eral of them bound FMRP with high affinity in vitro. The microarray data and computer predictions garnered a list of mRNAs that are potential targets of FMRP. Many of these mRNAs encode important neuronal proteins such as semaphorin and the microtubule-associated protein MAP1B. Remarkably, Zhang *et al.* (*6*), working in a fly model of fragile X syndrome, show that the fly homolog of FMRP, dFXR, binds to and represses the translation of an mRNA encoding the fly homolog of MAP1B. They suggest that the regulation of MAP1B by dFXR is necessary for normal synaptic activity, because a MAP1B mutant is able to correct the synaptic anomalies elicited by dFXR deficiency.

The next step will be to analyze how the proposed mRNA targets are affected by FMRP deficiency or overexpression. The effects of binding to FMRP may vary for different mRNAs, because the G quartets can be found either in their coding sequences or in their 5′- or 3′-untranslated regions. Furthermore, of the 251 mRNAs whose distribution on polysomes was significantly altered in fragile X cells, half were found at an increased frequency and half at a decreased frequency, arguing against the possibility that FMRP is always a translational repressor. Indeed, the presence of a G quartet in an mRNA may provide a zip code indicating that the mRNA should be transported to a postsynaptic or other selected site in the cell.

Our understanding of the complexity and subtlety of the fragile X phenotype induced by FMRP's absence will certainly benefit from analysis of the mRNA targets of this protein. We also need to clarify whether FMRP shares some of its activities with its close relatives, FXR1P and FXR2P. The new work unveils exciting avenues for future research into fragile X syndrome.

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PERSPECTIVES: SURFACE SCIENCE

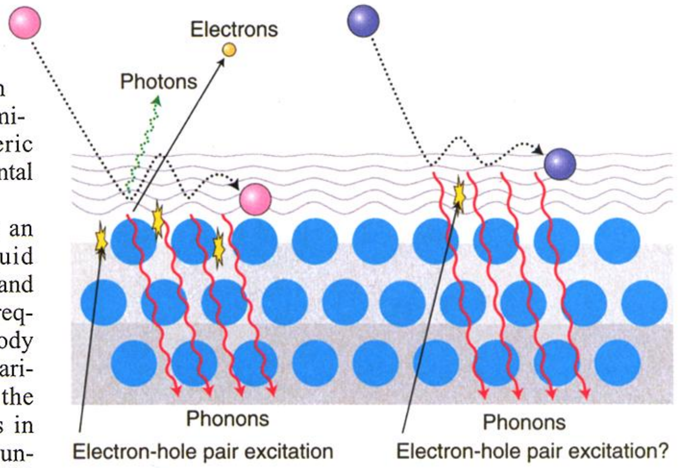
Hitting the Surface—Softly

Daniel J. Auerbach

In many chemical reactions, reactants first adsorb on a solid surface and then interact to form products. Such reactions play an important role in the industrial-scale production of chemicals, materials processing, atmospheric chemistry, biochemistry, and environmental science.

Adsorption—the process whereby an atom or molecule in the gas or liquid phase loses some of its initial energy and becomes bound on a surface—is a prerequisite to all these reactions. In many-body systems, energy can be lost through a variety of loss channels. Understanding the relative importance of these channels in the adsorption process is thus key to understanding these reactions. On page 2521 of this issue (*1*), Gergen *et al.* show that energy loss from electronic excitation of the solid may play a more pervasive role in adsorption than was previously believed.

As an incident particle approaches a solid surface (see the figure), it interacts with the electrons of the solid. By perturbing these electrons, it also generates interactions with the ion cores in the lattice. Two broad classes of energy-dissipation channels arise from these interactions: excitation of lattice vibrations (or phonons) and electronic excitations, which include particle emission, photon emission, and the excitation of electron-hole pairs.



Energy-dissipation channels in adsorption. At high adsorption energies **(left)**, many energy-dissipation channels are available, whereas at lower energies **(right)**, only phonons and electron-hole pair generation are possible.

At high interaction energies (see the left part of the figure), there is abundant evidence for electronic excitation. For some channels, particles or photons can be observed directly and their participation in the adsorption process established unambiguously. As early as 1905, Thomson (*2*) observed the emission of negative particles following adsorption of various gases on an alkali metal surface. Many examples of emission of electrons and ions (exoemission) and of photons (chemiluminescence) in highly exothermic reactions at surfaces are now known (*3*).

At lower energies (see the right part of the figure), the importance of electronic excitations in adsorption tends to decrease for several reasons. Processes like exoemision and chemiluminescence cannot occur below a certain energy threshold. Hence, only phonons and electron-hole pairs are available to dissipate energy. Furthermore, the electrons in the solid have more time to adjust smoothly to the perturbation of a slow incoming particle. The system therefore tends to evolve adiabatically, with energy dissipated to phonons rather than to nonadiabatic electronic excitations.

Direct observation of phonons or electron-hole pairs has been difficult. Most of our knowledge of their role in adsorption comes from comparison of theoretical calculations for these channels with experiments in which molecules are scattered from surfaces under well-defined incidence conditions (*4*, *5*). For example, measured adsorption probabilities and angular and velocity distributions of Ar and Xe scattered from a platinum surface (*6*, *7*) are in reasonable agreement with calculations that include phonon excitation but ignore electron-hole pair excitation (*8*). Similarly, adsorption probabilities of alkanes on the same platinum surface are in good agreement with calculations that omit electron-hole pairs (*5*).

These and related, more recent studies

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have led to the general conclusion that electron-hole pair excitations can be ignored or play at most a very minor role in low-energy adsorption. There are, however, important reasons to be cautious about this conclusion. There are small but systematic discrepancies between experiments and theory, and most simulations use semiempirical potentials with many adjustable parameters. Recent calculations show that electron-hole pair excitations can play a substantial role in some systems (*9*).

Direct measurements of electron-hole pair excitation can add much to our knowledge of the adsorption process. Gergen *et al.* (*1*) report such measurements for adsorption energies of 0.2 to 3.5 eV. The authors use a Schottky diode, which enables the detection of electrons from adsorption-induced electron-hole pair excitations, provided that they have energies greater than the Schottky barrier. The energy distribution of the electrons produced is not well known, and it is thus difficult to estimate the absolute detector sensitivity. Notwithstanding these difficulties, the probability of electron-hole pair excitations in these systems is estimated to range from 6 to 100%, implying that electron-hole pairs can indeed play an important role in energy dissipation for a wide variety of adsorption systems.

Gergen *et al.*'s report represents an important step in obtaining systematic information on electron-hole pair generation in atomic and molecular interactions with surfaces. With improved detector fabrication and the use of detectors with variable energy thresholds, it should be possible to map the energy distributions of electrons generated and to measure excitation probabilities more quantitatively. The use of molecular beam techniques to control the energy and angle of incident species can potentially provide great detail about the dynamics of electron-hole pair generation.

Electron-hole pair generation has recently been invoked as a mechanism for vibrational relaxation at surfaces (*10*). The use of Schottky diode detectors will enable a direct test of this hypothesis and provide much needed detail of the electron-hole pair generation. The prospects for future advances are bright.

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PERSPECTIVES: ENZYMOLOGY

Coenzymes and Radicals

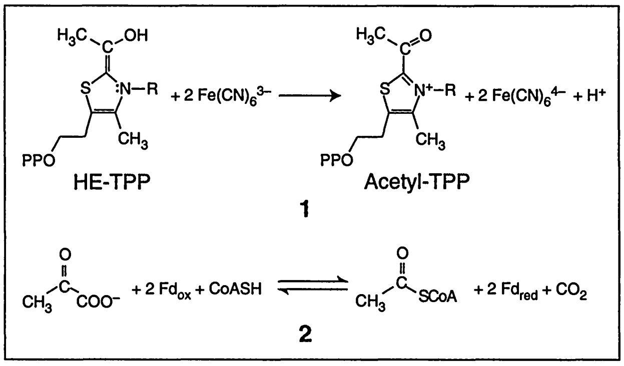
Perry A. Frey

In recent years, organic radicals have come into their own as transient intermediates in enzymatic reactions. Spectroscopic data from electron paramagnetic resonance (EPR) implicate these highly reactive species in the actions of enzymes that catalyze a wide range of biological reactions, including electron transfer, isomerization, oxidation and oxygenation, reduction, DNA repair, and biosynthesis of antibiotics and DNA.

Because of their transient nature, little is known about the structure of the radical species and their mode of action. On page 2559 of this issue, Chabrière *et al.* (*1*) provide a rare view of the structure of a biological radical within its catalytic site. They present the crystal structure of the enzyme pyruvate:ferredoxin oxidoreductase (PFOR), crystallized with the intermediate radical form of hydroxyethylidene–thiamine pyrophosphate (HE-TPP). The structure of the radical shows that the thiazole ring is puckered, a feature that affects its electronic structure.

The participation of organic radicals in enzymatic reactions requires the action of coenzymes, which bind to the enzyme and are essential for its activity but are not permanently altered by the reaction. Many of these coenzymes traditionally facilitate polar (nonradical) reactions. Evidence that traditional coenzymes such as TPP do double duty as radical initiators or facilitors of radical reactions continues to accumulate (*2–10*). Many coenzymes induce substrate radical formation in enzymatic reactions and/or appear at least transiently in radical forms. Some participate in protein radical formation or participate in the biosynthesis of coenzymes such as biotin, heme, and thiamine, presumably by initiating radical formation in precursors (*11*).

TPP has long been known to react through radical intermediates. Most TPP-dependent enzymes can be assayed by observing the reduction of ferricyanide. The enzymatic intermediates are aldehyde derivatives of TPP such as HE-TPP. Two equivalents of ferricyanide oxidize HE-TPP to acetyl-TPP (see reaction 1 in the first figure), which then undergoes hydrolysis to acetate and TPP. As a compulsory one-electron acceptor, ferricyanide must first produce an oxidized, radical form of HE-TPP as an intermediate, which then undergoes a second round of one-electron oxidation to acetyl-TPP. The radical intermediate has not been observed spectroscopically but must have been present, presumably at a low concentration. It has been generated in electrolytic experiments (*10*).



Key reactions. Ferricyanide oxidizes HE-TPP to acetyl-TPP (reaction 1). PFOR catalyzes the TPP-dependent reversible reaction of pyruvate with coenzyme A (CoA) and ferredoxin (Fd) to produce CO_2, acetyl CoA, and reduced ferredoxin (reaction 2).

The enzyme PFOR catalyzes the TPP-dependent reversible reaction of pyruvate with coenzyme A (CoA) and ferrredoxin to produce CO_2, acetyl CoA, and reduced ferredoxin (see reaction 2 in the first figure). During this reaction, TPP-dependent decarboxylation of pyruvate first produces HE-TPP, which then reacts with CoASH and two molecules of oxidized ferredoxin to produce acetyl CoA and two molecules of reduced ferredoxin. Just like ferricyanide, ferredoxin must accept electrons one at a time. The two-electron oxidation must therefore proceed in one-electron steps, and a radical form of HE-TPP must exist at least transiently. This radical has long been known from spectroscopic studies and has been repeatedly reported in the literature as a stable species (*4–6*).

The electronic structure of the HE-TPP radical can be formulated at two protonation levels. Removal of one electron from HE-TPP leads to a cation radical, in which

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