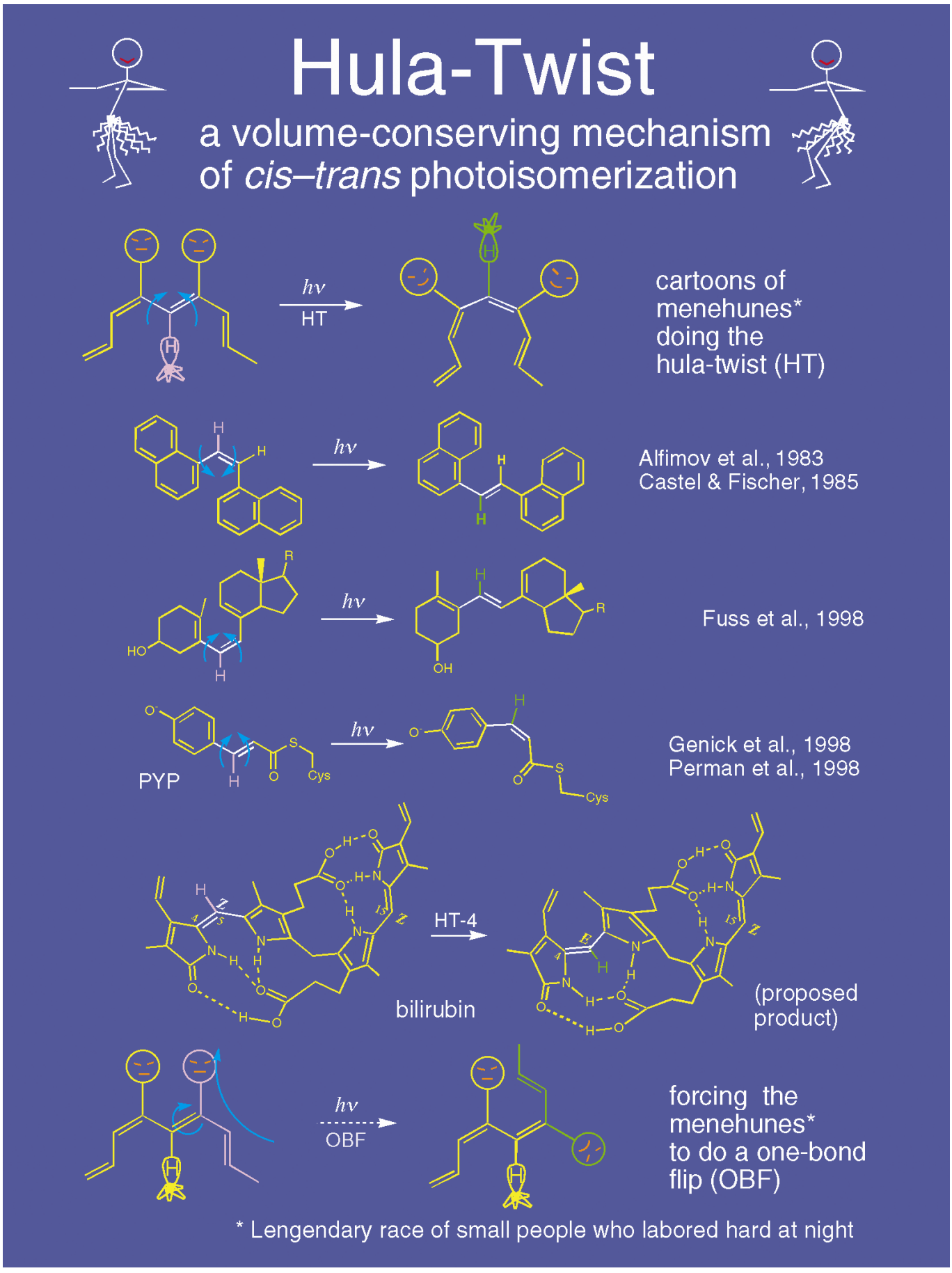

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Examples of Hula-Twist in Photochemical *cis–trans* Isomerization

Robert S. H. Liu*[a] and George S. Hammond[b]

Abstract: Liu and Hammond recently reasoned that the hula-twist (HT), a volume-conserving *cis–trans* isomerization mechanism, is involved in reactions of confined systems. We now show that HT can be applied to various reported photochemical isomerization of chromophores (small organic systems as well as photoactive bio-pigments). The results, when taken as a whole, argue powerfully that HT is a common supramolecular photoisomerization reaction mechanism.

Keywords: medium effect · photoisomerization · polyenes · reaction mechanisms · supramolecular chemistry

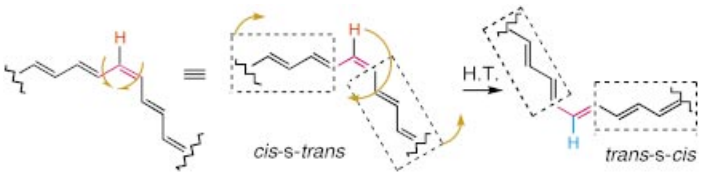
Introduction

The common model of photochemical *cis–trans* isomerization is torsional relaxation of the double bond with reduced excited state bond order, reaching ground state products diabatically. It is a one-bond-flip (OBF) process, turning over one half of the molecule. However, since the first picosecond time-resolved study on the primary photochemical process, demonstrating that the seemingly volume-demanding 11-*cis* to all-*trans* isomerization of the retinyl chromophore was accomplished within 6 ps,[1] there have been serious doubts that this conventional mechanism for photoisomerization can be applied to protein-bound polyenes. (Improved instrument resolution has since shortened photochemical reaction time to less than 1 ps.[2]) Hence, in 1978, Warshel proposed the volume-conserving bicycle-pedal (BP) mechanism for the excited visual chromophore.[3] The implication of one-photon two-bond isomerization, however, does not agree with the observed fact of one-photon one-bond isomerization in visual pigment. In fact, it has since been shown theoretically[4] and experimentally[5] that a BP-like motion involving simultaneous rotation of two alternating single bonds is a rapid ground state process appropriate for confined polyenes.

In 1985, Liu and Asato[6] postulated the concept of hula-twist (HT) as a volume-conserving photoisomerization process for confined polyenes, including the visual chromophore of rhodopsin. The HT mechanism for *trans* to *cis* isomerization is illustrated in Scheme 1 (left) in the form of conversion of a W-array of atoms to a U-array. In contrast, the conventional OBF process for isomerization results in the conversion of a W to a sickle.

Scheme 1.

For a polyene, the salient stereochemical consequence of the HT process is the simultaneous double bond and adjacent single bond isomerization. Only one C–H unit undergoes out-of-plane translocation, while the remaining portions of the molecule slide along in the general direction of the plane of the molecule (Scheme 2).



Scheme 2.

In 1998, the first definitive experimental example of hula-twist, which demonstrated the required two-bond isomerization, was reported by Fuss and co-workers.[7]

In 2000, Liu and Hammond[8] unveiled a general mechanistic scheme for all photoisomerization reactions that incorporates the hula-twist as a key component for photoisomerization of small molecules in solid solutions as well as polyene chromophores that are protein bound. The essence of this generalization can be summarized in two major points.

1) Without media constraints (i.e., in solution or in the vapor phase), photoisomerization from the excited singlet state

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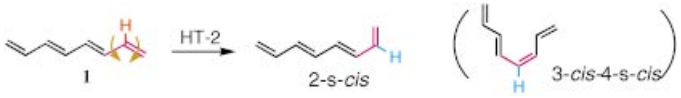
proceeds by way of the conventional one-bond-flip (OBF) process. Hula-twist (HT), if it occurs, is an undetectable minor process.

2) With media constraints (e.g., in a solid solution, a protein cavity, or in other interactions that restrict conformational mobility of substrates), the OBF process could be completely suppressed, revealing instead the otherwise less probable hula-twist process.

In support of the second point mentioned above, Liu and Hammond[8] pointed out scattered literature examples of photochemical conformational isomerization reactions consistent with the hula-twist concept. Since then a careful review of literature revealed more relevant examples.[9] The purpose of this paper is to point out these reports and to interpret or re-interpret results to show that not only they are consistent with HT, but that some are sufficiently detailed that they can be taken as supporting evidence for HT.

Regioselective Isomerization of Excited Polyenes

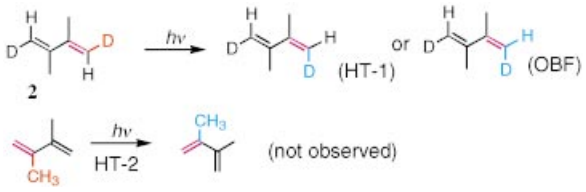
In an *n*-octane matrix at 4.3 K, all-s-*trans*-all-*trans*-1,3,5,7-octatetraene (**1**) was reported to undergo reversible conformational isomerization change to its 2-s-*cis* conformer.[10] Not only can the previously undefined reaction be now readily accounted for by a single HT-2 process (Scheme 3),[8] but also,



Scheme 3.

given the sensitivity of the reaction toward available reaction volume, the observed regiospecificity (at center 2) can be readily rationalized. HT at any central carbon atom would lead to a highly bent structure (e.g., the 4-s-*cis*-3-*cis* structure shown from HT-4, Scheme 3,) incompatible with the *n*-octane matrix.

Following this line of reasoning one might expect HT-1 to be a facile process. This undetectable process has, in fact, been elegantly demonstrated by Squillacote with *trans*,*trans*-1,4-dideutero-2,3-dimethyl-1,3-butadiene (**2**) studied under argon matrix isolation conditions at 20 K.[11] The observation of the absence of s-*trans* to the s-*cis* conformational isomerization, but rather configurational isomerization at the 1-(or 4-)position was interpreted as being consistent with a preference for the conventional OBF mechanism of isomerization at the terminal double bond. However, given the matrix isolation condition, we suspect HT may be involved. In fact, the combined results appear to be more consistent with such a view. Steric inhibition of HT-2 due to replacement of H-2 in butadiene[12] by the bulkier methyl[11] should reduce the quantum yield of the 2-s-*cis* conformer, channeling deactivation preferentially through the uninhibited HT-1, for which either HT-D or HT-H will give the same observed product (Scheme 4). (Note that while OBF and HT-1 give the same product in these two cases, they are distinctly different processes, one involving rotation of both C–H units, the other, rotation of one C–H unit.)



Scheme 4.

Conformer-Specific Isomerization of Diarylethylenes

Quantum yields of photoisomerization of *trans*-stilbene decrease rapidly upon increase of solvent viscosity. The decrease in reactivity is accompanied by an increase in the quantum yields of fluorescence.[13] These trends are attributed to the presence of a viscosity dependent barrier to the torsional decay process of the planar excited *trans* to the perpendicular form.[14, 15] For samples in frozen media, the isomerization reaction is stopped and the fluorescence reaches a maximum efficiency.[13] The photoreactivities of the *cis* isomer of some of the diarylethylenes are less sensitive to solvent viscosity. The net result is an increase of the *trans* isomer in the photostationary state upon increase of solvent viscosity. In fact, in many diarylethylenes, the photoisomerization becomes exclusively *cis* to *trans* in frozen media.[16]

In reporting such stereospecific photoisomerizations, Alfimov[17] and Fischer[18] further noted the formation of *unstable conformer(s) of the* trans *product*. Thus, a photochemical entry to the unstable conformers of the product isomer was discovered.[16] However, no explanation for the origin of the unstable products was ever offered.

Since the work of Alfimov and Fischer was carried out in frozen solid solutions, again, the HT mechanism should be expected to apply. In the case of *cis*-1,2-bis-*β*-naphthylethylene (**3**), conformational analyses[19] and also wavelength dependent fluorescence studies of Fischer et al.[20] revealed that only one conformer (**3a**) is likely to be present at room or lower temperatures. Being symmetrical, there is only one distinct mode of HT or OBF. HT gives the high-energy, hindered conformer **3a**, while OBF gives the stable conformer **3b** of the *trans* product (structures shown in Scheme 5). Thus, the reported result of formation of high-energy conformer(s) of the *trans* product (it is unclear whether the high-energy conformer was produced *exclusively*)[17, 18] is not consistent with the sole involvement of the OBF process. Rather, it is

Abstract in Chinese:
呼拉扭轉 (Hula-Twist, HT) 是一個保留體積的順-反異構化反應機構。劉 (Liu) 與漢盟 (Hammond) 最近推想結論利用此機構進行光反應者是包圍的發色團。現今我們呈現 HT 的確能用來解釋文獻上已報導過的一些含有被限定的發色團(小的有機系統和有光學活性的色素)的光異構化反應。由多方研討結果，HT 應被認為是一般超分子光異構化反應。

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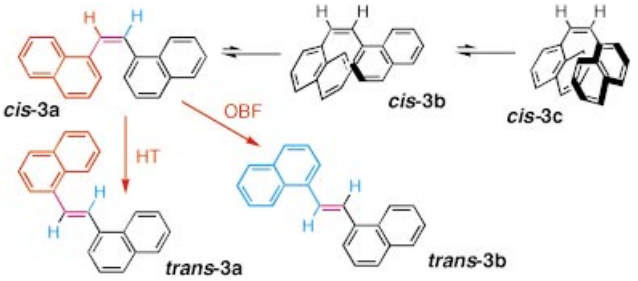


Scheme 5.

consistent with HT being the major, if not the only mode of isomerization. Thus, the photoisomerization of *cis*-**3** could, in fact, be considered the first demonstrated example of HT.

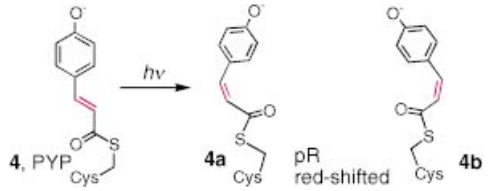
The absence of HT processes for the *trans* isomer is likely to be due to a tight solvent cage surrounding the planar *trans*-structure with the result of the free reaction volume being too small to allow even for the volume-conserving HT process. However, it should be noted that the difference in the intrinsic barriers for isomerization of *trans* and *cis* stilbenes[21] could also play a significant role in this temperature-dependent photochemical property.

In two other reported examples (1-β-naphthyl-2-phenylethylene[22] and 1,2-bis-β-naphthylethylene),[17, 18] formation of the high-energy conformer(s) could also be accounted for by the HT mechanism. However, because of the likely presence of more than one conformer in the starting material,[21, 22] OBF could also lead to unstable conformer(s). Hence, the photochemical result is not useful for the purpose of determining the nature of isomerization process in these two cases.

In this regard it is worth noting that the observation of a *trans*-rich photostationary state of the attached stilbene unit in a blue-fluorescent antibody (mAb) in a recent report was considered unusual and suggested to be related to leakage from the photoequilibrated *cis*–*trans* mixture to dihydrophenanthrene.[23] In our opinion, this is unlikely because for the latter explanation to hold, it would require the unlikely event that the electrocyclization would proceed at a faster rate than isomerization. Furthermore, the *trans*-rich composition is consistent with the reduced efficiency of *trans*-to-*cis* reaction of a stilbene unit in a restricted (confined) environment.

Photoactive Yellow Protein

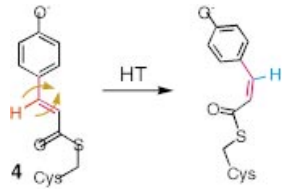
The most exciting recent development in studies of photosensitive naturally occurring pigments has been the rapid progress made with the recently discovered photosensitive pigment photoactive yellow protein (PYP), a cytosolic light receptor responsible for the repulsive response of the bacteria toward (swimming away from) intense blue light. In the short span of a little over a decade since its discovery,[24] many of the details (its photo-cycle, protein sequence, and its crystal structure at 0.82 Å) are known.[25] Its chromophore (**4**) is rather simple, and the *trans* to *cis* photoisomerization has been well characterized (Scheme 6). The most exciting development has been the two independent X-ray crystallo-



Scheme 6.

graphic studies on the primary photoproduct. First, its structure (**4a**) was determined by using the cryo-cooling (−100 °C) steady-state technique;[26] then independently time-resolved (1 ns) X-ray crystallography at 287 K led to structure **4b** for the red-shifted pR intermediate.[27] The two structures appear to be the same although they were presented as mirror images of each other. In describing the structure **4a** for the photoproduct, the authors[26] emphasized that the chromophore demonstrated an apparent preference for isomerization at the smaller thioester end of the double bond rather than the larger phenoxide ring. Also, the strained energy stored in the form of a highly distorted chromophore (double bond twisted by 80°!) triggers subsequent protein reorganization and signal transduction.

However, in our view, the fact that the chromophore is confined within a protein matrix makes it necessary to invoke HT for the isomerization process. In Scheme 7 we show that



Scheme 7.

the HT process at the β-carbon, an option not considered by previous workers, leads to a structure which is identical to that of **4b**. Considering the firm belief of the unlikely possibility of turning over of the phenoxide ring expressed by the authors of both X-ray studies,[26, 27] one could accept these structural works as remarkable demonstrations of the HT process.

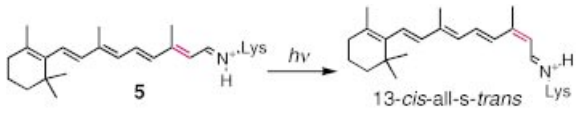
However, to establish the case beyond doubt, it will be necessary to carry out similar work with an unsymmetrically labeled ring that can provide information on the faciality of the ring and its relative orientation with respect to the thioester group during the photochemical transformation.

Retinoid-Binding Proteins

The primary photochemical processes of the chromophore in the larger retinoid-binding proteins (e.g., bacteriorhodopsin and rhodopsin) are more complex. Crystal structures have become available only recently, and its stereospecificity in binding interaction[28] could suggest a highly rigid binding site that might inhibit not only the volume-demanding OBF movement of the chromophore, but also the sideways movement of the polyene chain necessary to complete a HT

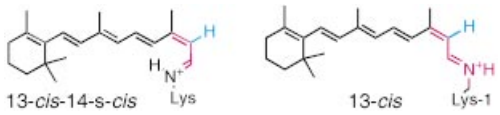
motion. The currently available structural evidence are examined separately for bacteriorhodopsin and rhodopsin.

Bacteriorhodopsin (bR): The X-ray crystal structure of the first stable photoproduct (K) of bR (at ~5 Å)[29] as well as that of bR (1.55 Å)[30] are now available. They clearly show that the photoisomerization to the first stable intermediate K involves the conversion of the all-*trans*-all-s-*trans* chromophore (**5**) to a 13-*cis*-all-s-*trans* chromophore (Scheme 8).



Scheme 8.

And, as with PYP, the photochemical reaction takes place within the cavity that contains the original all-*trans* chromophore. The stereochemical consequence is not in agreement with the 13-*cis*-14-s-*cis* structure (Scheme 9) arrived at by Tavan and Schulten[31] and by the HT-14 process.[32]

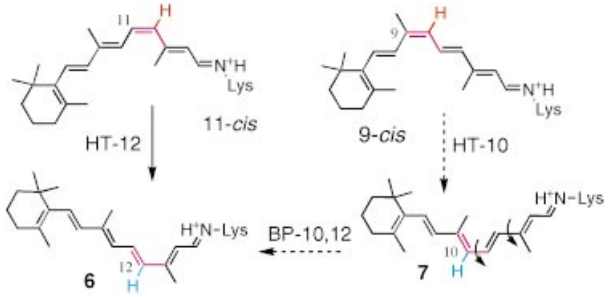


Scheme 9.

Upon further consideration of the restrictions imposed by the binding cavity of the all-*trans* chromophore of bR, we now would like to suggest the following sequence of events. It starts with HT-14 for the protein-bound excited polyene chromophore. However, spatial constraint does not allow the chromophore to complete the HT process, diverting instead to other conformational changes. In a sense the reaction is controlled by longitudinal restriction,[33] that is, the elongated tethered all-*trans* structure being much longer than the 13-*cis*-14-s-*cis* structure (see below) predicted from HT. We suspect the initial two-bond twist motion of HT-14 could only reach a geometry near the mid-point, sufficiently advanced to permit internal conversion to the ground-state potential surface and to produce detectable new photoproducts. Thereafter, an ensuing ground-state-allowed bicycle-pedal process (BP-14,16) would transfer the *cis*-linkage to the butyl tether at which further conformation adjustments are readily achievable. This conjecture remains to be proven. Also, it remains to be answered whether J, the precursor of intermediate K, is in any way related to structures in the proposed sequence of events.

Rhodopsin: The X-ray crystal structure of rhodopsin (2.8 Å) has become available only recently[34] and that of the first stable photoproduct bathorhodopsin, at this time, is still unknown. Therefore, for the consideration of the photochemistry of rhodopsin, we must rely on indirect spectroscopic evidence and other information related to the primary photochemical process.

In a molecular modeling study, Ishiguro recently postulated that the primary photochemical process of the rhodopsin chromophore is HT-12,[35] a suggestion consistent with an earlier analogous study[36] and an evident improvement over the earlier suggestion of HT-11. Initial motion of HT-12 has also been detected in recent time-resolved studies described in a review chapter.[37] The structure of the first stable product bathorhodopsin, however, remains to be proven. Ishiguro suggested the 12-s-*cis*-all-*trans* structure (**6**, see Scheme 10).[35]



Scheme 10.

For the photochemical conversion of 9-*cis*-rhodopsin to bathorhodopsin, he further suggested a direct, extended HT process involving simultaneous rotation of a three carbon (C10–C12) fragment to give the common batho-product. Considering the demonstrated steric inhibition of HT when flipping a methyl group instead of an H atom is involved (see results of 2,3-dimethylbutadiene cited above), we believe the latter suggestion is highly unlikely. Alternatively, we would like to point out that structure **6** can be reached by the sequence of a volume-conserving photochemical HT-10 process giving 10-s-*cis* **7**, followed by a thermally allowed[4] bicycle-pedal process, BP-10,12.

These suggestions, however, require that the protein matrix permits the substantial in-plane displacement of the polyene chain (a sliding movement of the middle portion of the polyene chromophore from a "downward bent-bow" to an "upward bent-bow"). In the case of bacteriorhodopsin, the crystal structure for its primary photoproduct clearly showed that there is no significant lateral area displacement of any portion of the polyene chain. If a similar situation exists for bathorhodopsin, a modified view will have to be considered. In fact, recently Kakitani[38] has argued for a twist-and-shear (T&S) mechanism leading to an all-*trans*-all-s-*trans* structure (6-s-*cis*) for bathorhodopsin. In our view the T&S mechanism is equivalent to the stepwise mechanism suggested above for bacteriorhodopsin, that is, an initial HT-12-like process followed by a series of BP processes with the result that transfers the s-*cis* linkage to the butyl tether. This issue, especially the structure of bathorhodopsin, will likely be resolved (same as K in bR) in the near future. Then, the remaining issue will be the exact nature of photorhodopsin, the precursor of bathorhodopsin, that has been detected under fast kinetic conditions,[39] that is, its role in, for example, the cascade scheme mentioned above.

The highly strained primary photoproduct detected during irradiation of PYP (double bond twisted by 80°, see above)

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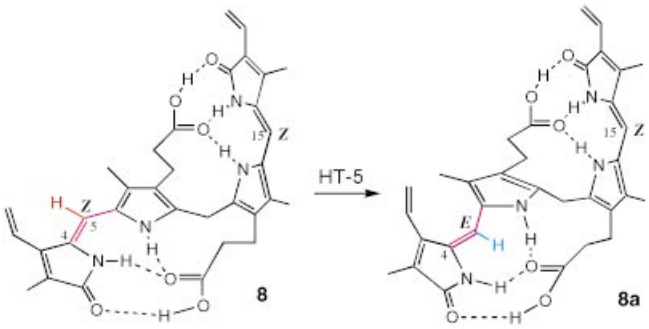
raised the interesting possibility of intramolecular thermal reaction of a primary photoproduct competing against relaxation of surrounding protein residues. This was, in fact, exactly the explanation offered[28] for reversion of bathoiodopsin to iodopsin, a cone pigment, upon warming the former to temperatures $> -80\,^{\circ}C$, demonstrated elegantly as early as 1959 in a series of low-temperature spectroscopic studies.[40] It is a feature that makes the cone pigment different from the rod pigment rhodopsin.

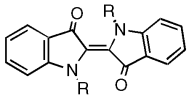
Other systems

Phototherapy of jaundice: The room-temperature photoisomerization reaction of bilirubin involved in phototherapy of jaundice was elucidated in an elegant study some time ago.[41] We now would like to point out that the observed photochemical results are consistent with the involvement of HT. Bilirubin (**8**), a *Z*,*Z* isomer, is known to contain an extensive internal hydrogen-bonding network that is disrupted in its isomerization to an *Z*,*E* isomer. The OBF process must break at least half of the H-bonds all at once, estimated to have an energy in excess of 10 kcal mol^{-1},[41] a value evidently too large to overcome for an excited molecule with a short S_1 lifetime. In Scheme 11 the folded structure of *4Z*,*15Z*-bilirubin with the internal hydrogen-bonding network, according to Lightner is shown on the left.[42] The proposed structure of the primary photoproduct (*4E*,*15Z*) following the HT-5 transformation of the *4Z*,*15Z* isomer (see below), prior to disruption of any one of the hydrogen bonds, is shown on the right.



Scheme 11.

The situation is reminiscent of the photoreactivities of indigo dyes **9a**. With a tetrasubstituted double bond it cannot isomerize by HT, and internal hydrogen bonding apparently also stops the OBF process. Its photostability has been well documented.[43] Upon *N*-alkylation (**9b**, i.e., removal of hydrogen bonding) isomerization becomes an efficient process,[44] presumably by OBF because of the absence of a vinyl C–H unit necessary for HT (Scheme 12).

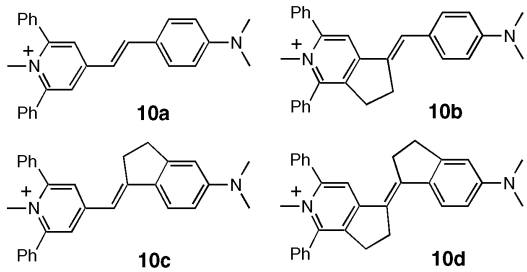


9a: R = H
9b: R = CH_3

Scheme 12.

However, with a C–H unit on the double bond (at C5 and C16), bilirubin should be able to undergo the volume conserving HT process without immediately disrupting the H-bond network. We therefore propose the possible formation of a strained (double bond twisted) intermediate (see **8a** in Scheme 11 above following HT-5) from photoexcitation of bilirubin. The ensuing ground-state reaction, triggered by the strain energy in the twisted double bond would lead to sequential disruption of the hydrogen bonds in that half of the molecule leading eventually to the strain-free *E*,*Z* isomer observed. Such a sequence of events would parallel the steps in PYP, in which the highly strained double bond is known to trigger disruption of surrounding protein organization, similar to disruption of the H-bonding network in bilirubin. A concerted search for a primary photoproduct of bilirubin, therefore, appears timely.

Cyanine dyes: Thus in bilirubin, the restraining force that masked the OBF process is not the medium but rather the network of internal H-bonding. In this context, we find the set of cyanine-dyes **10a–d** used by Rettig and co-workers for studies of fluorescence and geometric isomerization processes particularly interesting (Scheme 13).[45] Structurally, they are



Scheme 13.

similar to those proposed as new model compounds for testing the HT mechanism.[8] Significantly, drastically different excited state lifetimes for these four compounds were observed, specifically the lifetime of the doubly ring-fused compound **10d** being almost two orders of magnitude longer than the other three. Surprisingly, this difference in lifetimes was detected at room temperature in fluid solution (ethanol solvent). It was suggested that "the enhanced non-radiative decay of compounds **10a–c** is related to the flexibility of functional groups that are linked by a single bond to the remainder of the molecule …. (or the loose-bolt theory)."[45] We note that the observed lifetimes would also be consistent with the involvement of HT for the vinyl-H-containing compounds **10a–c** and the absence of such a process for **10d**, one without a vinyl-H. In the latter case, OBF is the only possible process for isomerization, a flipping process that requires the breaking of interactions between the polar substrate and solvent molecules. Apparently, such a process is not competitive with the HT processes of **10a–c**, which do not require disruption of such solvent–solute interactions.

Relative ease in displacing solvent molecules has also been invoked to account for regioselective photoisomerization of polyenes in the vitamin A series.[46]

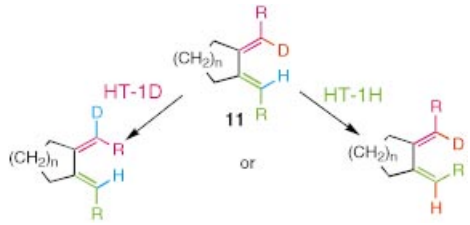
Phytochrome: In reviewing the photochemistry of the tetrapyrrole chromophore of phytochrome, Williams and Braslavsky pointed out the fact that mechanistically BP is unlikely for the photoisomerization process because it has generally been accepted as a ground-state-allowed process. At the same time, they did not rule out possible involvement of HT, a known excited-state process, for the photoisomerization reaction of this unique chromophore with a very low excitation energy.[47]

In conclusion, we believe these new examples, in addition to those of Fuss[7] and others cited earlier,[8] when taken together, state a convincing case that HT is a common supramolecular mechanism for photoisomerization.

The question of possible rate acceleration of HT imposed by the medium

A possible implication from the generalization discussed above is that HT is a slow process observable only when the common OBF process is impeded. This is likely to be a correct situation for substrates in an amorphous solid solution. However, we envision situations when this generalization no longer applies. In fact, there could be conditions when the concerted two-bond twist process, seemingly an entropically unfavorable process, could be assisted by the medium through specific interaction(s) with the host. For example, in several native systems there are good indications that confinement actually leads to acceleration of rates of isomerization. Thus, for rhodopsin the excited state lifetime, controlled by the rate of photoisomerization,[2] is approximately ten times smaller than that for the corresponding free 11-*cis*-retinal protonated Schiff base (PSB) in solution,[48] a likely case of protein assistance of HT. Similar numbers are available for bR[49] and all-*trans*-PSB.[50] It will be of importance to determine the specific structural features that lead to the enhancements. Even for simple cyanine dyes **10a–c**, if the above suggestion of involvement of HT is correct, the rates are remarkably fast ($1.3-2.5\times10^{10}\,s^{-1}$ in ethanol)[45] and not surprisingly appear to be medium dependent (slower in a more viscous solvent).[45] Thus, for simple organic systems, the effect of different frozen media on rates and regioselectivity of isomerization of polyenes should be examined in order to identify the scope and limitations of this unique supramolecular photochemistry.

Furthermore, at this stage, it is unclear to us as to how the two-bond twist motion of HT will affect the electronic vibrational coupling that is so important in determining the rates of radiationless transition between the S_1 and S_0 states for any molecule.[51] Since HT is envisioned a diabatic process between these two states, this coupling or the magnitude of the corresponding Franck–Condon factor[51] will likely play a significant role in determining the overall rate of reaction. We hope that our papers will stimulate theorists to examine such radiationless transitions and the energy changes along the complete pathway of HT in detail. At the same time, experimentalists will be able to play a major role in designing and preparing simple model systems that might be able to elucidate the relative importance of the above-mentioned factors in controlling rates of HT. For example, the preference of photoisomerization of dienes around the C–H or C–D center of the general structure **11** will be of great interest (Scheme 14). The C–H center should be favored if electronic vibrational coupling (the higher C–D vibrational level would lead to a smaller β, the Franck–Condon Factor) is the determining factor. The C–D center will be favored if the size of the group being transposed is the determining factor (H is effectively larger than D because C–H vibrational amplitude is larger than that of C–D).



Scheme 14.

(When taken into consideration of the magnitude of the deuterium (vinyl) isotope effect detected in stilbene,[52] the magnitude of isotope effect for compound **11** could be considerably larger than what is normally observed for secondary deuterium isotope effects.)

Other concerted two-bond twist processes

On occasion, we have been asked to compare the HT process with some other concerted processes mentioned in the literature. We would like to make a few comments. First, HT is not the same as the pyramidal inversion process of a C=N or an N=N bond. It is correct that both processes involve reactions centered at one atom rather than rotation at the formal double bonds (as in OBF). However, pyramidal inversion involves rehybridization of the atom (to sp hybrid) at the reaction center which is not possible when the center does not have a lone-pair electron as in cases of C=C bonds of present concern. However, there was one paper dealing with photoisomerization of aryl azines (Ar–CH=N–N=CH–Ar) in which a mechanism called the "crank-shaft" mechanism was proposed to account for viscosity-independent photochemical behavior of an unsymmetrically substituted azine.[53] A simultaneous three-bond rotation process was proposed that had features, including being a volume-conserved process, resembling the HT concept discussed above.

HT can be considered as concerted disrotatory motions of two adjacent bonds. A relevant question is how to compare HT to a parallel motion that involves instead conrotatory motions of two adjacent bonds. The likely answer is that the energy required for the latter should not be too different from the former if one compares the two processes executed by isolated molecules in vacuum. Indeed, recent conical intersection (CI) calculations seem to show that both intermediates lie on parallel minimum energy pathways during decay of excited polyenes.[54] However, it should also be clear that if interactions with the medium are included, then the latter could be prohibitively disfavored. In fact, it will be interesting

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to find out the energy required for a process that corresponds to a combination of both processes. For example, it could be one involving the HT motion (*dis*) during the first half of the double twist motion then switching to the latter (e.g., *con*) to complete the reaction (including the possibility that the latter being strictly a ground-state process). The net result could be the formation of a product with only a configurational change, not accompanied by a simultaneous conformational change of an adjacent single bond. Could this be the correct way to describe reactions of anchored polyene chromophores such as the all-*trans*-retinyl chromophore in bR ?[29] It deserves closer scrutiny.

It should also be noted that the concerted two-bond twist process is analogous to parallel ground-state processes observed under confined conditions. Thus, similar two-bond twist motions have been discussed in studies of conformational dynamics of proteins, membranes, and polymers. In proteins, such a concerted process has long been suggested to be involved in transition between different helices of homopeptides, while in membranes a parallel process is known as β-coupled rotation. These processes were all observed under mild conditions.[55]

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