Supramolecular organic photochemistry: Control of covalent bond formation through noncovalent supramolecular interactions and magnetic effects

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Supramolecular organic photochemistry, a field concerned with the interaction of light with supramolecular assemblies of organic molecules, has been inspired by the remarkable structural and dynamic features of guest@host chemistry, particularly as exemplified by enzymes. Exemplars of supramolecular organic photochemistry from soft-matter hosts (micelles) and hard-matter hosts (porous solids) are discussed with an emphasis on how noncovalent interactions, which are at the heart of supramolecular chemistry, can be systematically exploited to control the catalytic and magnetic effects on the formation of covalent bonds from photochemically produced pairs of radicals.

From Molecular to Supramolecular Chemistry

The concept of the organic molecule as an assembly of atoms held together by covalent bonds is a key intellectual unit in chemistry. Chemists have mastered concepts of the covalent bond and demonstrated their mastery through the use of the concepts to design the synthesis of remarkably complex organic molecules and to correlate molecular structure and dynamics with the physical and chemical properties of organic compounds. In the same manner that molecular chemistry may be considered to be the chemistry of atomic assemblies, which are held together by covalent interatomic bonds, supramolecular organic chemistry may be considered to be the chemistry of molecular assemblies that are held together by noncovalent intermolecular bonds (1, 2).

Enzymes As Exemplars of Guest@Host Supermolecules

Perhaps the highest levels of sophistication of applications of supramolecular chemistry are found in living systems, consisting of elegant supramolecular assemblies of organic molecules that make up the machinery whose structures and dynamics enable and support life functions. An important class of life's supermolecules are guest@host complexes (the @ symbol indicates noncovalent bonding between molecular species) for which a "guest" molecule, whose chemistry is of direct interest, is modified catalytically as the result of noncovalent binding to a macromolecular "host." For example, enzymes are macromolecular protein hosts that catalyze the important reactions of noncovalently bound guest organic molecules.

Enzymes are remarkably specific both in the selection of the guest molecules they bind and in the reactions they catalyze (3). The high degree of catalytic selectivity of enzymes results from the very specific structural demands of binding of a guest to an "active site" of the protein framework of the enzyme. The structure and action of enzymes has provided chemists with both a stimulus and an inspiration to design "synthetic enzymes" to provide exemplars for the understanding of supramolecular structure and dynamics that display excellent catalytic and selectivity efficiencies for practical applications. A key supramolecular feature of enzymes is their capacity for "molecular recognition" by which admission to, and binding with, the active site by a particular molecular guest is extremely selective and is based on the enzyme's ability to recognize the guest's size, shape, and chemical characteristics. The process of molecular recognition of the guest from all other molecules in a surrounding aqueous environment and of transport of the guest to the active site involves a sequence of diffusional steps starting with the recognition of the substrate by the exterior of the global enzyme supramolecular assembly, followed by binding of the guest to the external surface of the enzyme. The guest is then vectorially shuttled from the external surface through the enzyme's internal structure until it reaches and is bound to the active site. The active site possesses a size/shape geometry and chemical functionality that are complementary to the size/shape of the guest and which allow specific chemistry of the guest to be catalyzed by the host. Once the chemistry is achieved, because the product's size/shape/chemical characteristics are not complementary to those of the active site, the product is released and the active site becomes capable again of binding another molecular guest.

Host@Guest Supermolecules As Nanoscopic Reaction Vessels

The active sites of enzymes, whose spatial dimensions are of the order of a nanometer (1 nm = 10 Å), are truly nanoscopic reaction vessels for conducting catalytic reactions, involving the making and breaking of covalent bonds of bound guest molecules. A challenge in supramolecular catalysis of synthetic enzymes is to design systems that selectively and efficiently catalyze covalent bond formation from inherently reactive species such as pair of radicals through the noncovalent, intermolecular interactions associated with guest@host complexes. A range of nanoscopic reactors have been used (4) to conduct organic photochemical reactions in the fluid or "soft-matter" phases (micelles, microemulsions, liquid crystals, and polymer films) and in the solid or "hard-matter" phases (zeolites, silica gel, crystals, and semiconductors). We shall consider one exemplar from soft matter (micelles) and one from hard matter (zeolites).

In ordinary molecular solvents, a dissolved molecule may be considered as a guest that is surrounded by a wall or as solvent molecules that form a host "cage" about the guest (5). Micelles and zeolites may be viewed as "supercages" that surround the guest. A supercage influences the chemical and/or physical properties of the guest in a qualitative and/or quantitative manner compared with the molecular solvent cage as a reference. The active site of an enzyme represents the cage *par*

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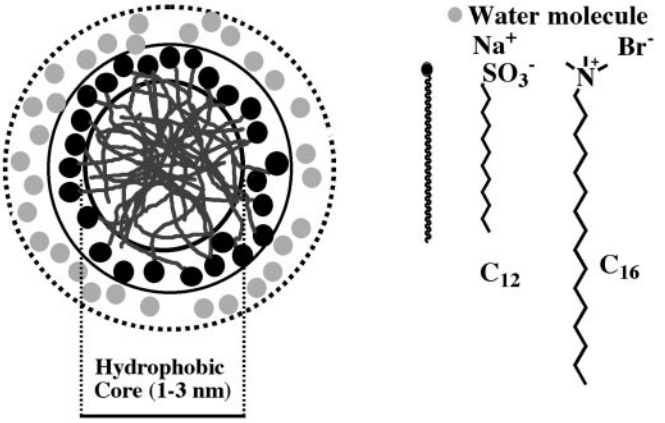


Fig. 1. Schematic representation of a micelle. The black circle represents the ionic portion of the head group (e.g., SO_3^-), whereas the long tail depicts the hydrophobic alkyl chain. SDS (C_{12}) and cetyltrimethylammonium bromide (C_{16}) are typical anionic and cationic micelle-forming surfactants, respectively.

excellence for controlling the chemistry of incarcerated guest molecule.

Micelles As Soft-Matter Enzyme Mimics

Micelles are supramolecular assemblies consisting of bipolar molecules called surfactants. Surfactants, named because of their surface active properties, typically consist of a relatively long hydrophobic organic chain that serves as a "tail" to a polar or ionic head group (Fig. 1). In dilute aqueous solution, surfactants exist as monomer (i.e., a conventional solubilized molecule), but above a certain concentration, the surfactants spontaneously and cooperatively organize to form a supramolecular assembly (6) termed a "micelle." The micelle possesses an internal hydrophobic core consisting of the organic chains and an external surface consisting of the hydrophilic polar or ionic head groups (Fig. 1 *Right*). On a time average globular micelles are roughly spherical in shape and of the order of 1–3 nm in diameter (Fig. 1 *Left*), which qualifies micelles as nanoscopic reactors for bound guest molecules. The micelle may be viewed as a primitive model of an enzyme with the hydrophobic core as the analogue of the active site. The micelle core is a "soft," liquid-like structure and differs from that of an ordinary organic solvent in that the guest is constrained to remain in the hydrophobic region of the micelle, which provides a "supercage" or nanoscopic reactor space for the guest.

Molecular and Supramolecular Organic Photochemistry

Let us consider a strategy in which conventional molecular photochemistry (7) is used to cleave a covalent bond in a bound guest molecule to produce a geminate radical pair that is bound in an "active site," which will control the subsequent covalent bond formation of the pair to form a stable molecule. In solution (molecular chemistry), the geminate radical pair is a highly reactive species and does not require energetic activation for covalent bond formation, which occurs very rapidly and efficiently. Enzymes can activate bond breaking of key covalent bonds of the guest through the geometric disposition of chemical functionality that geometrically complements the bound guest. In organic supramolecular photochemistry (8), photons absorbed by the guest provide the activation required to break covalent bonds of the guest.

The "Cage Effect" As a Signature of Supramolecular Systems

When photolysis causes the cleavage of a bond in a guest adsorbed in a micelle to produce a pair of radicals (a geminate radical pair), there is a certain probability, P, that the geminate pair will recombine in the micelle and a probability, $(1 - P)$, that the partners of the pair will diffuse out of the micelle. The probability, P, that the geminate pair will recombine in the micelle is termed the geminate "cage effect." In nonviscous solvents, the cage effect of recombination of the geminate pair produced from photolysis of ketones is a few percent or less (9), because the walls of the molecular solvent cage are very soft and porous and cannot effectively constrain the separation of the geminate pair.

The cage effect for the probability of recombination of geminate radical pairs produced by the photolysis of ketones in micelles has been used as an exemplar to demonstrate the supramolecular effects on covalent bond formation (10). For the same ketones as guests in micelle hosts, the probability of geminate pair recombination can be systematically controlled from a few percent up to about 100% by controlling the complementary hydrophobicity of the guest geminate pair and the host micelle core (Table 1).

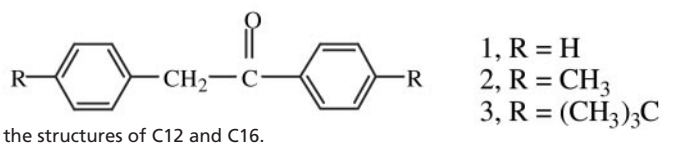
Magnetic and Supramolecular Effects on Covalent Bond Formation

Magnetic field and magnetic isotope effects are commonly observed for photochemical reactions that produce triplet geminate radical pairs in supercages (11, 12). The intersystem crossing (ISC) step converting ^{3}I (triplet geminate pair) to ^{1}I (singlet geminate pair) is responsible for the common occurrence of spin effects in photoreactions in supramolecular systems. The key concept in spin chemistry is that the ISC step ^{3}I to ^{1}I is a magnetic reactivity switch! The switch is based on spin selection rules, which forbid ^{3}I from directly forming singlet products, ^{1}P, through radical–radical combination (or disproportionation) until ISC to a singlet state,^{1} I, occurs.

A qualitative model (11) that integrates supramolecular chemistry and spin chemistry is shown in Fig. 2. When the time scale of the ISC step is of the order of nanoseconds to microseconds, large spin effects caused by applied laboratory magnetic fields or by magnetic isotopes are expected theoretically and found experimentally on the value of P (11, 12). Because the size of the supercages of micelles are of the order of 1 nm, spin effects are commonly observed on the values of P for covalent bond formation between geminate triplet radical pairs in nanoscopic supercages. The model of Fig. 2 provides an intellectual and scientific basis for experimental variation of supramolecular guest@host complexes in the search of

Table 1. Cage effects on secondary geminate pair recombination

Ketone	Earth's field	13,000 gauss	Surfactant
1	30%	16%	C16
2	59%	31%	C16
3	95%	76%	C16
2	30%	15%	C12



See Fig. 1 for the structures of C12 and C16.

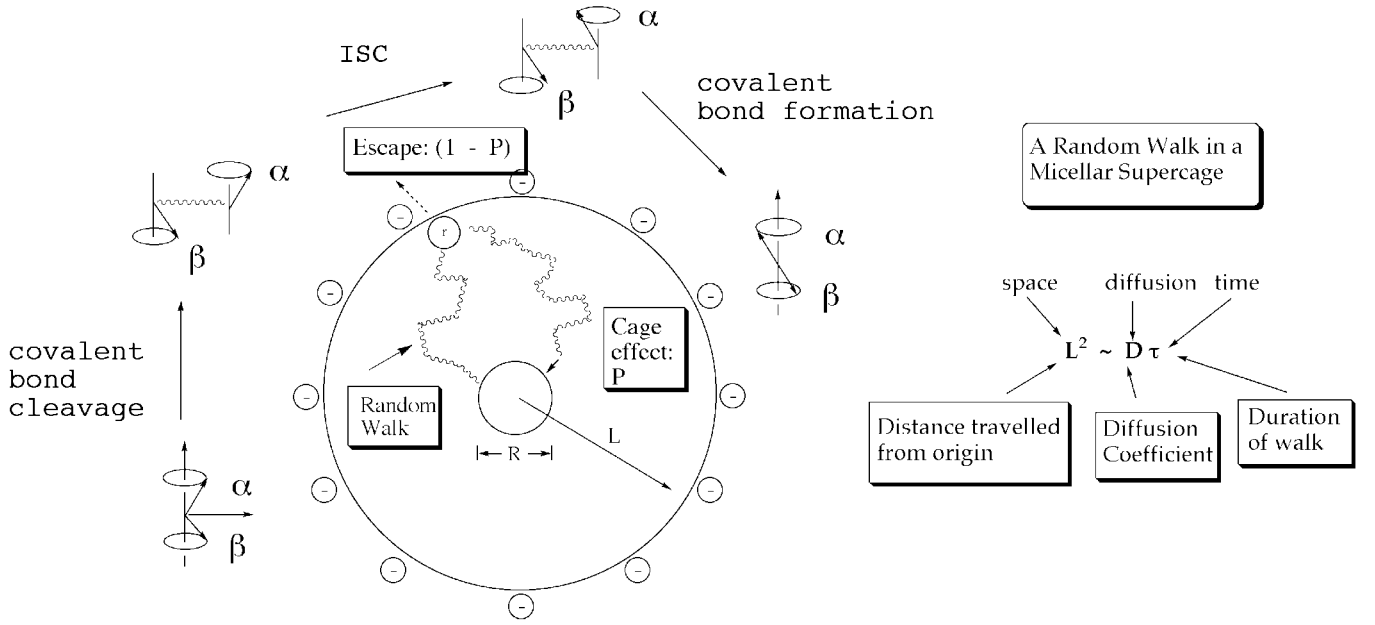


Fig. 2. Model of a nanoscopic supercage and the origin of magnetic effects on covalent bond formation. The large circle represents a supramolecular host that serves as a nanoscopic supercage for a geminate pair of radicals (the small circles represent a dynamic triplet radical pair, ^{3}I). A triplet geminate radical pair is produced by photolysis. The pair undergoes a random walk in the supercage under the constraints of the ''viscosity'' and spatial dimensions of the supercage. Under the influence of magnetic interactions the pair undergoes ISC to a singlet during the random walk. After reencounter, the singlet pair forms a covalent bond with a probability, *P*. The latter undergo relative diffusion (*D* = diffusion constant) from an initial site about a supercage of radius *L* with an average reencounter period of τ. For a random walk, τ is proportional to L^2/D. For a supercage with a diameter of the order of about 1 nm (10 Å), the value of τ is of the order of nanoseconds to microseconds for values of *D* corresponding to nonviscous to moderately viscous solvents.

reaction control by spin effects: (*i*) control the relative diffusional motion (D) of the pair, which will depend on the size, shape, and chemical structure of the partners of the guest pair; (*ii*) control the size (L), shape, and chemical structure of the host supercage; and (*iii*) control the magnetic parameters (hyperfine coupling, applied fields, g-factors, etc.) influencing the rate of ISC of the pair. Generally, other processes (e.g., escape from the supercage, spin-independent chemical reactions, etc.) compete with the ISC step. Because the ISC step is controlled through magnetic effects and product formation selectivity depends on the competition between ISC and spin independent reactions, magnetic effects can operate on the ^{3}I to ^{1}I process to exert a control on eventual covalent bond formation selectivity from ^{3}I.

A second important supramolecular aspect of the model is the intermolecular radical–radical interactions of electron exchange that plays an important role in determining the magnitude of the observed spin effects (11). Thus, the combination of weak noncovalent supramolecular interactions between the radicals of a pair and weak exchange and magnetic interactions between the electron spins of the pair can control the reaction pathways of radical–radical reactions to selectively make strong covalent bonds in supercages.

Magnetic Effects on Covalent Bond Formation in Supramolecular Systems

Fig. 3 provides a schematic integration of the photochemistry (formation of the geminate triplet pair), the spin dynamics (triplet to singlet intersystem crossing of the geminate pair), chemical dynamics (covalent bond formation of the geminate pair), and diffusional dynamics (random walk separation and reencounter of the geminate pair) in relationships between the magnitude of the cage effect and the size and ''viscosity'' of the supercage microreactor.

The application of an external magnetic field strongly (10) reduces the probability of cage recombination of geminate pairs in micellar supercages (Table 1). This

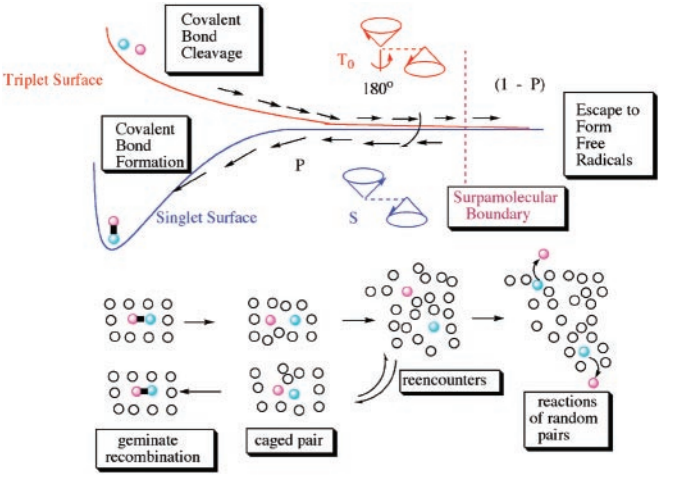


Fig. 3. Representation of the hyperdynamics involved in the recombination reaction of a triplet geminate radical pair. The arrows moving along the singlet and triplet energy surface indicate the motion of the representative point of the nuclei of the radical pair. The spin dynamics is represented by the vector notation 1. The diffusional dynamics is represented below the surfaces as in Fig. 2. The boundary for a hypothetical supercage is shown. The shaded circles represent geminate radicals.

effect results from the strong coupling of an external magnetic field with the electron spins that inhibits the electron spins from undergoing ISC. This action slows down the rate of singlet formation and allows the radicals to escape more efficiently out of the supercage, reducing the probability of the cage effect (Figs. 2 and 3). The presence of a ^{13}C at the carbonyl position of the acyl radical of the primary pair leads to significant magnetic isotope effects on the cage reactions of the primary geminate radical pair (12). This effect occurs because the presence of ^{13}C (a magnetic isotope) at the carbonyl carbon of the radical pair accelerates the rate of ISC of the primary pair relative to ^{12}C (a nonmagnetic isotope that occurs in 99% natural abundance), thereby speeding up the rate of ISC to the singlet pair and causing more efficient covalent bond formation and a higher cage effect.

Zeolites As Hosts for Supramolecular Organic Photochemistry

Zeolites are crystalline porous solids possessing an "open" or porous internal surface whose framework is constructed from SiO_4 and AlO_4 tetrahedra connected through oxygen bridges (13). The open framework structure starts with pores on the external surface that determine the guest molecules which can diffuse into the interconnected channels of the internal surface. The dimensions of the pores and channels are of the order of 3–10 Å, the size of small organic molecules such as benzene (molecular cross section about 5 Å). In some cases, the channels of the internal surface form intersections that are roughly spherical and are considerably larger than the channels. For example (14, 15), the diameter of the roughly cylindrical pores and channels of zeolites possessing the MFI topology (silicalite and ZSM-5) are about 5 Å, but the diameter of the roughly spherical intersections is about 9 Å. The intersections are the likely "active sites" for reactions in zeolites, because they offer the greatest degree of void space for reacting molecules to interact. Thus, although zeolites as solids are formally "hard matter," their internal void space is "soft." As a result, zeolites can serve as hosts for guest molecules. In the case of the FAU family of zeolites (Fig. 4), the pores on the external surface are about 8 Å in diameter and the internal supercages are about 13 Å in diameter.

Zeolites As Hard-Matter Enzyme Mimics

Many of the selective reactions catalyzed by zeolites can be viewed as reactions that are nonselective under "molecular" conditions (homogeneous solvents) but which have become selective as the result of the size/shape/chemical effects imposed on the guest@host complex by the protein zeolite. In these cases, the enzyme may be viewed as suppressing a high inherent molecular reactivity of a species by directing alternative reactions of a guest toward a specific pathway, which is not possible in homogeneous solution conditions because the alternative reaction is too slow to compete with other available, very fast, reactions.

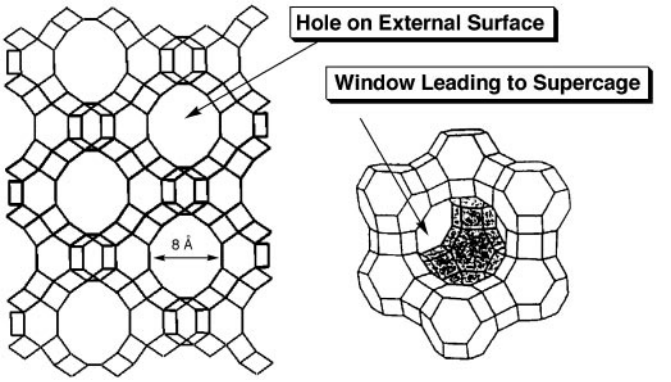
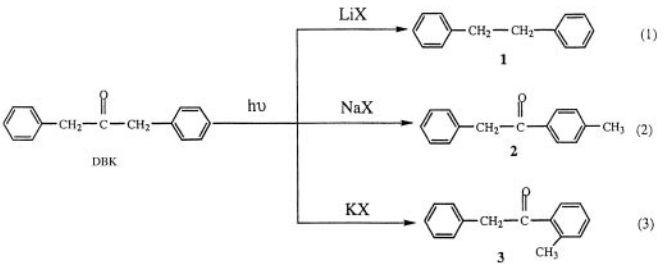


Fig. 4. Schematic of the external surface (*Left*) and the supercage (*Right*) of an FAU zeolite.

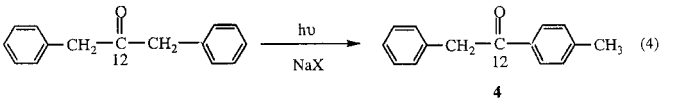
Although zeolites are robust porous solids and a form of hard matter, they possess a number of structural similarities to "soft-matter" enzymes (16). To the extent that these similarities are valid, the chemist is inspired to combine the attractive features of the robust, chemically inert framework of an inorganic structure, a zeolite crystal, with the spectacular selectivity and activity of enzymes. Nature demands high selectivity and catalytic conditions to carry out life's chemistry and does so with enzymes through the use of a very special supramolecular host structure, the protein "framework" of an enzyme. The protein framework provides (*i*) the "walls" of the active site and protects it from undesirable side reactions; (*ii*) the binding sites on the external surface, which are "portals" for selective binding, and the "channels" on the internal surface through which the substrate molecules are "sieved" on their vectorial excursion to the active site; (*iii*) the sterically demanding "void" space at the active site for adsorption of the substrate; (*iv*) and the chemical "tools" within the active site to accomplish the required substrate transformation selectively, efficiently, and catalytically. Zeolites mimic these properties of enzymes to a certain measure.

Negative Catalysis As a Mechanism for Selective Covalent Bond Formation in Supramolecular Systems

In some cases, enzymes achieve selectivity by transforming substrates into unstable and reactive intermediates that would normally undergo rapid and nonselective reactions in homogeneous media. Enzymatic selectivity in these cases is provided by a sort of negative catalysis (17), if we define catalysis in terms of the action of a host in promoting a chemical transformation without being consumed and do not demand that a catalyzed reaction be characterized by a faster rate than some reference uncatalyzed reaction. Negative catalysis slows down some reactions of a reactive intermediate that would occur in homogeneous solution and thereby allows the reactive intermediate to undergo reactions that are too slow to be observed under "molecular" conditions. Reaction selectivity is achieved by using supramolecular effects to hinder certain rapid, indiscriminate molecular reactions and leaving other target reactions to occur "by default." A number of enzymatic reactions involve carbon-centered free radicals, which are reactive intermediates that tend to react by radical–radical reactions nonselectively and at diffusion-controlled



Scheme 1.



Scheme 2.

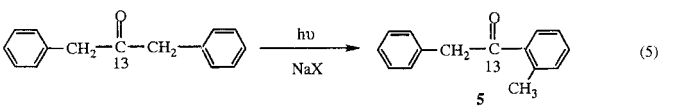
rates in ordinary solvents (17). An implication of these examples of negative catalysis is that the highly reactive radicals are "stabilized" and protected from reaction as the result of their guest relationship in the active site. Negative catalysis is also a property displayed by zeolite hosts for guests that undergo covalent bond formation by geminate radical combination.

Supramolecular and Magnetic Control of Covalent Bond Formation Between Guest Geminate Radical Pairs in Zeolite Hosts

The supercages of the internal surface of zeolites provide nanoscopic reactors that control covalent bond formation of geminate radical pairs produced by photolysis of guest molecules adsorbed in the zeolite host (18, 19). In contrast to the soft and flexible walls of micellar supercages, the walls of zeolite supercages are hard and inflexible. Thus, the steric effects resulting from the interactions of a geminate radical pair adsorbed in a zeolite supercage can be severe. These steric interactions are responsible for the size/shape selectivity of reactions that occur in zeolites. The steric interactions experienced by a guest in a zeolite supercage can be modified by the adsorption of a co-guest or by variation of the cations that are associated with the negative aluminate anions of the zeolite framework. Examples of the effect of cation on the photochemistry of dibenzylketone (DBK) (1) are given in equations 1–3 of ref. 20 for the DBK@zeolite complexes, where the zeolite is a faujasite possessing internal supercages whose diameters are about 13 Å (Fig. 4). This family of zeolites possesses cations in the supercage to balance the negative charges in the framework. For an appreciation of the size of the void space of the supercage, up to 6 benzene molecules can fit snugly in the supercage.

With Li^+ as the cation, the major product, **1**, results from decarbonylation followed by coupling of benzyl radicals (Eq. **1**, Scheme 1); with Na^+ as the cation, the major product is the isomeric rearranged ketone, **2** (Eq. **2**); with K^+ as the cation, the major product is the isomeric ketone, **3** (Eq. **3**). The structures of the products are controlled by the free volume available in the supercage containing the guest ketone and the photochemically generated geminate radical pair and the competing rates of covalent bond formation and rotation of the geminate radical pair.

As in the case of micelles, product formation from photolysis of ketones bound as guests in zeolite hosts is strongly influenced by magnetic field and magnetic isotope effects. For example (21), photolysis of ^{13}C carbonyl carbon-enriched dibenzylketone (DBK) yields **4** as the major product, whereas photolysis of ^{12}C carbonyl carbon (natural abundance) DBK yields **5** as the major product (Eqs. **4** and **5**, Schemes 2 and 3). These magnetic isotope effects are explained, as in the case for the cage effect discussed above, as being the result of faster ISC of the triplet to the singlet for the ^{13}C-enriched geminate pair, which allows covalent bond formation to occur faster in competition with relative rotational motion of the pair.



Scheme 3.

Conclusion

The enzymatic catalysis of covalent bonds between carbon atoms is a critical step in many essential life processes catalyzed by enzymes. The principles of supramolecular chemistry allow the design of simple models of enzymes that can mimic their catalytic action. Two examples, micelles and zeolites, can serve as enzyme mimics for controlling, in catalytic fashion, the selectivity of formation of covalent bonds between geminate radical pairs generated by photolysis of ketone as ketone@micelle or ketone@zeolite supermolecules. A model of supercages whose dimensions are of the order of 1 nm reveals the possibility of significant magnetic effects on the formation of covalent bonds between geminate pairs in supercages. Such effects are readily observed and very significant in determining the probability and selectivity of covalent bond formation between geminate radical pairs bound to supercages.

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