J|A|C|S COMMUNICATIONS

Published on Web 12/11/2008

Bicycle-Pedal Isomerization in a Rhodopsin Chromophore Model

Igor Schapiro, Oliver Weingart, and Volker Buss*

Department of Chemistry, University of Duisburg-Essen, 45141 Essen, Germany

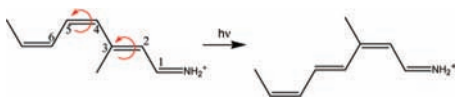
Received July 17, 2008; E-mail: volker.buss@uni-due.de

The primary event of vision in the vertebrate eye is the photoisomerization of 11-*cis*-retinal, which is covalently bound as a protonated Schiff base (pSb) to the visual protein rhodopsin. With its high selectivity and efficiency—the quantum yield is 65%, and the first photoproduct is formed within 200 fs[1]—the photoreaction of rhodopsin is considered the archetype of a chemical reaction optimized by nature to achieve a specific molecular response.[2]

In 1976, in a study of this reaction, Warshel proposed what he called the "bicycle-pedal (BP) model"[3] in which the concerted rotation about parallel pairs of double bonds propagates the cis conformation of the C11═C12 double bond to the terminal C═N bond. On the basis of semiclassical molecular dynamics calculations he predicted that the isomerization of 11-*cis*-retinal pSb could be accomplished in 200 fs, which was more than an order of magnitude faster than the accepted value at that time. From a modified model[4,5] in which the internal strain imposed on the chromophore by double bond rotation was balanced against the external strain exerted by the protein environment, Warshel later concluded that the rotation and configuration inversion of the central C11═C12 bond was coupled with reverse twisting of the C9═C10 and other bonds, a view that was recently corroborated by advanced QM and QM/MM methodology.[6−10]

Neither the BP mechanism, which would lead to a system with a shifted cis bond, nor Liu's hula-twist (HT) isomerization model[11,12] are able to account for the strongly twisted, but definitely all-trans-configurated geometry[13] observed in the primary rhodopsin photointermediate.[14] On the other hand, BP motion has been apparently confirmed in the solid state photoisomerization of substituted *cis*,*cis*-butadienes[15,16] where the rigid glass acts as a restraining medium similar to the protein pocket and supports a volume-confining reaction path. We have found now the first ab-initio-based evidence that the protonated Schiff base shown as the reactand in Scheme 1 can isomerize in a BP manner by concerted rotation of two conjugated double bonds to yield the product shown in Scheme 1. While the event is rare—only one in 47 trajectories studied showed this behavior—the calculations prove that BP is possible and can, at least energetically, compete with the simpler one-bond rotation.

Scheme 1



The starting geometry of 4-*cis*-pSb was taken from the CASSCF/6-31G∗ (the IUPAC name is 2*E*,4*Z*,6*Z*-3-methylocta-2,4,6-trien-1-iminium) optimized structure. Starting vectors for the excited-state trajectories were obtained after Franck−Condon excitation of zero-point energy sampled ground-state structures. Details of the computational setup have been described elsewhere.[17] In all, we have studied close to 50 unique trajectories which yielded mainly

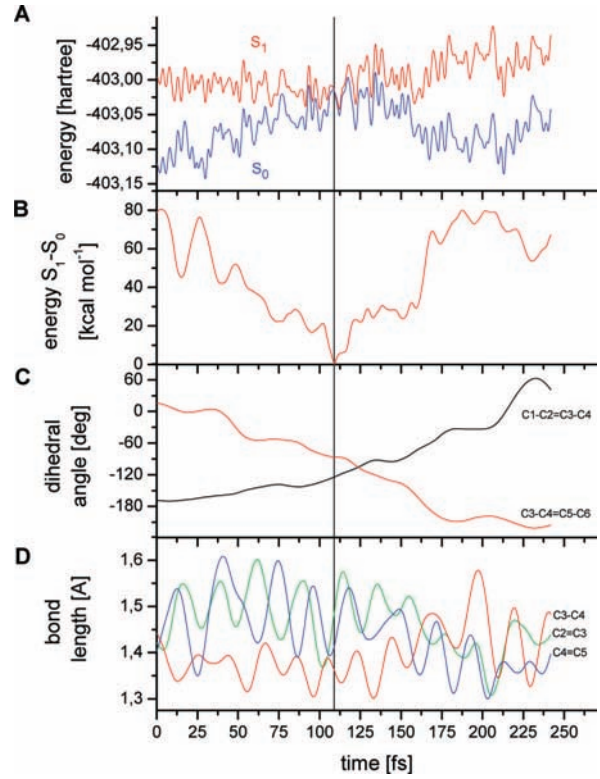


Figure 1. Time-development of some calculated properties in the BP conversion of 4-*cis*-pSb (from top): S_0 and S_1 energies; S_1-S_0 energy difference; C2═C3 and C4═C5 dihedrals; and stretching coordinate of the three bonds involved. Excitation occurred at $t = 0$, and hopping back to the ground state (vertical bar) occurs at $t = 109$ fs.

the all-trans product (more than 72%) through isomerization of the C4═C5 bond, while the remainder returned to the starting configuration or involved rotation about the C2═C3 bond (Table S1, Supporting Information). However, we observed one trajectory that gave the double-bond shifted product shown in Scheme 1. It is analyzed in more detail in Figure 1.

Initially the excited-state trajectory follows a well-established pattern: inversion of the π-density alternation activates strong stretching modes of the C2═C3 and the C4═C5 double bonds (panel D), which is reflected in a huge oscillation of the S_1-S_0 energy difference (panel B). Dephasing of these modes coupled with increasing torsional motion causes a drastic decrease of the S_1-S_0 energy difference which, at 109 fs into the simulation, becomes small enough (0.8 kcal·mol^{-1}) to initiate a hop to S_0 (vector-rotation method).[18,19] During this process the bonds rotate in the same sense ("conrotatory") as envisaged in the BP isomerization model.[3] The rotation is concerted but not synchronous, because at the time of hopping the twist of the two double bonds differs significantly (−124° and −86°, respectively). Continuing on the S_0 surface the energy difference starts to increase again, and

10.1021/ja805586z CCC: $40.75

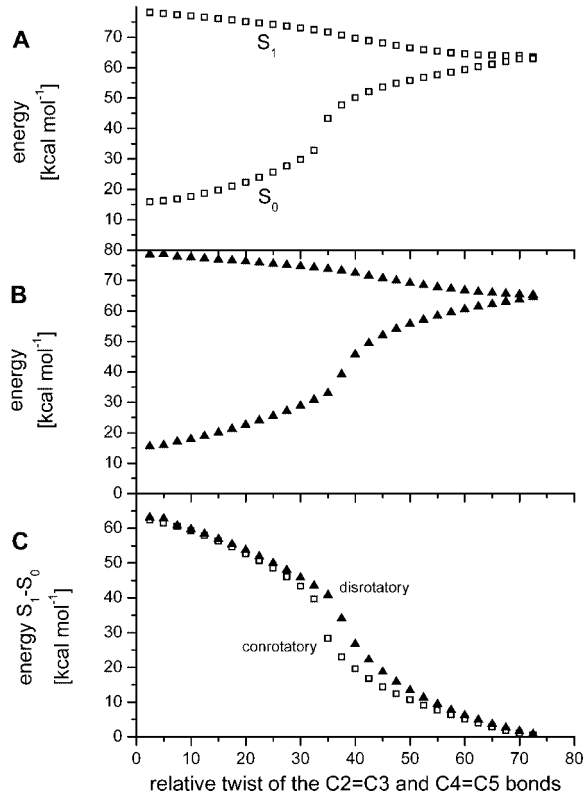


Figure 2. Synchronous conrotatory (A) and disrotatory (B) two-double-bond isomerization of 4-*cis*-pSb. The energy of the planar optimized geometry in the ground-state is taken as the reference point. (C) S_1-S_0 energy gaps of the two modes as a function of the twist angles.

both double bonds relax by continued rotation until both have reached their final cis and trans configurations, respectively.

To study the reaction in more detail we have calculated an idealized BP-path based on a strictly synchronous rotation of the two double bonds (section S2, Supporting Information). Starting with planar 4-*cis*-pSb and increasing the two dihedrals stepwise by 2.5° the intermediates were energy-minimized in the first excited-state at the same level of theory that was used for the molecular dynamics (MD) simulations. The results are shown in panel A of Figure 2. The graph shows a very flat excited-state energy profile in contrast to the S_0 surface with a discontinuous increase around 35° which is not observed in the restrained optimization of one double bond rotation in retinal model chromophores.[9,20−22] A conical intersection[23] (CI) is reached with a residual energy gap of 0.6 kcal·mol^{-1} at 72.5°. In the case of one double bond rotation the CI was reached in the range of 75−80° in vacuo[21] and in rhodopsin.[24,25]

Not related to the BP mechanism, but topologically similar is the disrotatory pathway in which the two double bonds rotate in the opposite sense. For this mechanism which for steric reasons is forbidden in the volume-confined space of the protein an analogous scan was calculated. Astonishingly the energy profile (panel B) is very similar to the conrotatory motion, although the geometries of the intermediates differ strongly. They approach the conical intersection in a very similar manner, and the final gap is almost identical (0.8 kcal·mol^{-1}). Small differences are obvious from panel C in which the S_1-S_0 energy gaps of the two modes are plotted as a function of the twist angles. However, both modes have no barrier in the excited-state and since our study does not include the environment we conclude that both pathways are feasible in conjugated double-bond systems.

In summary, we have shown the first ab initio calculated realization of the BP mechanism in a protonated Schiff base by molecular dynamics simulations. The event is rare in agreement with evidence that such a pathway is followed only in a space-confining environment. The outcome underscores the importance of MD simulations of a microcanonical ensemble to examine photochemical mechanisms. In contrast to minimum energy path calculations and other static methods, this technique allows an exploration in principle of all regions of the potential energy surface. Furthermore it provides information about quantum yields and lifetime distribution of possible products. In the case of 4-*cis*-pSb we have identified and characterized three different products so far[17] which demonstrate the multiplicity of possible pathways.

Acknowledgment. This research has been supported by the DFG Forschergruppe Retinal Protein Action.

Supporting Information Available: Cartesian coordinates of starting and hopping geometries, computational details and product distribution of the 4-*cis*-pSb model. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Kukura, P.; McCamant, D. W.; Yoon, S.; Wandschneider, D. B.; Mathies, R. A. *Science* **2005**, *310*, 1006–1009.
(2) Okada, T.; Palczewski, K. *Curr. Opin. Struct. Biol.* **2001**, *11*, 420–426.
(3) Warshel, A. *Nature* **1976**, *260*, 679–683.
(4) Warshel, A; Barboy, N. *J. Am. Chem. Soc.* **1982**, *104*, 1469–1476.
(5) Warshel, A.; Chu, Z. T.; Hwang, J. *Chem. Phys.* **1991**, *158*, 303–314.
(6) Weingart, O. *J. Am. Chem. Soc.* **2007**, *129*, 10618–10619.
(7) Gascon, J. A.; Batista, V. S. *Biophys. J.* **2004**, *87*, 2931–2941.
(8) Gascon, J. A.; Sproviero, E. M.; Batista, V. S. *Acc. Chem. Res.* **2006**, *39*, 184–193.
(9) Andruniow, T.; Ferre, N.; Olivucci, M. *Proc. Natl. Acad. Sci.* **2004**, *101*, 17908–17913.
(10) Frutos, L. M.; Andruniow, T.; Santoro, F.; Ferré, N.; Olivucci, M. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 7764–7769.
(11) Liu, R. S. H.; Asato, A. E. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 259–263.
(12) Liu, R. S. H. *Acc. Chem. Res.* **2001**, *34*, 555562.8.
(13) The all-trans assignment does not include the C6═C7 bond.
(14) Nakamichi, H.; Okada, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4270–4273.
(15) Saltiel, J.; Krishna, T. S. R.; Laohhasurayotin, S.; Fort, K.; Clark, R. J. *J. Phys. Chem. A* **2008**, *112*, 199–209.
(16) Furukawa, D.; Kobatake, S.; Matsumoto, A. *Chem. Commun.* **2008**, 55–57.
(17) Weingart, O.; Schapiro, I.; Buss, B. *J. Phys. Chem. B* **2007**, *111*, 3782–3788.
(18) Weingart, O.; Schapiro, I.; Buss, V. *J. Mol. Model.* **2006**, *12*, 713.
(19) Schäfer, L. V.; Groenhof, G.; Boggio-Pasqua, M.; Robb, M. A.; Grubmüller, H *PLoS Comput. Biol.* **2008**, *4*, 3.
(20) Yamamoto, S.; Wasada, H.; Kakitani, T.; Yamato, T. *J. Mol. Struct.: THEOCHEM* **1999**, 461−462;463−471.
(21) Migani, A.; Sinicropi, A.; Ferre, N.; Cembran, A.; Garavelli, M.; Olivucci, M. *Faraday Discuss.* **2004**, *127*, 179–191.
(22) Ben-Nun, M.; Molnar, F.; Schulten, K.; Martinez, T. J. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 1769.
(23) Martinez, T. J. *Annu. Rev. Phys. Chem.* **2007**, *58*, 613.
(24) Strambi, A.; Coto, P. B.; Frutos, L. M.; Ferre, N.; Olivucci, M. *J. Am. Chem. Soc.* **2008**, *130*, 3382–3388.
(25) Following the recommendation of a referee we have extended the calculations to evaluate the effect of dynamic electron correlation on the relaxed scans depicted in Figure 2. Since geometry optimization at the CASPT2 level is not feasible for systems this size, we have performed CASPT2 calculations along the CASSCF-optimized path (CASPT2//CASSCF) instead. We also applied the same treatment to several one-bond isomerization trajectories of the same retinal model. Overall we find that CASPT2//CASSCF affects the two and the one double-bond isomerization from our MD simulations in a similar way. For a detailed discussion see Supporting Information, section S5.

JA805586Z