Reflection on Medium Effects on Photochemical Reactivity

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ABSTRACT
In reexamining medium effects on photochemical reactions, we have emphasized those on unequilibrated excited species such as the Franck−Condon species. Despite recent advances in femtochemistry, such a discussion in molecular photochemistry is uncommon, and the problem remains challenging on account of the extremely short-lived excited species. However, in such cases, a small perturbation resulting from, for example, weak guest−host interactions could turn into a determining factor in dictating the course of a photochemical channel of deactivation. Examples of medium-directed diabatic processes have been examined with this idea in mind. A modified view on rhodopsin photoisomerization is presented along with the consideration that confinement does not necessarily lead to inhibition of reactions of the trapped substrate.

Introduction

Recently in providing a general perspective on photochemical reactivity, we categorized photochemical reactions into two groups, those from equilibrated excited molecules and those from short-lived unequilibrated molecules.[1] We used examples of alkenes and polyenes and showed that their photoisomerization reactivity could fall into either of the two groups.

By its nature, the first group should have reactive species with longer lifetimes, usually in nanoseconds or microseconds. Hence this reactivity should be relatively insensitive to minor environmental perturbation. On the other hand, for the short-lived vibrationally excited species, it became obvious to us that the environment could play an important role in dictating the course of photophysical and photochemical relaxation processes. Since medium or host effects (sometime referred to as supramolecular effects) are topics of current general interest,[2] we would like to examine a few general features of medium effects in organic photochemistry, paying particular attention to their possible roles on excited state species, particularly the short-lived unequilibrated excited species.

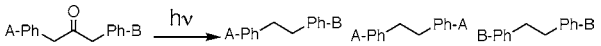
Much has been written describing how host or medium effects can alter the nature or product ratio of photochemical reactions.[2] A close examination revealed that many of the reported examples were results of altered ground-state properties of the nascent primary photoproducts. Yet there are also other reactions where the medium effects are primarily on the excited-state species. In the following, we illustrate with examples that fall into these two types, paying more attention to those on the excited species. Our discussion will be limited mostly to examples studied in condensed media.

Medium Effects on Photochemical Reactions

Medium Effects on Ground-State Photoproducts. Photochemical reactions are kinetically controlled reactions that often allow formation of strained molecules otherwise not accessible via thermal reactions. The well-known early examples were bicyclobutane,[3] quadricyclane,[4] and strained trans-cycloalkenes.[5] More recent spectacular examples that involved ingenious ways of trapping unstable photoproducts are cyclobutadiene,[6] pentalene,[7] and benzyne[8] in argon matrix or in Cram's molecular containers (the hemicarcerands).

The conditions that made formation of these strained systems possible are more than low temperature for stabilizing photoproducts. The rigid medium employed also provided the necessary inert, restricted environment to stop any bimolecular processes that could lead to degradation of the products. The latter includes dimerization (e.g., for cyclobutadiene and pentalene) or reaction with other molecules (e.g., nucleophilic additions to benzyne or electrophilic addition to trans-cycloalkenes). Clearly, for these host-enhanced photoproducts, the medium effects were not on altered photochemical reactivity. The medium provided an environment to stabilize the primary products. In this regard, a myriad of other photochemical studies carried out under argon matrix or other inert host conditions (including direct observation of carbenes, nitrenes, and free radicals)[9] are all examples of ground-state stabilization of primary photoproducts.

Several other often cited cases of medium-directed photochemical reactions[4] fall into the same category. For example, photochemical decarbonylation of unsymmetrical dibenzyl ketone **1** in solution gives random radical



1	in solution	50%	25%	25%
	in micelle	100%	--	--

coupled products, but in micelles, it gives only the "in-cage" unsymmetrical, coupled product.[10] This medium control on radical recombination reaction is not much different from the well-established cage effects in thermal or photochemical decomposition of peroxides or azo-compounds,[11] albeit the new observation involved the clever use of a reaction condition that suppressed diffusion of radicals completely.

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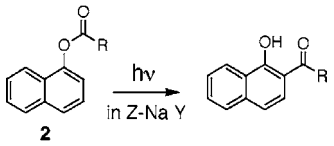
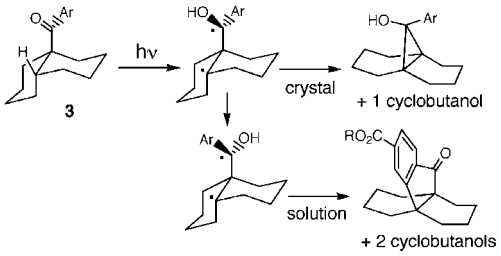
Another example is the reduction of the complex product mixtures (8) from photo-Fries rearrangement of the ester **2** in solution. The single product, obtained from



irradiation in zeolite-Y, derived from coupling of free radicals produced in the immediate vicinity.[12] And, the "latent photochemical property" of the ketone **3**[13] in the



crystalline state giving the cyclopropyl product is also the consequence of medium control of the initially formed intermediate. Restricted conformational equilibration of the diradical intermediate by the rigid crystalline medium excluded possible formation of the ring-addition product.[13]

Medium Effects on Excited-State Species. Some of the medium effects acting directly on excited species have been amply described in the literature although usually discussed in a different context. Hence, solvent polarity has been used for controlling relative energies of the n,π^* and π,π^* states thereby controlling, for example, the ease of H-abstraction by excited ketones.[14] External heavy atom effects can perturb relative contributions of the excited singlet and triplet states of the photochemistry and photophysical decay of excited molecules.[15] And selective dimerization of olefinic bonds forced to lie in close proximity in crystals was first elegantly demonstrated by Schmidt.[16] These well-documented effects on relaxed excited species will not be reviewed in this Account.

Many unimolecular photochemical reactions are now known to cross directly from the excited singlet state potential surface of the reactant to the ground-state surface of the product (diabatic processes).[17] Such chemical transformations involve very short-lived intermediates, for example, either the Franck–Condon species or something close to it. The reactions must, therefore, be extremely rapid, competitive with the very fast intramolecular vibrational redistribution (IVR) processes (10–100 fs).[18] (The latter is much faster than vibrational energy transfer to the medium (1–10 ps)).[19]

Fragmentation was the first type of ultrafast photochemical reaction of which the primary process was investigated by femtosecond time-resolved spectroscopy (e.g., dissociation of I–CN[20] and I_2[21] and dehalogenation of 1,3-dibromopropane[22]). In the case of iodine in an argon matrix, it was shown that the wave packet from stimulated emission of the dissociating excited iodine

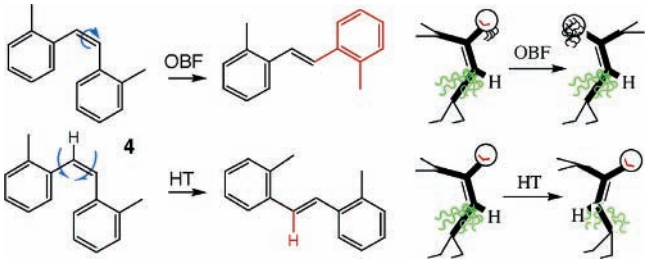


FIGURE 1. One-bond-flip (OBF, top) and Hula-twist (HT, bottom) motions of a simple diarylethylene, *o*,*o*-dimethyl-*cis*-stilbene, **4**. Changing color denotes reversing sides of that portion of the molecule. The cartoon figures describe pictorially the turning over of the "body parts" during the two transformations.

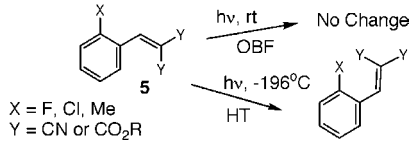
differed dramatically from that of the isolated excited iodine. The method even allowed the detection of nascent iodine atoms recoiling from collision with the host.[21]

Photoisomerization brought by direct irradiation[23] is another ultrafast reaction. Starting from Franck–Condon trans and cis excited species, the excited potential curves are lowered through double bond twisting until they reach the perpendicular structure, which touches the ground-state potential curve. The rate of decay from either side of the excited-state potential curve is very rapid, for example, ~300 fs for the nearly barrierless decay of *cis*-stilbene.[24] Hence, such processes are very sensitive to external perturbation such as solvent viscosity. In stilbene, viscosity-dependent barriers are present on potential curves of both isomers.[25] Quantum yields of fluorescence increase upon increase of solvent viscosity until they reach maximum values in frozen solutions. Proportionately, the isomerization yield decreases. The Kramer equation relates fluorescence lifetime with frictional force exerted by the medium (solvent viscosity) on the torsional relaxation process of the excited *trans*-stilbene.[25] Volume demand was shown to affect regioselectivity of photoisomerization of vitamin A derivatives.[26] All these observations recognize the importance of medium effects on torsional relaxation of the excited species.

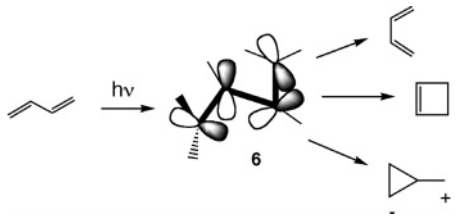
Medium also affects mechanisms of photoisomerization. While the trans to cis isomerization of 1,2-diarylethylenes is completely stopped in frozen solution, the efficiency of the cis to trans photoisomerization is oftentimes moderately high in rigid organic glasses.[27] It has been noted that the retained photoreactivity of the cis isomer is likely due to the revelation of a dormant mechanistic process that becomes observable when the more favored mechanism in solution is blocked by the rigid medium.[28] The new dormant mechanism is the volume-conserving hula-twist (HT) process and the favored process in solution is the one-bond-flip (OBF) process or the commonly accepted torsional relaxation (see Figure 1 for *o*,*o*′-dimethyl-*cis*-stilbene, **4**).[29] The unique consequence of this medium effect has prompted consideration of other forms of constraints in inhibiting the OBF process. Possible examples are dipolar solvent–solute interactions in perturbing fluorescence of cyanine dyes,[29,30] internal H-bonding in affecting bilirubin photo-

chemistry,[29,31] and the sheer bulk effect in photoisomerization of stilbene dendrimers.[32]

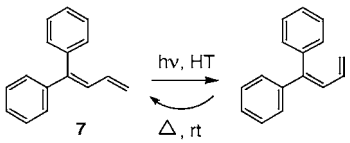
Hula twist involves simultaneous isomerization of a pair of adjacent single and double bonds. Its manifestation is most readily demonstrated through irradiation of compounds with distinguishable conformers under conditions where thermal equilibration of conformers is impeded. Thus, for the symmetrically substituted styrenes (**5**), the observed photochemical change is only consistent with involvement of the HT mechanism.[33]



A general picture that has emerged from recent theoretical studies of the excited singlet state of butadiene is that the initially excited species funnels through a conical intersection of a triply orthogonal tetraradicaloid **6**.[34] From

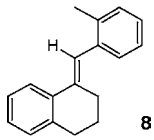


there it leads to electrocyclization, ring closure to a methylenecyclopropane intermediate, and configurational (if observable) or conformational isomerization. However, for a simple diene trapped in an argon matrix[28,35] or a larger diene **7** in EPA glass,[36] only the volume-conserving HT process was observed giving a new conformer.

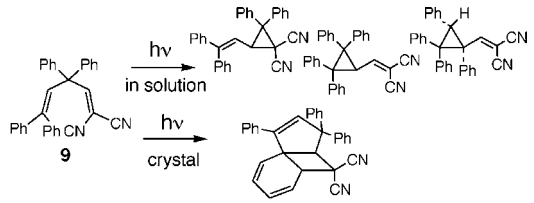


For properly substituted stilbenes (e.g., **4** and related analogues) simultaneous configurational and conformational isomerization when irradiated in an organic glass at liquid nitrogen temperature is consistent only with HT.[37] In contrast, only configurational isomerization (i.e., OBF) was detected when these compounds were irradiated in solution. However, there is also the view that HT might be happening to all photoisomerizations regardless of the nature of the medium. In solution, rapid disappearance of the unstable s-cis conformers would hamper their detection.[24]

That the cis isomers of 1,2-diarylethylenes hula twist easily in the glass while the trans isomers do not[27,37] is likely due to the different local empty space available for reaction. The planar trans should be more conformationally homogeneous (fine structures in the absorption spectra), suggesting possibly a better organized, more tightly interacting, solvent cage that prevents execution of even the volume-conserving HT. *cis*-Stilbene is nonplanar, which should lead to a less closely interacting solvent cage, providing the necessary room for isomerization. Thus, HT is the result of a medium-controlled photochemical reactivity. In agreement, the nonplanar *E*-isomer of **8** is also reactive at low temperature.[37]

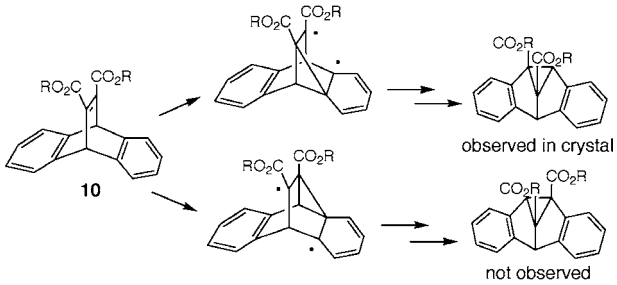


The case of detection of the dormant HT after suppression of the more likely OBF finds analogy in other confined chromophores. For instance, for compound **9**,[38]



solution irradiation led to exclusive formation of di-π-methane rearranged products.[39] In the crystalline state, a 2 + 2 cycloaddition product was formed instead. Thus, the medium has a profound effect on the chemical reactivity of these short-lived excited species (at 77 K, averaging in the nanosecond region.)[40]

Medium effects can reveal themselves in a different way. Enantioselective di-π-methane rearrangement[39] of **10**

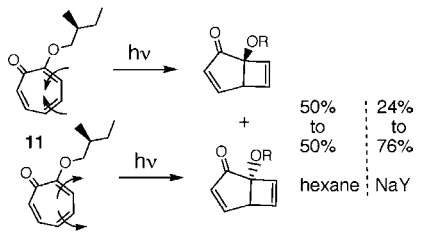


in crystals[41] seems to be controlled by a preferential vibration mode of the excited species that initiates a preferred mode of 1,3-bonding in the primary photochemical step.

Symmetry-correlated reactions brought about by light are another form of rapid adiabatic reactions,[34] where there is no excited intermediate and its excited state lifetimes are short (e.g., 44 and 18 fs for, respectively, the $1B_u$ and $2A_g$ excited states of butadiene).[42] Expectedly, such reactions are sensitive to medium perturbation. For example, the relative amounts of cyclobutene and bicyclobutane formed by irradiating butadiene vary with solvent.[3] And in argon matrix (at 10 K), cyclobutene and bicyclobutane formation disappeared altogether, leaving only conformational equilibration.[35]

External perturbation is also reflected in torquoselectivity in diene $4e^-$ electrocyclizations.[43] The chiral alkoxy tropolone **11**[44] gave a mixture of the bicyclo [3.2.0] products (from two disrotatory modes of ring closure) with

no apparent enantioselectivity. However, when **11** was "stuffed" into a zeolite, a diastereomeric enrichment in excess of 52% was achieved. Clearly in a likely forced coiled conformation of the side chain in the zeolite cavity, the relative ease of the two possible modes of electrocyclization (the torquoselectivity) becomes evident. This indirect medium effect demonstrates clearly the sensitive nature of the excited-state chemical reactivity of the chromophore.



Does Confinement Necessarily Mean More Steric Inhibition?

Confinement of substrates obviously results in the loss of freedom of diffusion. However, it is also important to recognize that confinement does not mean increased steric inhibition of all motions exerted by the host molecule onto the substrate. In fact, in some cases confinement could mean *less restriction of some motions (hence possibly increased reactivity) than in common solvents*.

Consider a zeolite with a cavity of the dimension of less than twice the size of a substrate. When the cavity is "filled" with such a substrate, by necessity it leaves an empty space of considerable size (or filled with the smaller solvent molecules if available). On the other hand, in solution, such a substrate is constantly surrounded by solvent molecules. Thus, we have the interesting scenario that a rigid host could have less of an inhibitory effect on some excited-state processes of the substrate than the solvent molecules. It follows that the amorphous medium of organic glass is likely to have closer interactions between the substrate and the host molecules much more so than in organized media, such as crystals, zeolites, and proteins. In latter cases, the binding cavities are maintained by the rigid "scaffolding" for each case.

For example, photostationary state values in cis/trans isomerization can be measured accurately. For stilbene trapped in a zeolite (NaY/hexane), such values are identical to those obtained in the uninhibited medium hexane.[45] Hence, the host effect on excited stilbene is negligible. In contrast, *trans*-stilbene in β-cyclodextrin gives a smaller amount of the cis isomer.[46] Its excited-state decay constants were also found to vary with the size of the cyclodextrin.[47] On the other hand, no cis isomer was detected in an organic glass (see above).

There are times when a specific form of guest−host interaction (especially in biopigments) plays a more dominant role in determining the fate of an excited "trapped" substrate than any conceivable steric effect. In this regard, it is important to realize that protein "encapsulated" substrates often present a very different form of "guest−host" interactions from those encountered in most man-made host systems. A substrate in a protein cavity is usually "anchored" at one, two, or sometimes more sites through covalent, ionic, or hydrophobic interactions as part of the protein−substrate recognition process. These anchors are usually not perturbed during the short lifetime of the excited singlet state; they therefore often become the most dominant restraining forces in dictating the manner in which the chromophore reacts. For man-made hosts, specific interactions with guest molecules are still of rare occurrence;[48] therefore a substrate is rarely "held back" in any specific manner by the host except some form of increased steric inhibition.

Photoactive Yellow Protein (PYP). PYP is a chromoprotein (∼14 kD) that directs bacteria away from the damaging UV light.[49] The phototrigger is the trans to cis isomerization of a simple thio-cinnamoyl chromophore (**12**). The short chromophore is anchored at both ends, one linked to Cys-69 and the other with the *p*-phenoxy-oxygen hydrogen-bonded to Glu-46 and Tyr-42.[50] While rigidly anchored at both ends (within the short excited lifetime, picosecond), the chromophore still manages to isomerize, forming the cis photoproduct.[51] A unique isomerization process must be involved that is compatible with the binding site restrictions. A simple conformational analysis of the anchored chromophore suggests a possible route.[52]

Figure 2 shows that HT (at the β-H) photoisomerization (parts a−c) results in an untenable large displacement of the phenoxy anchor site. On the other hand, a bicycle-pedal (BP) motion involving the double bond and a nearby ester single bond (double arrows in Figure 2a) would lead to the trans to cis isomerization of the double bond and a simultaneous flipping of the ester carbonyl group (part b), both features observed in the crystal structure of the primary photoproduct.[51] The BP model was originally proposed as a volume-conserving mechanism for isomerization that involved simultaneous rotation of two double bonds.[53] In this case, only one double bond is involved, making it equivalent to a OBF process. The small change near the polar end of the chromophore (see figure) can easily be accommodated through slight reorganization of the single bonds around the surrounding amino acid residues and within the cinnamoyl chromophore.[52] It is an isomerization process uniquely fitted to the binding cavity of PYP.

An interesting complication was revealed in a recent reanalysis of the X-ray crystal structure of PYP.[54] Apparently two forms of the *trans*-cinnamoyl chromophore are present even in low temperature (110 K) crystals. It appears to us that interconversion of the two forms is connected by a BP motion[53] (Figure 3A) that is very similar to that detected in crystals of *trans*-stilbene (**13**) (Figure 3B) and azobenzene.[55] These studies revealed an interesting role of the intermolecular empty space in crystal scaffolding. Such an empty space while allowing the BP process does not allow HT motion, which requires space for translational motion of at least half a molecule.[56]

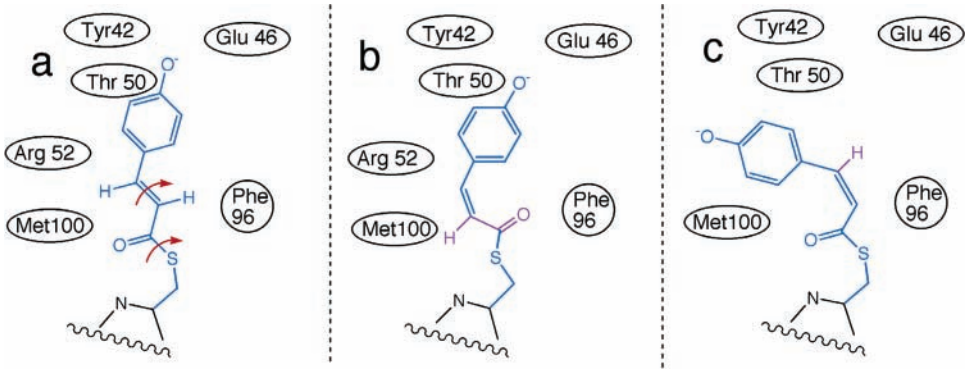


FIGURE 2. The thiocinnamate chromophore structure (**12**) of PYP from the reported crystal structure:[50] (a) its dark structure relative to nearby amino acid residues; (b) the photoproduct from the concerted BP process (curved arrows in panel a); (c) the hypothetical structure from HT of the β-H, showing displaced phenoxy oxygen.

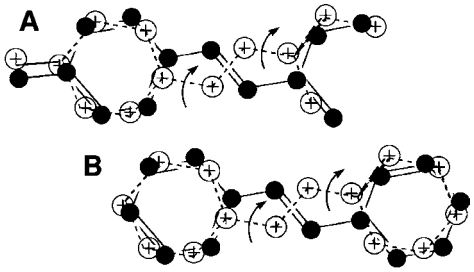
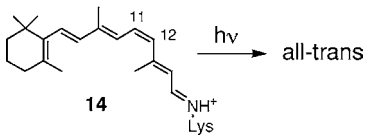


FIGURE 3. Equilibrating rotamers in crystals of (A) *trans*-cinnamoyl (**12**) chromophore of PYP and (B) *trans*-stilbene (**13**) (structures in both connected by a BP motion). The structures are essentially those in the literature.[54,55]

Also, we suspect that the unusual *Z*,*Z* to *E*,*E* photoisomerization of *Z*,*Z*-muconate bis(*n*-butylammonium) salt crystals[57] is helped by the empty space between molecules making possible the downhill one-way isomerization that is known for other hindered simple aromatic olefins in solution.[58]

Rhodopsin. The visual pigment rhodopsin is a globular lipoprotein of ~40 kD that appears as a compact seven helical bundle with the 11-cis retinyl chromophore anchored at one end to Lys-296 through a protonated Schiff base (PSB) linkage and the six-ring fitted into a hydrophobic pocket at the other end of the opsin binding site.[49] Its crystal structure was first reported in 2000.[59] Thereby, the location of the 11-cis retinyl chromophore (**14**) and the shape of the binding pocket are clearly defined.



The significance of the unusual environment of the chromophore in the binding cavity on its photoisomerization process was discussed recently.[60] The 11-cis retinyl chromophore is situated near the edge of the helical bundle with one side of the key $C_{11}-C_{12}$ cis-unit (left in Figure 4) leaning against transmembrane (TM) helix-3 and the other side facing an open space encircled by the large 4,5-TM connecting loop. This loop is known to be rigid,[61] due to the Cys-187−Cys-110 disulfide bond and its β-sheet

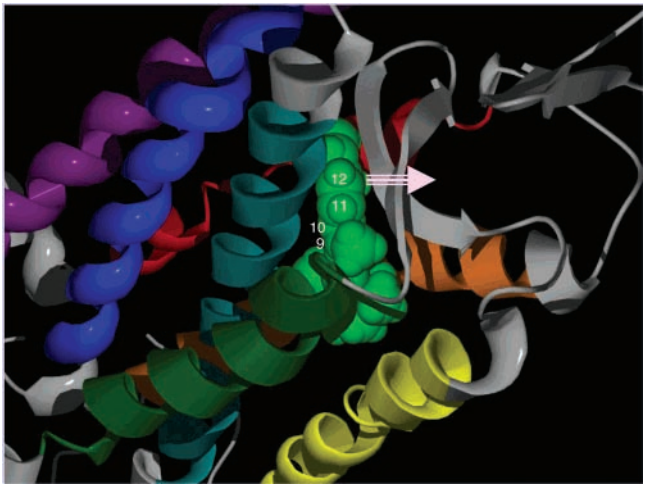


FIGURE 4. Partial X-ray crystal structure of rhodopsin[59b] with the 11-cis retinyl chromophore (light green) facing helix-3 (aqua), Cys-187 below H-12 and the empty space surrounded by 4,5-TM loop (the gray portion connecting the green and the yellow helices) on the right, into which the isomerization takes place (see arrow).

structure. Therefore, it is an empty space uniquely created by the "scaffolding" of opsin.

The quantum yield of photoisomerization of rhodopsin ($\Phi = 0.65$)[62] is several times higher than that of the same 11-cis retinyl PSB in solution ($\Phi = 0.15-0.20$).[63] The rate of isomerization of the enclosed chromophore (146 fs),[64] which agrees with the 200 fs appearance time of the primary photoproduct,[65] is also much faster than that of the free chromophore (1−2 ps).[66] This unusual enhanced efficiency of reaction can be accounted for by the unique environment around the key 11,12 cis linkage of the chromophore.

Light absorption causes H-12 to "bang" into Cys-187 causing reactive movement of the key atoms of the chromophore.[60] These atoms can turn either toward the left or toward the right of the chromophore (Figure 4). Only rotation into the open space on the right (see arrow) can lead to isomerization. Rotation toward the left should be stopped quickly by helix-3, resulting in an accelerated return to rhodopsin. It is interesting to note that the quantum yield of isomerization of rhodopsin appears to be temperature-independent (identical at room temperature and 77 K),[67] an unappreciated simple fact[68] that is

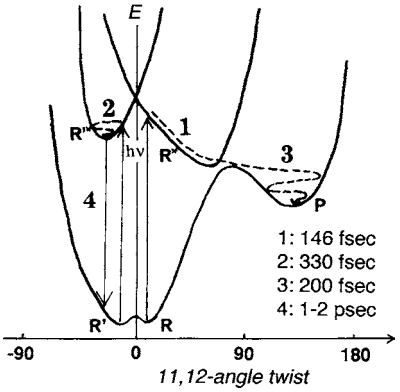


FIGURE 5. Hypothetical potential curves for ground and excited states of rhodopsin (R) and photorhodopsin (P). The decay (1 and 2) or product appearance (3) constants are those from the literature.[64,65] The two observed decay processes lead eventually to rapid isomerization (3) or back to rhodopsin (4).

more consistent with a nearby empty space than close-lying protein side chains. Therefore, in rhodopsin we have a case of confinement that facilitates excited-state deactivation (both chemical and physical)!

We suspect that the observed two decay processes of excited rhodopsin are due to excitation of two different ground-state rotamers as shown graphically in Figure 5. After light absorption, the molecule could land on different excited potential surfaces that lead to chemical isomerization or physical decay. Considering that different rotamers have recently been reported in crystals of PYP and *trans*-stilbene (see above), this suggestion of a nonhomogeneous ground-state structure of rhodopsin may not be far-fetched. Furthermore, Figure 5 suggests the interesting possibility that the active conformer of rhodopsin may have a quantum yield of isomerization much larger than the currently accepted value of 0.65, if the latter turns out to be an averaged value of the active and inactive conformers of rhodopsin. (Note that the small wavelength-dependent quantum yield of photoisomerization of rhodopsin[62] is consistent with the presence of two rotamers of slightly different absorption properties. An organic analogy of two rotamers in crystals is in the literature.[55,69])

Since the ease of rhodopsin isomerization is now believed to reflect the empty space on one side of the 11-12 double bond, the condition of restricted space favored for HT is no longer there. Indeed, recent molecular modeling[70] and X-ray crystal structural studies[71] on bathorhodopsin (the first stable photoproduct following the unstable photorhodopsin) suggest that the 11,12-double bond isomerization is not accompanied by a simultaneous adjacent single bond isomerization as expected for HT. Apparently, many small twists of nearby single and double bonds in a direction opposite to that of the 11,12-bond twist allow the anchors to remain unperturbed during the OBF isomerization. The resultant 6-s-cis-all-trans structure for the retinyl chromophore of bathorhodopsin was concluded from earlier calculated[72] and spectroscopic results.[73] The presently available X-ray crystal structures[63] are unfortunately of too low resolution to provide meaningful structural information on the retinyl chromophore.

A major difference between the chromophores of PYP and rhodopsin is their lengths plus the lengths of the tethers that link the chromophore and the anchors. As a result, rhodopsin and its lengthy butyl tether can "absorb" the double bond configurational change without a major change at one C−C bond. This is not possible in PYP.

While the anchored nature of the chromophores in PYP and rhodopsin restricts possible modes of isomerization, the empty space nearby each chromophore has made the rapid isomerization possible. The rate could be further accelerated if there is increased steric crowding as a result of light absorption in rhodopsin.[60] It will be a challenge for the chemist to be able to design model systems that can provide a unique cavity that will lead to lower steric inhibition of molecular motion near the reaction site of a trapped substrate molecule than in common solution so as to enhance its reactivity.

In a way, this discussion is an extension of treatment of "reaction volume", "active and passive walls", and "soft and hard walls" in the literature.[74] We have shown that there may be "holes" in rigid matrixes that can permit atomic motion that is evidenced by chemical change. Not only is there possible ultrafast chemical reaction in the "inner space", but in some cases the host may hold a chromophoric molecule in a configuration that leads to ultrafast decay of the FC excited species. Literature shows that in special cases these rates to a new product or to the original ground state can be faster than those encountered in solution. It appears to us that medium effects at this kinetic frontier present a new dimension for photochemical control.

Summary

We have examined effects of host molecules on photochemical reactivity of trapped molecules. Some of the effects are on the nascent ground-state products, including ease of diffusion. The effects on the excited states can also be on diffusion characteristics of the reactive excited molecules. However, the more interesting and challenging cases are those when the medium effects are manifested in their competition against fast decay of the Franck−Condon excited species. The common examples include many concerted unimolecular adiabatic reactions that could be highly sensitive to the surrounding environment. For these cases, the design of host systems for systematic manipulation of excited decay of the guest molecule for revelation of new and unusual mechanistic process(es) or for enhancing reactivity or enantioselectivity remains a continuing challenge to photochemists.[6] Additionally, in considering medium effects in general, we caution against the notion that confinement automatically suggests steric crowding around the trapped substrate. There are times when confinement could give a less inhibited environment for reaction (especially in organized media) than, for example, that in a common solvent. Tapping such a medium effect could be a new way of controlling photochemical reactivity. And, organic glass medium, while amorphous in nature, should provide closer host−guest

interactions than those in many organized media with rigid structural scaffolding.

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References

(1) Liu, R. S. H.; Hammond, G. S. Photochemical Reactivity of Polyenes: From Dienes to Rhodopsin, from Microseconds to Femtoseconds. *Photochem. Photobiol. Sci.* **2003**, *2*, 835−844.

(2) (a) *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991. (b) Garcia-Garibay, M. A., Ramamurthy, V., Scheffer, J. R., Eds. Symposium-in-print: Molecular Assembly and Reactivity of Organic Crystals and Related Systems. *Tetrahedron* **2000**, *56*, 6595−7049.

(3) Srinivasan, R. A Simple Synthesis of Bicyclo[1.1.0]butane and its Relation to the Internal Conversion of Electronic Energy in 1,3-Butadiene. *J. Am. Chem. Soc.* **1963**, *85*, 4045−4046.

(4) Hammond, G. S.; Turro, N. J.; Fischer, A. Photosensitized Cycloaddition Reactions. *J. Am. Chem. Soc.* **1961**, *83*, 4674−4675.

(5) Bonneau, R.; Joussot-Dubien, J.; Salem, L.; Yarwood, A. J. A Trans Cyclohexene. *J. Am. Chem. Soc.* **1976**, *98*, 4329−4330.

(6) Chapman, L.; McIntosh, C. L.; Pacansky, J. Cyclobutadiene. *J. Am. Chem. Soc.* **1973**, *95*, 614−617.

(7) Bally, T.; Chai, S.; Neuenschwander, M.; Zhu, Z. Pentalene: Formation, Electronic and Vibrational Structure. *J. Am. Chem. Soc.* **1997**, *119*, 1869−1875.

(8) (a) Chapman, O. L.; Mattes, K.; McIntosh, C. L.; Pacansky, J.; Calder, G. V.; Orr, G. Benzyne. *J. Am. Chem. Soc.* **1973**, *95*, 6134−6135. (b) Warmuth, R. Benzyne: Strained Alkyne or Cumulene? − NMR Characterization. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1347−1350.

(9) (a) Tomioka, H. Versatile Reactions Undergone by Carbenes and Nitrenes in Noble Gas Matrices at Cryogenic Temperatures. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1501−1524. (b) Sanders, W.; Bucher, G.; Wierlacher, S. Carbenes in Matrixes − Spectroscopy, Structure and Reactivity. *Chem. Rev.* **1993**, *93*, 1583−1621.

(10) Turro, N. J.; Cherry, W. R. Photoreactions in Detergent Solutions. Enhancement of Regioselectivity Resulting from the Reduced Dimensionality of Substrates Sequestered in a Micelle. *J. Am. Chem. Soc.* **1978**, *100*, 7431−7432.

(11) Hammond, G. S.; Wu, C. S.; Trapp, O. D.; Warkentin, J.; Keys, R. T. Cage Effects in the Decomposition of α,α′-Azoisobutyronitrile and Related Compounds. *J. Am. Chem. Soc.* **1960**, *82*, 5394−5399.

(12) Gu, W.; Warrier, M.; Ramamurthy, V.; Weiss, R. G. Photo-Fries Reactions of 1-Naphthyl Esters in Cation Exchanged Zeolite Y and Polyethylene Media. *J. Am. Chem. Soc.* **1999**, *121*, 9467−9468.

(13) Cheung, E.; Kang, T.; Scheffer, J.; Trotter, J. Latent Chemical Behavior Revealed in the Crystalline State: Novel Photochemistry of a *cis*-9-Decalyl Aryl Ketone. *Chem. Commun.* **2000**, 2309−2310.

(14) See: Turro, N. J. *Modern Molecular Photochemistry*; The Benjamin/Cummings Publishing Co.: Menlo Park, CA, 1978; Chapter 10.

(15) (a) Cowan, D. O.; Drisco, R. L. *Elements of Organic Photochemistry*; Plenum: New York, 1976. (b) Ramamurthy, V. Photoprocesses of Organic Molecules Included in Zeolites. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991, pp 429−493.

(16) Schmidt, G. M. J. Photodimerization in the Solid State. *Pure Appl. Chem.* **1971**, *27*, 647−678.

(17) For example: Klessinger, M.; Michl, J. *Excited States and Photochemistry of Organic Molecules*; VCH Publishers: New York, 1994; pp 309−324.

(18) Zewail, A. H. Femtochemistry: Atomic-scale Dynamics of the Chemical Bond Using Ultrafast Lasers. *Angew. Chem., Int. Ed.* **2000**, *39*, 2586−2631.

(19) Elsaesser, T.; Kaiser, W. Vibrational and Vibronic Relaxation of Large Polyatomic Molecules in Liquids. *Annu. Rev. Phys. Chem.* **1991**, *42*, 83−107.

(20) Wan, C.; Grupa, M.; Zewail, A. H. Femtochemistry of ICN in Liquids: Dynamics of Dissociation, Recombination and Abstraction. *Chem. Phys. Lett.* **1996**, *256*, 279−287.

(21) Liu, Q.; Wang, J.-K.; Zewail, A. H. Femtosecond Dynamics of Dissociation and Recombination in Solvent Cages. *Nature* **1993**, *364*, 427−430.

(22) Kötting, C.; Diau, E. W.-G.; Baldwin, J. E.; Zewail, A. H. Direct Observation of Resonance Motion in Complex Elimination Reactions: Femtosecond Coherent Dynamics in Reduced Space. *J. Phys. Chem. A* **2001**, *105*, 1677−1682.

(23) (a) Mullikan, R. S.; Roothaan, C. C. I. The Twisting Frequency and the Barrier Heights for Free Rotation in Ethylene. *Chem. Rev.* **1947**, *41*, 219−231. (b) Saltiel, J.; Agostino, J. D.; Megarity, E. D.; Metts, D.; Neuberger, K. R.; Wrighton, M.; Zafiriou, O. C. The cis−trans Photoisomerization of Olefins. *Org. Photochem.* **1973**, *3*, 1−113.

(24) Fuss, W.; Kosmidis, C.; Schmid, W. E.; Trushin, S. A. The Photochemical cis−trans Isomerization of Free Stilbene Molecules Follows a Hula-twist Pathway. *Angew. Chem., Int. Ed.* **2004**, *43*, 4178−4182.

(25) Waldeck, D. H. Photoisomerization Dynamics of Stilbenes. *Chem. Rev.* **1991**, *91*, 415−436.

(26) Liu, R. S. H.; Asato, A. E.; Denny, M. Medium and Substituent-directed Stereoselective Photoisomerization of Polyenes in the Vitamin A Series. Application of Dellinger-Kasha Model. *J. Am. Chem. Soc.* **1983**, *105*, 4829−4830.

(27) (a) Alfimov, M. V.; Razumov, V. F.; Rachinsky, A. G.; Listvan, V. N.; Scheck, Yu. B. Photochemical Production of Non-equilibrium Conformers in Glassy Solutions of Diarylethylenes at 77K. *Chem. Phys. Lett.* **1983**, *101*, 593−597. (b) Castel, N.; Fisher, E. Frozen-in Non-equilibrium Rotamers in 1,2-diarylethylenes Obtained by Low-temperature Irradiation. *J. Mol. Struct.* **1985**, *127*, 159−166.

(28) Liu, R. S. H.; Hammond, G. S. The Case of Medium-Dependent Dual Mechanisms for Photoisomerization: One-Bond-Flip and Hula-Twist. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 11153−11158.

(29) Liu, R. S. H. Photoisomerization by Hula-Twist: A Fundamental Supramolecular Photochemical Reaction. *Acc. Chem. Res.* **2001**, *34*, 555−562.

(30) Glasbeck, M.; Zhang, H. Femtosecond Studies of Solvation and Intramolecular Configurational Dynamics of Fluorophors in Liquid Solution. *Chem. Rev.* **2004**, *104*, 1929−1954.

(31) Lightner, D. A.; McDonagh, A. F. Molecular Mechanisms of Phototherapy for Neonatal Jaundice. *Acc. Chem. Res.* **1984**, *17*, 417−424.

(32) Uda, M.; Mizutani, T.; Hayakawa, J.; Momotake, A.; Ikegami, M.; Nagahata, R.; Arai, T. Photoisomerization of Stilbene Dendrimers: The Need for a Volume-Conserving Isomerization Mechanism. *Photochem. Photobiol.* **2002**, *76*, 596−605.

(33) Krishnamoorthy, G.; Asato, A. E.; Liu, R. S. H. Conformational Isomerizations of Symmetrically Substituted Styrenes. No-reaction Photoreactions by Hula-twist. *Chem. Commun.* **2003**, 2170−2171.

(34) (a) Olivucci, M.; Ragazos, I. N.; Bernardi, F.; Robb, M. A. A Conical Intersection Mechanism for the Photochemistry of Butadiene: A MC-SCF Study. *J. Am. Chem. Soc.* **1993**, *115*, 3710−3721. (b) Fuss, W.; Lochbrunner, S.; Muller, A. M.; Schikarki, T.; Schmid, W. E.; Trushin, S. A. Pathway Approach to Ultrafast Photochemistry: Potential Surfaces, Conical Intersection and Isomerization of Small Polyenes. *Chem. Phys.* **1988**, *116*, 2034−2048.

(35) Squillacote, M. E.; Semple, T. C.; Mui, P. W. The Geometrics of the S-cis Conformers of Some Acyclic 1,3-Dienes: Planar or Twisted? *J. Am. Chem. Soc.* **1985**, *107*, 6842−6846.

(36) Krishnamoorthy, G.; Schieffer, S.; Shevyakov, S.; Asato, A. E.; Wong, K.; Head, J.; Liu, R. S. H. S-cis Conformers in Low-Temperature Irradiation of Dienes. Hula-twist Mechanism of Isomerization. *Res. Chem. Intermed.* **2004**, *30*, 397−405.

(37) Imamoto, Y.; Kuroda, T.; Kataoka, M.; Shevyakov, S.; Krishnamoorthy, G.; Liu, R. S. H. Photoisomerization by Hula-twist. 2, 2′-Dimethylstilbene and a Related Ring-fused Analog. *Angew. Chem., Int. Ed.* **2003**, *42*, 3630−3633.

(38) Zimmerman, H. E.; Zuraw, M. J. Photochemistry in a Box. Photochemical Reactions of Molecules Entrapped in Crystal Lattices. *J. Am. Chem. Soc.* **1989**, *111*, 7974−7989.

(39) Zimmerman, H. E. The Di-π-Methane Rearrangement. In *Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Song, P.-S., Eds., CRC Press: Boca Raton, FL, 1994; pp 184−193.

(40) Zimmerman, H. E.; Armesto, D.; Amezua, M. C.; Gannett, T. P.; Johnson, R. P. Unusual Organic Photochemistry Effected by Cyano and Methoxy Substitution. *J. Am. Chem. Soc.* **1979**, *101*, 6367−6383.

(41) Scheffer, J. R.; Pokkuluri, P. R. Unimolecular Photoreactions of Organic Crystals: The Medium Is the Message. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991, pp 185−246.

(42) Fuss, W.; Schmid, W. E.; Trushin, S. A. Ultrafast Electronic Relaxation of s-*trans*-Butadiene. *Chem. Phys. Lett.* **2001**, *342*, 91−98.

(43) For example: Niwayama, S.; Houk, K. N. Competition between Ester and Formyl Groups for Control of Torquoselectivity in Cyclobutene Electrocyclic Reactions. *Tetrahedron Lett.* **1992**, *33*, 883−886.
(44) Joy, A.; Uppili, S.; Netherton, M. R.; Scheffer, J. R.; Ramamurthy, V. Photochemistry of a Tropolone Ether and 2,2-Dimethyl-1-(2*H*)-naphthalenones within a Zeolite Enhanced Diastereoselectivity via Confinement. *J. Am. Chem. Soc.* **2000**, *122*, 728−729.
(45) Laksminarasimhan, P. H.; Sunoj, R. B.; Karthikeyan, S.; Chadrasekhar, J.; Johnson, L. J.; Ramamurthy, V. Direct Energy and Electron-Transfer Sensitized Geometric Isomerization of Stilbene within Zeolites: A Comparison between Solution and Zeolite as Reaction Media. *J. Photochem. Photobiol. A* **2002**, *153*, 41−54.
(46) Syamala, M. S.; Devanathan, S.; Ramamurthy, V. Modification of the Photochemical Behavior of Organic Molecules by Cyclodextrin: Geometric Isomerization of Stilbenes and Alkyl Cinnamates. *J. Photochem.* **1986**, *34*, 219−229.
(47) Duveneck, G.; Sitzmann, E. V.; Eisenthal, K. B.; Turro, N. J. Picosecond Laser Studies on Photochemical Reactions in Restricted Environments: The Photoisomerization of trans-Stilbene Complexed to Cyclodextrins. *J. Phys. Chem.* **1989**, *93*, 7166−7170.
(48) For singly anchored guest−host systems, see, for example: (a) Ueno, A.; Osa, T. Host−guest Photochemistry in Solution. In *Photochemistry in Organized and Constrained Media*; Ramamurthy, V., Ed.; VCH Publishers: New York, 1991, pp 739−782. (b) Fujimoto, T.; Nakamura, A.; Inoue, Y.; Sakata, Y.; Kaneda, T. Photoswitching of the Association of a Permethylated α-cyclodextrin-Azobezene Dyad Forming a Janus [2]Pseudorotaxane. *Tetrahedron Lett.* **2001**, *42*, 7987−7989.
(49) van der Horst, M. A.; Hellingwerf, K. J. Photoreceptor Proteins, "Star Actors of Modern Times": A Review of the Function Dynamics in the Structure of Representative Numbers of Six Different Photoreceptor Families. *Acc. Chem. Res.* **2004**, *37*, 13−20.
(50) Genick, U. K.; Borgstahl, G. E. O.; Ng, K.; Ren, Z.; Pradervand, C.; Burke, P. M.; Srajer, V.; Teng, T.-Y.; Schildkamp, W.; McRee, D. E.; Moffat, K.; Getzoff, E. D. Structure of a Protein Photocycle Intermediate by Millisecond Time-Resolved Crystallography. *Science* **1997**, *275*, 1471−1475.
(51) Genick, U. K.; Soltis, S. M.; Kuhn, P.; Canestrelli, I. L.; Getzoff, E. D. Structure at 0.85Å Resolution of an Early Protein Photocycle Intermediate. *Nature* **1998**, *392*, 206−209.
(52) Imamoto, Y.; Kataoka, M.; Liu, R. S. H. Mechanistic Pathways for the Photoisomerization Reaction of the Anchored, Tethered Chromophore of the Photoactive Yellow Protein and its Mutants. *Photochem. Photobiol.* **2002**, *76*, 584−589. An incorrect interpretation of the crystal structure (the mirror image) led to the previous incorrect conclusion[29] that the photoproduct was that from the HT process.
(53) Warshel, A. Bicycle-pedal Model for the First Step in the Vision Process. *Nature (London)* **1976**, *260*, 679−683.
(54) Anderson, S.; Srajer, V.; Moffat, K. Structural Heterogeneity of Cryotrapped Intermediates in the Bacterial Blue Light Photoreceptor, Photoactive Yellow Protein. *Photochem. Photobiol.* **2004**, *80*, 7−14.
(55) Harada, J.; Ogawa, K. X-ray Diffraction Analysis of Nonequilibrium States in Crystals: Observation of an Unstable Conformer in Flash-Cooled Crystals. *J. Am. Chem. Soc.* **2004**, *126*, 3539−3544.
(56) Kaupp, G. Hula-twist within the Confinement of Molecular Crystals. *Photochem. Photobiol.* **2002**, *76*, 590−595.
(57) Odani, T.; Matsumoto, A.; Sada, K.; Miyata, M. One-way *E,Z*-isomerization of bis(*n*-Butylammonium) (*Z,Z*)-muconate under Photoirradiation in the Crystalline State. *Chem. Commun.* **2001**, 2004−2005.
(58) Arai, T.; Tokumaru, K. Photochemical One-way Adiabatic Isomerization of Aromatic Olefins. *Chem. Rev.* **1993**, *93*, 23−39.
(59) (a) Palczewski, K.; Kumasaka, T.; Hori, T.; Behnke, C. A.; Motoshima, H.; Fox, B. A.; Le Trong, I.; Teller, D. C.; Okada, T.; Stenkamp, R. E.; Yamamoto, M.; Miyano, M. Crystal Structure of Rhodopsin: A G Protein-Coupled Receptor. *Science* **2000**, *289*, 739−745. (b) See also: Okada, T.; Fujiyushi, Y.; Silow, M.; Navarro, J.; Landau, E. M.; Shichida, Y. Functional Role of Internal Water Molecules in Rhodopsin Revealed by X-ray Crystallography. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5982−5987.
(60) Liu, R. S. H.; Colmenares, L. U. The Molecular Basis for the High Photosensitivity of Rhodopsin. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 14639−14644.
(61) Davidson, F. F.; Loewen, P. C.; Khorana H. G. Structure and Function in Rhodopsin: Replacement by Alanine of Cysteine 110 and 187, Components of a Conserved Disulfide Bond in Rhodopsin Affects the Light-activation Metarhodopsin II State. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *85*, 8459−8463.
(62) Kim, J. E.; Tauber, M. J.; Mathies, R. A. Wavelength Dependence of cis−trans Isomerization in Vision. *Biochemistry* **2001**, *40*, 13774−13778.
(63) (a) Becker, R. The Visual Process: Photophysics and Photoisomerization of Model Visual Pigments and the Primary Reaction. *Photochem. Photobiol.* **1988**, *48*, 369−399. (b) Koyama, Y.; Kubo, K.; Komori, M.; Yasuda, H.; Mukai, Y. Effect of Protonation on the Isomerization Properties of *n*-Butylamine Schiff Base of Isomeric Retinal. *Photochem. Photobiol.* **1991**, *54*, 433−443.
(64) Chosrowjan, H.; Mataga, N.; Shibata, Y.; Tachibanaki, S.; Kandori, H.; Shichida, Y.; Okada, T.; Kouyama, T. Rhodopsin Emission in Real Time: A New Aspect of the Primary Event in Vision. *J. Am. Chem. Soc.* **1998**, *120*, 9706−9707.
(65) Wang, Q.; Schoenlein, R. W.; Peteanu, L. A.; Mathies, R. A.; Shank, C. V. Vibrational Coherent Photochemistry in the Femtosecond Primary Event of Vision. *Science* **1994**, *266*, 422−424.
(66) Kandori, H.; Katsuta, Y.; Ito, M.; Sasabe, H. Femtosecond Fluorescence Study of the Rhodopsin Chromophore in Solution. *J. Am. Chem. Soc.* **1995**, *117*, 2669−2670.
(67) Birge, R. R.; Callender, R. H. Quantum Efficiencies of Primary Photochemical Processes in Vertebrate Rhodopsin. In *Biophysical Studies of Retinal Proteins*; Ebrey, T. G., Frauenfelder, H., Honig, B., Nakanishi, K., Eds.; U. Illinois Press: Champaign, IL, 1987; pp 270−281.
(68) In summer 2004, Professor T. Ebrey reminded R.L. of this literature data.
(69) Cheung, E.; Tang, T.; Netherton, M. R.; Scheffer, J. R.; Trotter, J. Conformational Enantiomerism in Chiral Organic Salts Containing Crystallographically Independent Anion−Cation Pairs. *J. Am. Chem. Soc.* **2000**, *122*, 11753−11754.
(70) (a) Ishiguro, M.; Hirano, T.; Oyama, Y. Modelling of Photointermediates Suggests a Mechanism of the Flip of the β-Ionone Moiety of the Retinylidene Chromophore in the Rhodopsin Photocascade. *ChemBioChem* **2003**, *3*, 228−231. (b) Yamada, A.; Yamato, T.; Kakitani, T.; Yamamoto, S. Torsional Potential Works in Rhodopsin. *Photochem. Photobiol.* **2004**, *79*, 476−486. These modeling studies and the crystal structures (ref 71) cast doubt on the suggestion that the primary product, photorhodopsin, is a HT product. (Muller, A. M.; Lochbrunner, S.; Schmid, W. E.; Fuss, W. Low-temperature Photochemistry of Previtamin D: Hula-twist Isomerization of a Triene. *Angew. Chem., Int. Ed.* **1998**, *37*, 505−507.)
(71) Unpublished work of Dr. T. Okada communicated to R.L.
(72) Warshel, A.; Barboy, N. Energy Storage and Reaction Pathways in the First Step of the Vision Process. *J. Am. Chem. Soc.* **1982**, *104*, 1469−1476.
(73) Paling, I.; Pardoen, J. A.; van den Berg, E.; Winkel, C.; Lugtenburg, J.; Mathies, R. A. Assignment of Fingerprint Vibrations in the Resonance Raman Spectra of Rhodopsin, Isorhodopsin and Bathorhodopsin: Implications for Chromophore Structure and Environment. *Biochemistry* **1987**, *26*, 2544−2556.
(74) Ramamurthy, V.; Weiss, R. G.; Hammond, G. S. A Model for the Influence of Medium in Photochemical Reaction. *Adv. Photochem.* **1993**, *18*, 67−234.

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