Fast Photoisomerization of a Rhodopsin Model—An Ab Initio Molecular Dynamics Study**

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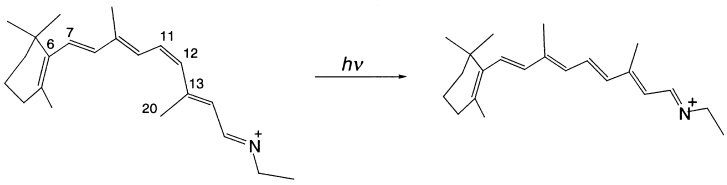
Dedicated to Professor Paul von Ragué Schleyer on the occasion of his 70th birthday

The protonated Schiff base (PSB) of 11-*cis*-retinal is the chromophore of rhodopsin, the photoreceptor in the retina of the vertebrate eye (Scheme 1). The photochemical isomerization to the all-*trans* form triggers a series of enzymatic



Scheme 1. Photoisomerization of the chromophore of rhodopsin, 11-*cis*-12-s-*trans*-retinal PSB (left), into the all-*trans* form (right). The structures are DFT-optimized geometries.[13b]

reactions known as the visual cascade which eventually leads to a neural signal.[1] Central for understanding the molecular basis of these processes is the geometry of the retinal chromophore which is derived from the 11-*cis*-12-s-*trans* conformer[2] and becomes twisted as a consequence of steric interaction. Evidence for this comes from resonance Raman[3] and, more directly, from circular dichroism (CD) spectroscopy:[4] after binding by the protein the optically inactive 11-*cis*-retinal displays distinct positive CD absorption bands corresponding to the absorption maximum of the chromophore in the UV/Vis region at 500 nm and at 340 nm. With different solid-state NMR techniques it has been possible to directly determine torsional angles of the chromophore[5] and distances between specific isotopically labelled positions[6] from which an approximate angle of 42° has been deduced between the C7-C8-C9–C10 and C13-C14-C15 planes.

Steric interaction with the protein and ensuing chromophore distortion is believed to be responsible for the extremely fast kinetics and the efficiency of the rhodopsin photoreaction which yields the first photoproduct after only 200 fs:[7] removal of the C13 methyl group, which according to spectroscopic data results in a flattening of the chromophore, reduces the quantum efficiency significantly from 0.65 to 0.47 or even less.[8, 9] With a methyl group in the 10-position the steric interaction is reintroduced; the quantum efficiency of this latter mutant is still subject to debate.[9, 10]

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[**] This work was supported by the Deutsche Forschungsgemeinschaft (Graduate College "Struktur und Dynamikheterogener Systeme").

In the absence of detailed knowledge about the kind of interaction present in the protein binding pocket, it is difficult to derive a theoretical description of the chromophore conformation. The results differ already for the uncomplexed PSB depending on the model used: according to high-quality ab initio calculations (RHF,[11] CASSCF,[12] and DFT[13]) the chromophore is planar. Car–Parrinello type molecular dynamics calculations, on the other hand, converge on a geometry with a 38° twist angle about the C12–C13 bond.[14] In the following we show that a very unspecific steric strain imposed on the chromophore induces a highly specific nonplanar deformation in the region from C11 to C13, and then demonstrate that it is exactly the deformation about these bonds which is the prerequisite for fast photoisomerization of a small retinal model system.

We assume that the retinal chromophore, as a consequence of the steric fit into the protein binding pocket, undergoes some kind of conformational change. To study with the least possible bias what this change might be we have introduced a nonspecific strain into the molecule, by widening all external bond angles (C7-C8-C9, C9-C10-C11, etc.) and contracting all internal bond angles (C6-C7-C8, C8-C9-C10, etc.) by the same amount, 2.5°. This makes the banana-shaped molecule slightly shorter (the C6–N^+ distance is reduced from 11.535 to 10.966 Å), but it is still approximately planar.[15] We then performed molecular dynamics calculations[16] with free optimization of all nuclear coordinates, keeping only the C6–N^+ distance fixed. The dynamics was monitored until all bond lengths and angles, including dihedral angles, had equilibrated. The relaxed structure (Figure 1) begins to establish after 200 fs, when both the C11–C12 and the C12–C13 bonds simultaneously start to twist.[17] Except for the helical geometry resulting from this twist in the region from C11 to C13 the chromophore is essentially planar from C7 to C12 and (slightly less) from C13 to N^+. The structure is remarkably similar to one found by Bifone et al.[18, 19] from

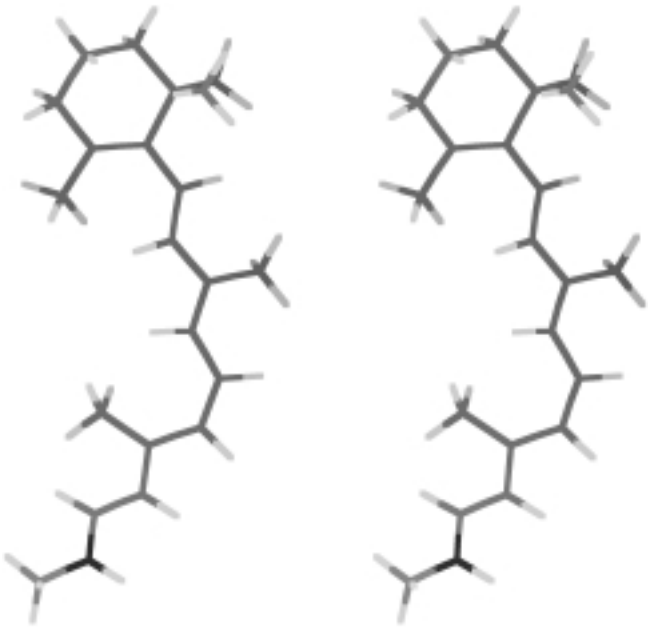


Figure 1. The relaxed geometry of 11-*cis*-retinal PSB after a molecular dynamics calculation with a fixed C6–N^+ distance of 10.966 Å (stereoview).

  1433-7851/00/3915-2784 $ 17.50+.50/0

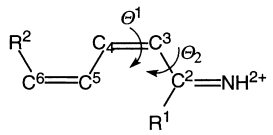
molecular dynamics calculations using experimentally determined constraints for the distance between the C13 methyl group and the C10 and C11 carbon atoms in rhodopsin. The structure they obtained is also highly twisted about the C11–C12 and the C12–C13 bonds.

The molecular dynamics calculations indicate that this geometry, in which the dihedral angle strain is concentrated in exactly the region where the photoisomerization is going to take place, does not require a highly specific protein interaction site; rather it is a consequence of the inherent tendency of the chromophore to twist about these bonds. Note that the geometry displayed in Figure 1 is without relevance to the question of absolute configuration of the chromophore since in the absence of chiral discrimination the molecular dynamics could have produced the mirror image with the same probabilty. We have established independently, based on the quantum-mechanical calculation of chiroptical data, the absolute sense of twist of the C12–C13 bond of the retinal chromophore in rhodopsin as positive, that is opposite to the one shown in Figure 1, with the 13-methyl group projecting towards the observer.[20] This conformation is the result of the chiral nature of the protein binding pocket.

The planar 11-*cis*-13-demethyl-retinal PSB, with the methyl group in the 13-position missing, stays planar and does not relax into a nonplanar conformation when subjected to the external strain. This agrees with the experimental finding that the chromophore of 13-demethylrhodopsin is less distorted in the region from C10 to C13 than the native chromophore.[9]

The excited state dynamics of the isomerization of 11-*cis*-retinal PSB has been studied recently by Robb and coworkers[21] with high-quality ab initio methods on a model chromophore, 3,5-pentadienal PSB. They found that the initial reaction of the Franck–Condon excited molecule on the S_1 surface is dominated by in-plane bond stretching before torsion of the molecule around the central *cis*-configured double bond sets in, followed by fast decay via a conical intersection. These calculations provide for the first time a realistic model including a time estimate for the photoisomerization of rhodopsin. A puzzle remains, however, which concerns the role of the methyl group: except for a slightly steeper initial slope at the beginning of the dynamic almost no acceleration was found in the α-methyl-substituted model compound compared to the unsubstituted one.

We have studied the effect of methyl substitution and dihedral distortion on this chromophore using ab initio molecular dynamics (AIMD). In this method quantum-mechanically derived forces are used to integrate Newton's equations of motion in the full space of $3N-6$ internal coordinates on the Born–Oppenheimer potential energy surface.[22] The successful application to ground-state dynamics has been described recently.[23] Our quantum-mechanical treatment of the excited state is essentially the same as Robb's, and so the results are directly comparable. The systems we have studied are shown in Scheme 2: ① is the parent PSB, twisted about the central C3–C4 bond by 10°, in ② there is an additional twist of 10° about the C2–C3 bond, ③ and ④ are the corresponding α-methyl-substituted derivatives, and ⑤ is the dimethyl derivative with dihedral angles taken from the central part of the strained 11-*cis*-retinal PSB



	R^1	R^2	Θ_1	Θ_2
①	H	H	10°	0°
②	H	H	10°	−170°
③	CH_3	H	10°	0°
④	CH_3	H	10°	−170°
⑤	CH_3	CH_3	14°	−167°

Scheme 2. Substitution pattern and starting geometries (dihedral angles Θ_1 and Θ_2) of the five pentadienal PSBs of this study.

shown in Figure 1. Except for ⑤ all systems were geometry-optimized in the ground state with only the dihedral angles shown kept constant. After excitation to the S_1 surface the trajectory was followed for simulation times between 50 and 80 fs.

The results are shown in Figure 2, where the change of the central dihedral angle Θ_1 is plotted against the simulation time. All systems need a certain amount of time before the

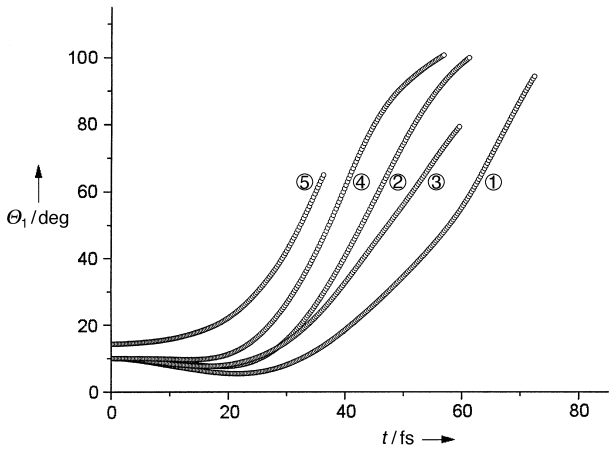


Figure 2. Comparison of the excited state dynamics of the five dienal PSBs of Scheme 2. The plot shows how the dihedral angle Θ_1 of the central double bond changes as a function of time.

torsional mode is activated; however, there are significant differences. The unsubstituted singly twisted PSB ① needs 62 fs to reach an (arbitrary) twist angle of 60°; this time is comparable to the one calculated by Robb[21c] for the same system. The additional twist in ② accelerates the torsion more (60° reached after 46 fs) than the α-methyl group in ③ with which this torsion is reached after 52 fs. When the doubly twisted PSB is methyl-substituted in the α-position we observe the strong rate acceleration in accord with the experimental evidence: ④ and ⑤ need only 39 and 35 fs, respectively, for the 60° torsion angle. Comparison of the latter two reveals in addition that the second methyl substituent (which stands for the C9 methyl group in retinal) is of less influence on the dynamics of the molecule than the higher initial torsion.

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The reason for the fast photoisomerization of ④ and ⑤ is the rotation about the C3–C4 and the C2–C3 bonds in opposite directions (Figure 3) coupled very efficiently by the α-methyl group: in the excited state the double-bond character is shifted from the C3–C4 bond to the C2–C3 (and the

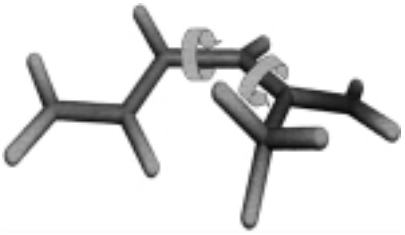

Figure 3. Coupled rotation about the C2–C3 and the C3–C4 bonds of the Schiff base ④ in the electronically excited state. The molecule is shown 20 fs into the simulation when the twist about both bonds as indicated by the two arrows has gained already considerable momentum.

C4–C5) bond. As a consequence the twisted CH_3-C2-N^+ fragment begins to rotate back into the plane of the C2–C3 bond with the methyl group pushing against the hydrogen atom at C5. Because the C3–C4 bond is torsionally softened this leads to a rapid increase of the twist of this bond. In effect the methyl group acts as a lever to set the inherently slow torsion of the central bond into motion, with the electronic excitation acting as a release mechanism.

We have shown that the photoisomerization of a short methyl-substituted pentadienal PSB twisted in a specific way that corresponds to the probable conformation of the 11-*cis*-12-s-*trans*-retinal PSB in rhodopsin is significantly enhanced over the unsubstituted PSB. Moreover, our calculations have shown that this conformation does not need a specific protein–chromophore interaction, but is realized as a result of a very general externally applied strain. Whether methyl torsion is sufficient to bring about fast excited state isomerization of larger rhodopsin models is the subject of on-going investigations.

Received: December 10, 1999
Revised: June 6, 2000 [Z14383]

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[15] The chromophore is not perfectly planar, because the geometry of 11-*cis*-retinal PSB was reoptimized by the same molecular dynamics procedure used later for relaxing the bent structure. The reoptimized geometry showed dihedral angles differing from 0 or from 180° by less than 2°, except for the C10–C11 bond (2.0°) and the C15–N^+ bond (3.2°).
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  1433-7851/00/3915-2786 $ 17.50+.50/0