpose, the construction of photocatalytic cycles involving substrate-transformation processes that are noncatalytic with respect to photons is of special interest (Scheme 1). Such types of light-driven systems, covering many different classes of photocatalytic reactions termed photoassisted processes, photosensitized reactions or catalyzed photolyses,[91–93] only work during continuous irradiation and thus provide a straightforward method to switch on and off or to modify the overall specific activity simply by variations of the photon flux. The construction of biomimetic substrate-transformation cycles according to the principles shown in Scheme 1 allows us to simulate the function of natural regulation mechanisms, such as reversible, noncompetitive inhibition of catalytic activity.

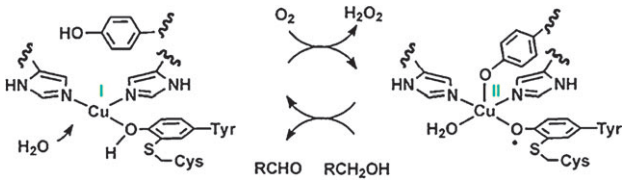
On the other hand, the removal of an irreversible inhibitor substance may be simulated by the introduction of a photolabile protection group in both natural and artificial systems. For example, the function of so-called "caged" systems can be rapidly switched on from an inactive resting state by the input of an external light signal.[94–98] It should be mentioned, however, that in contrast to the strategy of light-regulated photocatalytic systems, this kind of photochemical triggering of biological activity is only possible once per protecting group introduced. Nevertheless, many of these currently emerging tools for external signal transmission, phototriggering, and light-mediated activity control in biological and biomimetic systems will certainly contribute to rapid progress in the development of artificial photonic proteins[97,98] and might even revolutionize the elucidation and control of biochemical processes inside the living cell.

Selected Applications of the Concept

The integration of light-driven key-steps for the rational design of functional enzyme models provides an enormous versatility, which will be briefly illustrated in the following section. The selection of recently published examples includes a comparison of the efficiency of native and synthetic radical-enzyme catalysts, the application of photoredox-active multielectron reagents in artificial photosynthesis and the utilization of photochromic molecular switches for the reversible control of protein activity in living systems.

Controlled radical mechanisms are known to play a fundamental role in biocatalysis, and there are substantial efforts to understand and mimic these processes for synthetic applications.[99–102] Frequently, hydrogen-atom abstraction is considered to be the rate-limiting step in the catalytic oxidation of organic substrates by radical enzymes. A typical example is the transformation of alcohols into carbonyl com-

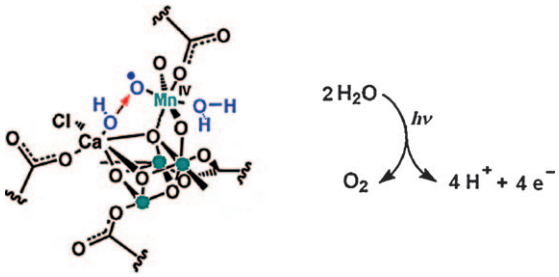
pounds catalyzed by oxidoreductases, such as the copper-dependent metalloenzyme galactose oxidase (Scheme 2). Very robust bio-inspired enzyme model systems, which successfully mimic the catalytic performance of galactose oxidase and related biocatalysts under irradiation, have recently been described.[104]



Scheme 2. Simplified redox cycle for the conversion of primary alcohols to the corresponding aldehydes coupled to peroxide production catalyzed by the radical metalloenzyme galactose oxidase.[105] The overall two-electron process formally corresponds to a hydrogen-transfer reaction with dioxygen acting as the H_2 acceptor.

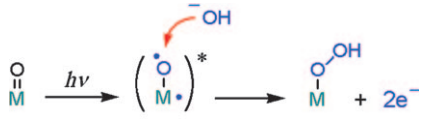
The probably most significant finding of this study was the fact, that the functional photochemical model was able to convert the corresponding substrates even more rapidly (with a turnover frequency about three times as high) as the native enzyme under identical conditions.[104] In contrast to the biocatalytic system, the reaction could be completely turned off and on again in the absence or presence of light. In other words, all the advantages of mild and environmentally benign enzymatic reaction conditions, such as the performance in water under ambient temperature and pressure, and the very efficient dioxygen activation directly using air, could be coupled to a robust synthetic catalyst that allows for a convenient and complete reaction control as an additional important benefit.

Another emerging domain of photochemical enzyme model compounds is the catalysis of otherwise very hard to achieve substrate conversions involving thermodynamically rather stable or kinetically inert molecules. For example, the partial low-temperature oxidation of alkanes such as methane, the fixation of dinitrogen, or the reductive transformation of carbon dioxide into more useful resources of carbon belong to this category. As already discussed in previous sections, the fundamental problems of providing efficient multielectron-transfer reagents have hampered significant progress in this challenging area. A classical example in this context is the desperate search for functional model compounds of the light-driven water-plastoquinone oxidoreductase, better known as photosystem II (PS II) of oxygenic photosynthetic organisms.[106,107] Enormous ongoing efforts are made to mimic the biochemistry of water cleavage into dioxygen, protons, and electrons, providing reducing equivalents for photosynthetic fuel production in artificial systems. At the core of this problem is the activation of substrate water for the first two-electron oxidation coupled to the formation of an oxygen–oxygen σ-bond.[108,109] The native catalytic site consists of a Lewis acidic calcium cation fixed in close proximity to redox-active manganese centers organized in a cluster structure, which forms the inorganic core of the water-oxidizing complex (WOC) or oxygen evolving complex (OEC) of photosystem II. A still speculative, but plausible mechanism for the decisive catalytic step in the water splitting reaction is depicted in Scheme 3.



Scheme 3. Schematic representation of the electron donor site of oxygenic photosynthesis.[106] The formation of the O–O bond is considered as the most demanding key step in the overall four-electron oxidation of H_2O to form dioxygen. A potential catalytic mechanism involves the nucleophilic attack of activated water (deprotonated in the coordination sphere of Ca) at a Mn^{IV}-oxyl radical species.

A straightforward model reaction involving a very similar O–O bond-formation step relevant to artificial photosynthetic water oxidation has already been demonstrated with high-valent multielectron-transfer photosensitizers based on antimony porphyrins.[86] Although the functional role of the calcium center has still been neglected and was simply replaced by driving the photocatalytic reaction at elevated pH, the most important finding of this work was the efficient formation of the two-electron water oxidation intermediate, hydrogen peroxide, under strictly anaerobic conditions, by using monochromatic visible-light irradiation (546 nm) to power this energy-storing process. Instead of a high-valent Mn^{IV}-oxyl radical species, as proposed for PS II (Scheme 3), the system is suggested to involve an excited-state intermediate with sufficient charge-transfer character to provide a strongly electrophilic metal–oxo site for the nucleophilic attack of hydroxide ions,[86,110] according to the simplified reaction sequence summarized in Scheme 4.



Scheme 4. Photochemical activation of stable metal–oxo species such as $M=Sb^{V}$ leads to the formation of a reactive oxyl-radical-type intermediate with a spin-density distribution favorable for O–O bond formation.[86] Hydrolysis and deprotonation regenerates the photocatalyst leaving hydrogen peroxide and reduction equivalents.

The electrons obtained in this partial water oxidation process are temporarily stored in the ligand periphery, forming metastable porphyrin radical anions, which are known to be powerful reductants for the catalytic evolution of dihydro-

gen.[111–113] This reaction closes a photoredox cycle for a simple, artificial, photosynthetic energy-conversion process based on H_2O_2 and H_2 formation with very interesting thermodynamic features already mentioned in Table 1.

Besides such purely synthetic artificial enzymes driven by light, an increasing number of photoresponsive systems based on chemical–biological hybrid architectures is currently emerging.[114] An illustrative example of such a hybrid system capable of switching enzymatic function in a reversible photocycle is given in Figure 6.

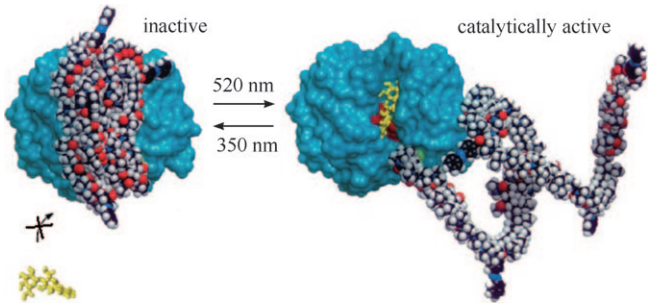


Figure 6. Wavelength-dependent regulation of hydrolytic activity in an artificial protein–copolymer conjugate. The access of substrates to the active site of the modified endoglucanase enzyme EG12A is reversibly blocked by light-induced structural changes of the attached polymer chain coil, simply containing *Z*(*cis*)–*E*(*trans*) isomerizable azobenzene subunits as photochromic switches (adapted from reference [115]).

The photochemical regulation of the catalytic performance of this artificial enzyme is based on the induction of larger structural changes localized in suitably attached subunits, which are designed to restrict access to the substrate binding pocket upon an external stimulus. A similar strategy that makes use of photochromic switches has also been followed for the external control of protein and metallopeptide conformation,[116,117] nucleic acid and ribozyme photoregulation,[118] and for the reversible blocking of ion channels in living systems,[119] with larger impacts to be expected for molecular-, cell-, and neurobiology. A comprehensive treatment of all these current developments, however, is not within the scope of the present concept article.

Conclusions

Photochemical key steps provide a powerful tool for the remote control of complex biological and biomimetic processes. Light-responsive catalysts can be rationally constructed according to the functional design principles extracted from natural enzymes. These compounds are able to trigger and drive challenging chemical reactions, such as selective substrate transformations, multielectron catalysis, and artificial photosynthesis under mild conditions, which otherwise could hardly be achieved at all. Besides first examples and proof-of-principle studies, a systematic exploitation of several of the ideas and concepts discussed in this article is still in its infancy. However, similar approaches are followed and rapidly progressing at the frontier of several pioneering research groups.[120] These developments have the potential to stimulate the search for a broad variety of photochemical applications ranging from such diverse fields as small-molecule activation, bio-inspired catalysis, or renewable fuel production up to the development of versatile new tools for medicinal chemistry and life sciences.

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