Photoisomerization by Hula-Twist: A Fundamental Supramolecular Photochemical Reaction

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Received October 23, 2000

ABSTRACT

The volume-conserving hula-twist *cis*/*trans* isomerization process has been incorporated in a general scheme for photoisomerization of polyenes, applicable to small organic molecules as well as to protein-bound polyene chromophores. The main theme is that in solution the conventional one-bond-flip mechanism dominates, while in frozen media (or under other forms of supramolecular constraint) the hula-twist mechanism takes over. Literature examples of photoisomerization obtained under confined conditions have been critically reviewed, the applicability of HT has been examined, and new systems unambiguously testing this volume-conserving process are proposed.

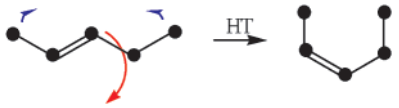
I. Photochemical *Cis/Trans* Isomerization—A Well-Known Reaction

Geometric isomerization is a common and important photochemical reaction for a linear alkene or a polyene. It has attracted the attention of many theoretical as well as experimental chemists for some time. The early notable major contributors are Wald, who demonstrated the importance of geometric isomerization in vision,[1] Zechmeister, who contributed much to isomerization of polyenes including vitamin A, β-carotene, and diphenylpolyenes,[2] and Mulliken, spear-headed the theoretical understanding of this reaction.[3]

More recent developments include the following. Havinga and the Leiden group showed that *cis/trans* isomerization is an integral part of photochemistry of compounds in the vitamin D series.[4] Hammond and Saltiel's classical work on stilbene[5] paved the way for the subsequent work on polyenes.[6] The identification of chemically distinct isomeric triplets of dienes[7] ushered in the detailed work on sensitized isomerization reactions.[8] Synthetic usage has been realized in, e.g., the preparation of all 16 isomers of vitamins A[9] and A_2.[10] The presence of a forbidden, doubly excited singlet state in polyenes has been established experimentally[11] and supported theoretically.[12] All of these, and voluminous fine papers that followed, perhaps could have contributed to the general impression that we now know everything about the photoisomerization reaction.

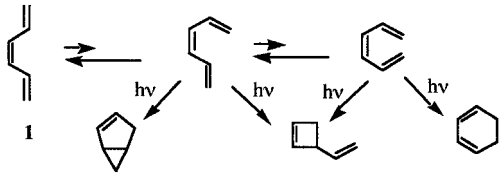
II. Photochemical *Cis*/*Trans* Isomerization—A Not-Fully-Understood Reaction

However, a careful examination of the literature reveals scattered results that are not accounted for by the existing knowledge on photoisomerization. To resolve such issues, Liu and Hammond recently advanced a general mechanistic scheme for all photoisomerization reactions[13] incorporating a concept (hula-twist) postulated more than 15 years ago,[14] which is repeated in the abbreviated form of "W"-to-"U" conversion.



Before we present this generalized scheme, the unexplained facts on photoisomerization will be summarized.

Systems Undergoing Non-NEER (Seemingly) Behavior. The concept of NEER (*n*on*e*quilibrating *e*xcited *r*otamers) was reached after an incisive analysis of product structures from direct irradiation of compounds in the vitamin D series.[4b] It was demonstrated independently with diene triplets[7] and later with simple trienes.[15] The case of *cis*-1,3,5-hexatriene (**1**) is illustrated below:



It shows that the electrocyclization or internal addition products are those corresponding to the original triene conformation, implying that excited-state species do not undergo conformation reorganization. This observation has since been broadened to many other systems, including diarylalkenes,[16] and other wavelength-dependent studies.[17] The inverse of this correlation will have to mean that any observation of a change of conformation from the reactant to the product is a violation of NEER. Several examples of non-NEER behavior are known in the literature.

In a matrix isolation study, Squillacote et al.[18] demonstrated that 1,3-butadiene undergoes *s-trans*/*s-cis* interconversion at 20 K as the only detected photochemical transformation, an obvious conformational change. The work was subsequently generalized to many other dienes[19] (more discussions below). Independently, Kohler and coworkers[20] showed that *all-trans*-1,3,5,7-octatetraene (**2**) isolated in an *n*-octane matrix at 4.2 K undergoes facile 2-*s*-*trans*/2-*s*-*cis* conformational interconversion (struc-

Born in the year of the tiger, Robert S. H. Liu was fortunate to have a determined mother, channeling his early school years through Shanghai, Hongkong, and the United States. Subsequently, he was fortunate to have been associated with four wise men: George S. Hammond (Caltech, 1961−1964), Howard E. Simmons (duPont, 1964−1968), and George Wald and George Porter (Harvard and Royal Institution, 1974−1975). And, he is fortunate to have his wife to maintain his sanity for 32+ years at Hawaii. To them, he dedicates this paper.

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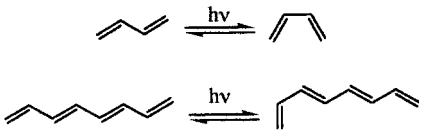
10.1021/ar000165c CCC: $20.00
Published on Web 05/15/2001

tures in the next section). In carrying out the butadiene and octatetraene work, both laboratories stressed the formation and properties of the unstable conformers rather than an understanding of the mechanistic pathway of their formation. Also, perhaps because of the absence of stable new products, none of these results were associated with the NEER phenomenon, or the lack of it.[21]



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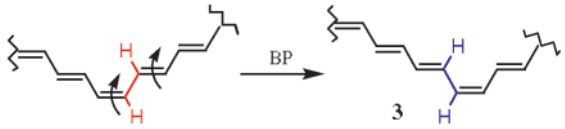
Photoisomerization of Diarylethylenes Frozen in Solid Solutions. The quantum yield of photoisomerization of *trans*-stilbene decreases rapidly upon an increase of the solvent viscosity. This reduced reactivity is accompanied by an increase in the quantum yields of fluorescence.[22] These trends are understandable on the basis of the conventional *trans*/*cis* isomerization mechanism (one-bond-flip, see below) with the effects attributed to the presence of a viscosity-dependent barrier on the torsional decay curve from the excited *trans* form to the perpendicular form.[22b−d] Upon freezing, such a one-bond-flip isomerization reaction is stopped with the fluorescence efficiency reaching a maximum. The photoreactivity of the *cis* isomer, on the other hand, shows a different pattern of medium dependence. In many *cis*-diarylethylenes, the isomerization remained observable in frozen media, the reaction thus becoming stereospecifically *cis* to *trans* under such conditions.[16]

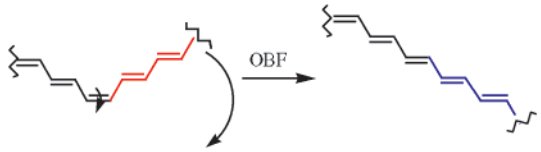
Interestingly, photoreaction in frozen media often leads to *unstable conformer(s) of the trans product*. Alfimov[23] and Fischer[24] have been given the credit for having discovered an entry to the unstable conformers,[16] although their observations are similar to those reported for the polyenes.[18,19] No explanation for the formation of such conformers was offered, and no mechanistic significance was ever attached to such observations. Separately, the medium effect has been shown to play a significant role in determining the regioselectivity of photoisomerization of polyenes.[25]

The Rapid Processes of Protein-Bound Polyenes. In the mid-1980s, when picosecond time-resolved spectroscopy was first applied to studies of the visual pigment rhodopsin, it was shown that the primary product bathorhodopsin appeared within 6 ps,[26] the limit of the instrument resolution at that time. (Subsequently this time period has been pushed back progressively to less than 1 ps.[27]) The question that was obvious to anyone concerned with the molecular process of the photoisomerization reaction was how the seemingly high-volume-demanding *cis*/*trans* isomerization of the 11-*cis*-retinyl chromophore, "sandwiched" between the protein matrix,[28] can be accomplished within a time scale that is much too short for protein reorganization.

The first attempt to rationalize the rapid rate of isomerization was that of Warshel, who proposed the volume-conserving bicycle pedal (BP) mechanism.[29]

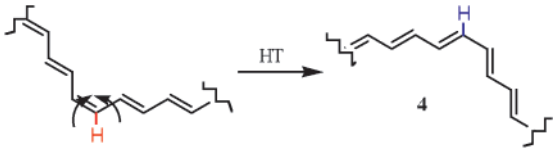


(Here and below, the color changes emphasize turning over of that portion of the molecule.) It is clear (structure **3**) that during the BP isomerization of the central *cis* double bond, only two C−H units of the polyene chain undergo 180° translocation rather than one-half of the molecule, as in a conventional one-bond-flip (OBF) *cis*-to-*trans* isomerization process.



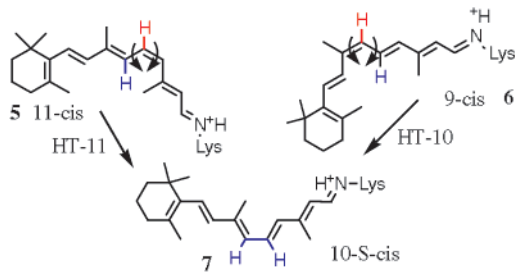
The BP proposal, however, predicts one-photon, two-bond isomerization, which is not consistent with the observed one-bond isomerized product in rhodopsin or in bacteriorhodopsin. Subsequent calculations showed that BP (around two single bonds) is possible as a ground-state process.[30]

Liu and Asato[14] proposed instead the volume-conserving process of simultaneous rotation of a pair of adjacent double and single bonds or a 180° translocation of one C−H unit to give structure **4** (see also "W"-to-"U", above).[14] The process was first labeled CT-*n* (*c*oncerted



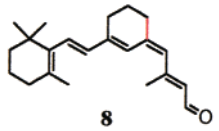
*t*wist at center *n*),[14] but the locally fetching name HT-*n* (*h*ula-*t*wist at center *n*) has gained more popularity.[31]

An obvious stereochemical consequence of the HT process is simultaneous configurational and conformational changes. Considering that the 11-*cis* and the 9-*cis* isomers of rhodopsin (structures **5** and **6**) both yielded the *all-trans* photoproduct bathorhodopsin upon irradiation,[32] it was proposed that bathorhodopsin has the 10-*s*-*cis*-*all*-*trans* retinyl structure (**7**), formed by way of HT-11 or HT-10.[14]



However, resonance Raman (RR) work[33] showed that the polyene conformation in bathorhodopsin is 10-*s*-*trans*.

Subsequently, it was shown that bathorhodopsin is preceded by another (untrappable) intermediate, photorhodopsin,[34] raising the question of whether the RR work on bathorhodopsin can be used as a meaningful test to determine the mechanistic details of the photoisomerization reaction.[35] However, an independent analogue study with a C9−C11 ring-fused analogue **8** also showed that the isomerization process can occur without involving conformational changes at the 10,11-bond, i.e., possibly HT-12 instead of HT-11.[36]



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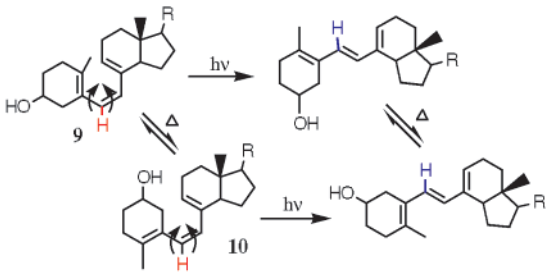
Development in bacteriorhodopsin paralleled that of rhodopsin. The untrappable J intermediate precedes K,[37] for which the crystal structure has recently become available (see below).[38] However, a discussion on a possible 14-*s*-*cis* conformation[39] appeared long before postulation of HT for this system.[40]

Since then, there have been many more excellent time-resolved spectroscopic studies reporting results on the photochemical reactions of many natural occurring photosensitive pigments that contain a polyene chromophore embedded in a protein host (many other retinal binding proteins,[41] photoactive yellow protein,[42] phytochrome,[43] and bilirubin[44]). All of them shared the common message that the photoisomerization is an extremely rapid process. But how?

III. Return of the Hula-Twist

Thirteen years after the postulation of hula-twist appeared the first experimental examples unambiguously identifying the HT process. In a low-temperature photochemical−spectroscopic study of isomers of pre-vitamin D (**9**, **10**), Fuss and co-workers[35] reported photochemical reactions resulting in exclusive formation of a double bond and an adjacent single bond isomerized product—in agreement with the predicted stereochemical consequence of HT processes. There are also new examples of non-NEER behavior.[45] More recently, from a molecular modeling study, Ishiguro postulated that the primary process of rhodopsin is HT-12,[46] a process suggested by us many years ago.[36]



The combined results of these unrelated non-NEER examples played an important role in our formulation of the general mechanistic scheme for photoisomerization.[13] Thus, in the Hawaiian summer of 2000, it struck this writer that the reaction conditions for these systems were similar, *all in rigid media*, while the other overwhelmingly large number of examples of photoisomerizations that exhibited the NEER behavior were all accumulated *in fluid solution (or in the vapor phase)*. And, the *trans*-stilbene results[22] suggest that the conventional OBF mechanism cannot take place in a frozen medium. Further assisted by G. S. Hammond,[47] it dawned on this writer that all these data are consistent with the simple idea that *the hula-twist is a less probable (high-energy) process, masked by the conventional OBF mechanism under common reaction conditions. Only in frozen media (or with other restraining forces) when the OBF mechanism is totally eliminated will the volume-conserving HT process reveal itself (or become competitively favorable).*[13] Because of the absence of competing processes, the quantum efficiency of such a less probable process could become appreciable, even approaching unity.

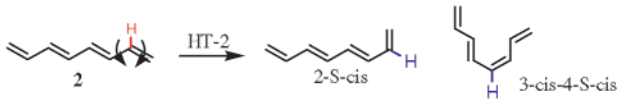
This dual mechanistic approach[13] is actually not a radically new idea. The concept closely parallels the "molecule-in-a-box" approach[48] that has become very popular in recent medium-directed photochemical studies.[48,49] In latter studies, it has been amply demonstrated that the use of well-chosen "boxes" (e.g., micelles, zeolites, cyclodextrins, or crystal lattice) can selectively freeze out some of the common solution photochemical processes of the included substrate, favoring instead other new or minor processes. Thus, supramolecular photochemistry, i.e., chemistry controlled by the medium as well as the substrate, can achieve new results in high regio- or stereoselectivity. In the present case, the only difference is that we do not need a preselected, specially constructed "box". As soon as the medium is frozen (not necessarily low temperature but rather less mobile relative to the excited-state lifetime of the substrate; thus, other constraints are equally acceptable), the supramolecular photochemical reactivity of HT takes over. Thus, it seems to us that HT is *a fundamental supramolecular photochemical reaction*.

IV. New Examples of HT

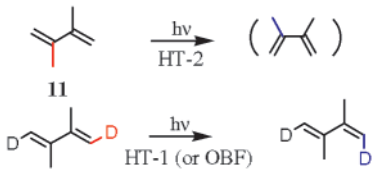
We shall examine how this dual mechanistic scheme can account for several cases of literature examples on photoisomerization whose relevance to HT was not recognized previously. We are also in a position to propose other new definitive examples of HT and to define the best conditions for identifying new examples of HT.

Known Photoisomerization Results. For the photochemical interconversions of 1,3-butadiene and 1,3,5,7-octatetraene (**2**) carried out in solids, we suggest the involvement of HT-2.[14] The regiospecificity observed for octatetraene (only at C-2) is likely a consequence of the limited linear-shaped space (in the *n*-octane matrix) available for reaction. Any other HT processes would generate a molecule of a shape incompatible with the host. For example, HT-4 would produce the bent 3-*cis*-

4-*s*-*cis* isomer shown. It follows then that HT-1 should be a facile process, but would be detectable only with appropriate stereochemical labels at the terminal positions.

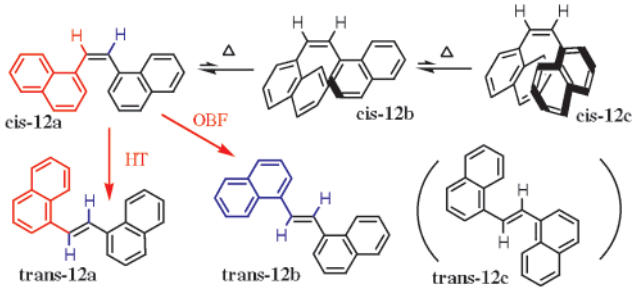


In fact, low-temperature photochemical experiments with a diene containing such stereochemical labels are already present in the literature, though a different mechanistic interpretation was offered. With 2,3-dimethylbutadiene, Squillacote and co-workers first reported[19b] the absence of *s*-*cis*/*s*-*trans* interconversion (instead giving irreversibly a cyclobutene product). Subsequently, in an elegant study of argon matrix isolation using *trans*,*trans*-1,4-dideuterio-2,3-dimethylbutadiene (**11**),[19a] they detected instead efficient isomerization of the 1,2-bond. They suggested that the OBF mechanism was involved. But, to us, these results and those for other dienes studied[19] can be readily and more consistently explained by the HT mechanism.[13] The absence of conformational stereomutation in 2,3-dimethyl-1,3-butadiene is likely due to steric inhibition for HT-2. Flipping a methyl group appended to a C is clearly more difficult than flipping an H atom appended to a C.



Meanwhile, HT-1 processes are unaffected, becoming the preferred chemical channel of deactivation. It matters little whether HT-1 is executed with a C−H or a C−D unit. The net result is the same: isomerization at the 1,2-bond.

For diarylethylenes, an interesting case is *cis*-1,2-bis-α-naphthylethylene (**12**) as part of the above-mentioned study of low-temperature irradiation of hindered *cis* isomers of diarylethylenes for producing the unstable conformer(s) of the *trans* isomers.[23,24] Conformational analyses of **12**[50] revealed that only one conformer (**a**) should be present at room or lower temperatures. Compound **12** being a symmetrical alkene, there is only one distinct mode of HT or OBF. HT gives the high-energy, hindered conformer **b**, while OBF gives the stable conformer **a**. Thus, the reported formation of an unequilibrated mixture of the *trans* product (unclear whether *only* the high-energy conformer was produced) is not consistent with the sole involvement of the OBF process. Rather, it is consistent with HT being the major, if not the only, mode of isomerization. Thus, unbeknownst to Alfimov and to Fischer, the photoisomerization of *cis*-**12** is, in fact, the first experimental example of HT—recorded two years before postulation of the HT concept![51]

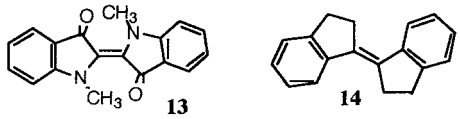


Two additional examples (*cis*-1-β-naphthyl-2-phenylethylene and *cis*-1,2-bis-β-naphthylethylene) were also described.[23,24] However, in both cases, because of the presence of more than one conformer of the *cis* isomer, the low-temperature irradiation result cannot be uniquely accounted for by either the HT or the OBF mechanism. Thus, they are not useful for identifying the specific mode of isomerization.[52]

The stereospecific one-way *cis*-to-*trans* isomerization in frozen media is likely due to the different solvent cages surrounding the two isomers. The cage surrounding the planar *trans* isomer is likely better organized and more tightly bound. That surrounding the nonplanar *cis* isomer is likely less well-organized, providing a slightly larger local cavity for reaction,[53] apparently sufficient for the volume-conserving processes such as HT. Interestingly, the only reported studies of HT were conducted with the *cis* isomers.[35]

Furthermore, there is no evidence against the premise that the few known cases of *cis*/*trans* isomerization in crystals, where again the *cis*-to-*trans* process dominates, do not involve HT.[54] It is interesting that in two recent studies of photochemical reactions in crystals, the volume-conserving BP processes have been detected as secondary ground-state reactions.[55,56] We are hopeful that similar studies, especially the technique of time-resolved X-ray crystallography,[55] will lead to direct observation of HT in small molecules in the near future (see PYP below).

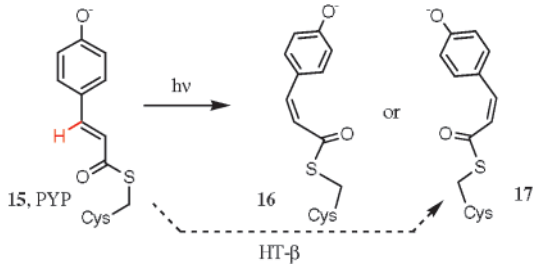
The *E*/*Z* isomers of *N*,*N*′-dimethylindigo dyes **13**[57] and the stilbene analogue **14**[58] are known to interconvert photochemically in solution. The ring constraints do not



allow any type of HT but have no effect on OBF processes. Therefore, their photoisomerizations refute the claim that HT is a general mechanism for all photoisomerization reactions.[35]

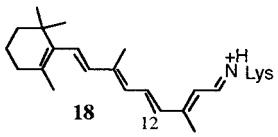
Recent highlights in photoisomerization of protein-bound polyenes are the following. The rapid progress in studies of the photoactive yellow protein (PYP) since its discovery a little over a decade ago led to much of the detailed knowledge: the chromophore **15**, the photocycle, and its crystal structure at 0.82 Å.[42] The most exciting developments have been two independent X-ray crystallographic studies. First, the structure of the photoproduct **16** was determined using the cryocooling (−100 °C) technique;[59] then, time-resolved (1 ns) X-ray crystal-

lography led to structure **17** for the red-shifted intermediate.[60] The two structures appear to be mirror images of each other.

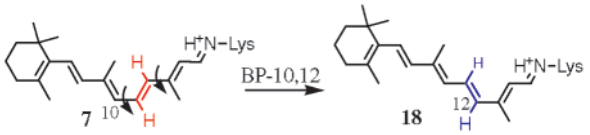


It was pointed out that the observed product was that from an OBF process of the smaller thiocarboxylate functionality.[59] However, given the fact that the chromophore is protein-bound, we prefer to invoke the more volume-conserving HT. Clearly (see structure above), HT at the β-carbon also gives **17**. (The alternative pathway of HT at the α-carbon would lead to an incorrect structure containing an s-*trans* conformation for the ene−ester linkage.) In fact, the PYP work can be viewed as an excellent example of the HT mechanism, provided that additional experiments will be conducted in order to establish that the phenoxy ring does not flip during the photochemical step (strongly implied in discussions of the X-ray studies).[59,60] An analogue with an unsymmetrically substituted phenoxy ring will have to be used.

For the structure of the bathorhodopsin, the first stable photoproduct from rhodopsin, Ishiguro suggested the 12-*s*-*cis*-*all*-*trans* structure (**18**)[46] and the conversion of 9-*cis*-

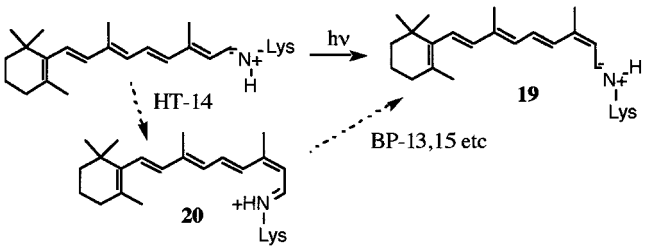


rhodopsin to bathorhodopsin by an extended HT process involving a three-carbon (C10−C12) fragment. Alternatively, we pointed out[52] that the12-*s*-*cis* structure **18** could be reached by photochemical HT-10 of 9-*cis*-rhodopsin followed by thermal BP-10,12 of the intermediate 10-*s*-*cis* structure **7** (see BP above):



The correct structure of bathorhodopsin will likely soon be resolved as a sequel to the recent solution of the crystal structure (2.8 Å) of rhodopsin.[61]

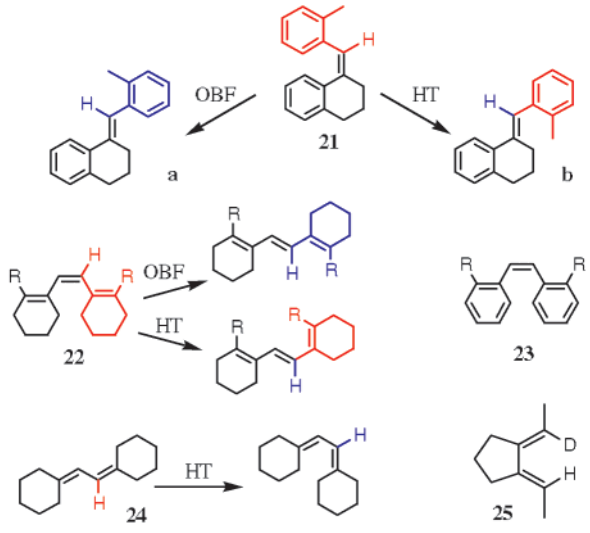
Accurate structures (1.55 Å) of bacteriorhodopsin (bR)[62] and its first stable photoproduct K[38] are now available. The observed 13-*cis*-*all*-*s*-*trans* retinyl chromophore for K[38] (**19**) is not in agreement with the postulated 13-*cis*-14-*s*-*cis* structure.[39,40] It is possible that, when anchored at the lysine unit at one end and the trimethylcyclohexenyl hydrophobic pocket at the other end, the chromophore cannot complete the HT-14 process to the greatly shortened 13-*cis*-14-*s*-*cis* structure (**20**). Instead, BP processes



as a follow-up ground-state reaction (see 9-*cis*-rhodopsin above) could lead to the transfer of the s-*cis* linkage eventually to the butyl tether. It is particularly worth noting that the s-*cis* kink present in the butyl tether of bR[62] is very likely a key factor that facilitated the latter process, making possible the overall conversion within the requirement of "longitudinal restriction",[38] as pointed out earlier.[40]

In bilirubin, *E*/*Z* isomerization by OBF appears to be impossible, as it would require the simultaneous breakage of the network of hydrogen bonding that holds the molecule in a unique conformation.[44b] The situation would be equivalent to the lack of isomerization of the non-*N*-alkylated indigo dyes.[57] But, in this case, the presence of a CH unit should make possible a HT process to produce first a strained intermediate, which could lead to sequential breakage of the H bonds in the ground state, similar to signal transduction in PYP from the strained primary product.

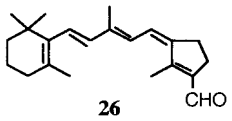
Proposed New Experiments. One added benefit from the general concept for photoisomerization is that it allows rational design of new systems for differentiation between HT and OBF mechanisms. For example, for the *cis*-stilbene analogue **21**, only one major conformer exists. HT will lead exclusively to the unstable conformer **b**, and OBF to the stable conformer **a**. Since in frozen solution only HT is



expected, conformer **b** will be formed. Upon warming and recooling, a red-shift will result, indicating the conversion of **b** to the more planar **a**. Compound **22** (and the corresponding stilbene analogue **23**) will also give distin-

guishable HT (unstable conformer) and OBF (stable conformer) products. Compound **24** will undergo HT, giving the *s-cis* conformer, but OBF will give no distinguishable new products. Compound **25** will show the importance of deuterium isotope effects on HT: a positive deuterium isotope effect (i.e., $k_D/k_H > 1$) indicates the importance of C−D or C−H vibrational amplitude in determining the relative ease of HT, while a negative effect indicates the importance of C−H (C−D) vibration in electronic relaxation.[63]

Other ring-fused retinal analogues can be used to test the HT-12 mechanism for photoisomerization of rhodopsin. For example, for analogue **26**, HT-12 is no longer possible. It will be of interest to determine whether the



26

excited pigment will find new channels of deactivation or instead become a new fluorescent pigment.

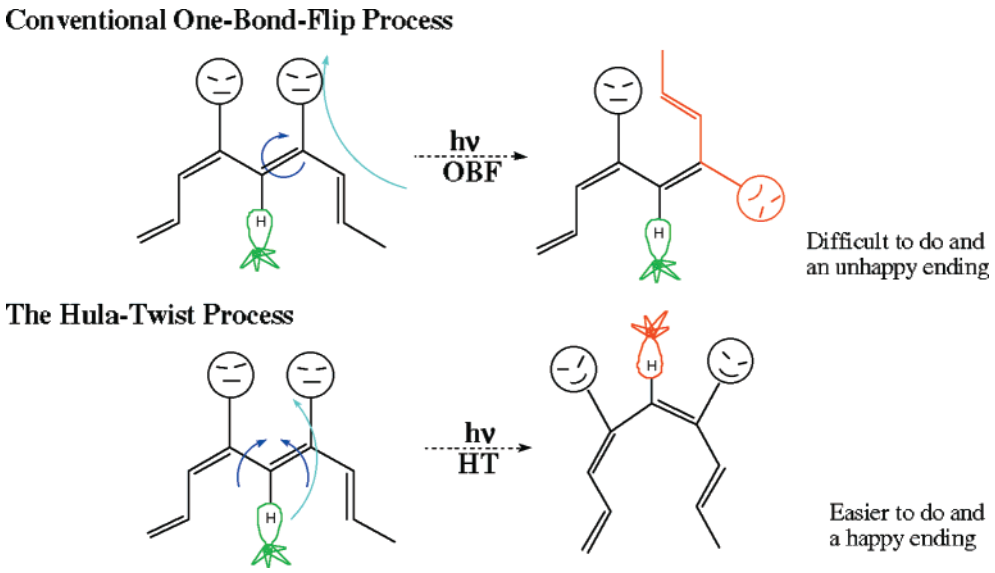
It should be noted that the currently popular, ever faster time-resolved spectroscopic techniques for liquid samples may not be the best for investigation of high-energy (less probable) processes (such as HT) that are masked by other rapid processes (such as OBF). Only under conditions when the latter processes are impeded can the less probable process be examined. Thus, the ideal condition for searching for HT in small organic systems is photochemical−spectroscopic studies of frozen (solid) samples (or samples embedded in other well-chosen host systems). The implication that such a process is likely to proceed at a slower rate, but with its efficiency enhanced through reduction of complicating competing processes, should be verified by experiments. It is also possible that under special conditions, the longer-lived triplet state might participate in reactions in a frozen system. For special cases of trapped chromophores, the host could enhance the rate of the otherwise slow process. This is particularly true for protein-bound polyenes, where reactivities might be enhanced at a specific double bond. Thus, for rhodopsin, the rate of photoisomerization has been accelerated (versus 11-*cis*-retinyl PSB in solution) to the extent that it challenges the best time-resolved instruments available.[27] This is a demonstration of protein assistance provided by the binding site. Therefore, to other unique features of the binding site of opsin (stereospecificity,[64] chiral induction,[65] wavelength attenuation)[66] we may now add enhanced rate of hula-twist. Also, for PYP, the high efficiency of isomerization[42] most likely reflects a huge rate acceleration from the low reactivity of *trans*-stilbene in frozen media.[22]

V. Future Outlook

It took 15 years since the postulation of the HT concept[14] before this writer was able to reduce the HT mechanism to a rational, physical organic thought process, defined by simple model compounds. In hindsight, the simplicity of the concept perhaps only reflects the limitation of our minds, or more accurately my mind: too often its imagination is limited by self-imposed, unnecessary boundaries. But, now with the conditions for detecting this volume-conserving two-bond-twist process better defined, I am hopeful that as we step into the 21st century, we are opening the floodgate for new examples of HT. Not only will the current paucity of simple organic examples of hula-twist be rectified, but also, it is hoped, more researchers will sense the island rhythm. Indeed, the next few years can be very exciting years.

I am grateful for the nearly 3 decades of uninterrupted support from NIH, U.S. Public Health Services (DK-17806). Its persistence allowed time for the slow maturing process of radically new ideas such as the one described in this paper. I am also grateful to my teachers, many friends, and colleagues who have constructively kept me honest and on my toes while I struggled with the HT concept. Among these, I would like to name G. S. Hammond, J. Saltiel, V. Ramamurthy, and A. E. Asato. I am also grateful to my

Scheme 1



family members, my secretary, and many students (graduate and undergraduate) for maintaining my humor even at times when every silver lining seemed to contain a dark cloud. Mahalo and Aloha!

Appendix

A few persons expressed to me their difficulties in visualizing the HT process from viewing the simple bond-line structures used in earlier publications[13,14] that are similar to those shown in this paper. First, I would like to recommend the use of framework molecular models whenever possible. I have also introduced color coding to clarify the movement (same color for no change of the sidedness of that portion of the molecule and different colors for inversion of sidedness). However, I found the most effective way was that used in a simple lecture demonstration with a volunteer using arms and bodies. This demonstration is now graphically illustrated in Scheme 1 to emphasize the difference between OBF and HT.

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AR000165C