Ab initio Study of the C6-C7 Conformation of Retinal Model Systems

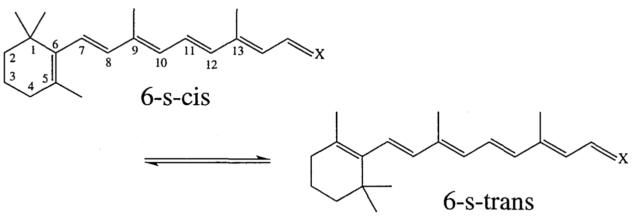
Frank Terstegen and Volker Buss*
Fachgebiet Theoretische Chemie, Gerhard-Mercator-Universität Duisburg, D47048 Duisburg, Germany

(Received February 14, 1996)

Ab initio calculations have been performed on model compounds of retinal and retinal derivatives, ß-ionone, ß-ionone Schiff base and protonated Schiff base and the corresponding hydrocarbon, to study the ring orientation as a function of the heteroatom and the state of protonation. Two 6-s-cis derived conformations are shown to exist in all four compounds. Stable close to planar 6-s-trans conformations were obtained for the protonated Schiff base and for the ketone only.

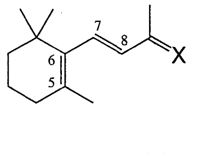
In both rhodopsin, the vertebrate visual pigment, and bacteriorhodopsin, the proton-pumping pigment of the salt-loving Halobacterium halobium, retinals act as specialized molecular tools that bring about well-investigated biochemical processes[1] Different models for the chromophores and their immediate environment have been proposed to account for the peculiar physico-chemical properties observed in these systems. In all of these models the three-dimensional structure of the retinal chromophore plays a prominent role.

One particular question concerns the orientation of the terminal cyclohexene ring with respect to the polyene chain. Two conformations can be envisioned, one derived from the planar (with respect to the double bonds) 6-s-cis-, the other from the 6-s-trans-configuration:



We have found, by employing *ab initio* MO methodology, that the nature of the substituent X, in particular whether it is an electron acceptor or not, is a determining factor for the ring orientation.

Hartree-Fock *ab initio* molecular orbital calculations on four model systems were performed using the GAUSSIAN program packages.[2,3] The model compounds chosen were the hydrocarbon **1**,[4] β-ionone Schiff base **2**, β-ionone **3**, and the protonated Schiff base **4**. These are the smallest molecules with steric requirements about the C6-C7 bond identical to the ones found in the retinoids proper. The electronic effect exerted by X will be somewhat enhanced due to the shorter conjugated chain,[5] something we find acceptable considering the saving in computer ressources.



$X = CH_2$ **1**
$X = NH$ **2**
$X = O$ **3**
$X = NH_2^+$ **4**

The potential energy of **1** as a function of the dihedral angle C5-C6-C7-C8 (Figure 1) was calculated with the 3-21G basis with complete geometry optimization except for this angle which was incremented in 10° steps for a complete 360° turn. For the other three compounds corresponding calculations were performed where local minima could be assumed. All minimum energy structures were then optimized at the RHF/6-31G** level, and the frequencies were calculated also at this stage to make sure that the geometries are true energy minima. Energies of the minimum energy structures calculated at this level are given in Table 1.

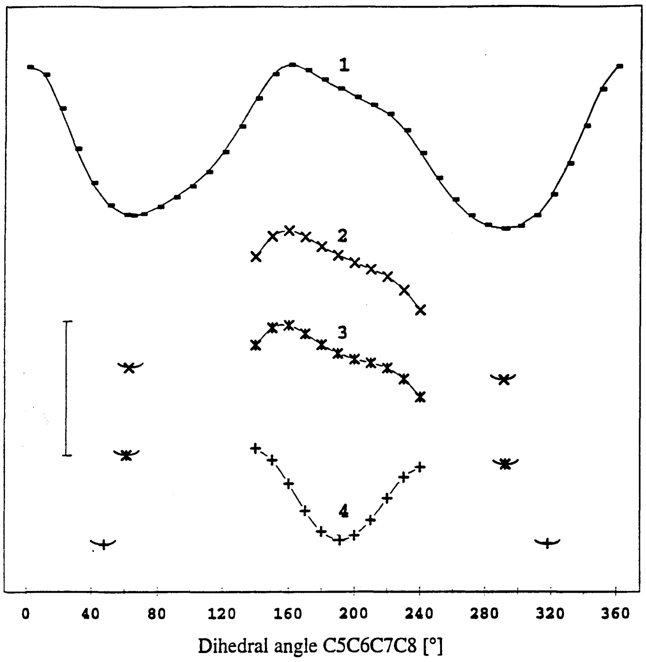


Figure 1. RHF/3-21G calculated energies of compounds **1** to **4** as a function of the dihedral angle C5-C6-C7-C8. The length of the vertical bar corresponds to an energy of 5 kcal/mol. The relative setting of the different curves is arbitrary.

For **1** we find (Figure 1) two minima, ca. 60° from 6-s-cis, separated by two maxima, one of which corresponds to the planar 6-s-cis conformation, the other, at ca. 160°, to a skewed 6-s-trans conformation. The non-symmetrical shape of the potential curve is caused by the non-planar conformation of the cyclohexene ring rendering conformations with opposite dihedral angles C6-C7 diastereomers, not enantiomers. In particular, the sloping plateau flanked by a maximum at one and a shoulder at the other side is caused by the two non-equivalent methyl groups at C1 and the different strain they exert as the C8 hydrogen moves past them during the rotation. In contrast the maximum around 0° is rather narrow and unstructured since it is caused mainly by eclipsing the C8 hydrogen with the C5 methyl group.

For the β-ionone Schiff base the torsional potential is essentially unchanged from the hydrocarbon, except that the shoulder around 220° is somewhat more distinct, an effect that is

Table 1. Geometries (Selected dihedral angles [°]), Total energies (Hartrees) and Relative energies (kcal/mol) for RHF/6-31G** optimized structures

		$\angle$C3C2C1C6	$\angle$C5C6C7C8	$E_{(HF)}$	ΔE
1	cis	45.3	61.8	-542.9588114	0.60
	cis′	44.2	294.8	-542.9597726	0
2	cis	45.5	60.7	-558.9629400	0.53
	cis′	44.2	295.1	-558.9637855	0
3	cis	45.7	59.6	-578.8055413	0.45
	trans	48.2	204.5	-578.8010657	3.26
	cis′	44.1	295.9	-578.8062595	0
4	cis	46.9	45.4	-559.3687389	0.81
	trans	45.3	190.1	-559.3700276	0
	cis′	41.9	320.0	-559.3689876	0.65

even more pronounced in the ketone **3**. This gradual change becomes abrupt as the carbonyl oxygen is replaced by an NH_2^+-group: the flanks of the plateau separate into two distinct maxima, and a third minimum is calculated, close to planar 6-s-trans, with an energy comparable to the two 6-s-cis minima!

The more elaborate 6-31G** calculations reproduce the trend found with the 3-21G basis set, though there are differences (Table 1). In the ketone the plateau around 200° at the 3-21G level develops a distinct stationary point, an energy minimum, at 6-31G**. This trend, the stabilization of the planar 6-s-trans geometry by the larger basis set, continues in the case of the protonated Schiff base, where the 6-s-trans minimum is now found to be even lower in energy than the two 6-s-cis minima.

Both 6-s-cis and 6-s-trans derived geometries are found in retinals in the solid state.[6] From a comparison with ^{13}C NMR spectra in the solid state the presence of 25 to 30% of the 6-s-trans conformation of several retinal derivatives in solution was deduced.[7] A conformational change from 6-s-trans in the solid to predominantly 6-s-cis in solution was observed for retinal iminium salts.[8] From solid state ^{13}C MASS[9] and deuterium NMR[10] of the deuterated chromophore the trans conformation of the 6-s bond in bacteriorhodopsin was inferred. Wada et al.[11] who compared theoretical and experimental ^{13}C shielding constants come to the same conclusion but point out that the correlation was insufficient to decide between the 6-s-cis and 6-s-trans form of the chromophore in rhodopsin. The relevance of the 6-s-cis/6-s-trans equilibrium with respect to the opsin shift of protonated retinal Schiff bases has been discussed by Herzfeld and co-workers.[12]

Theoretical evidence for a trans minimum structure is ambiguous. The most advanced calculations are those by de Lera et al.[13] who studied the possibility that protonation of retinal Schiff base might lead to a trans-derived minimum but fail to locate one.

In summary, the increased tendency to planarization, a consequence of the change from a rather localized to a more delocalized π-electron system, shifts the conformational preference at the C6-C7 bond of the protonated ß-ionone Schiff base from skewed 6-s-cis to almost planar 6-s-trans.

References and Notes

1 For review, see R.R.Birge, *Biochim. Biophys. Acta*, **1016**, 293 (1990).

2 M.J.Frisch, G.W.Trucks, H.B.Schlegel, P.M.W.Gill, B.G. Johnson, M.W.Wong, J.B.Foresman, M.A.Robb, M.Head-Gordon, E.S.Replogle, R.Gomperts, J.L.Andres, K.Raghavachari, J.S.Binkley, C.Gonzalez, R.L.Martin, D.J.Fox, D.J.Defrees, J.Baker, J.J.P.Stewart, and J.A.Pople, GAUSSIAN92, Rev. B. Gaussian, Inc.: Pittsburgh, PA 1993.

3 M.J.Frisch, G.W.Trucks, H.B.Schlegel, P.M.W.Gill, B.G.Johnson, M.A.Robb, J.R.Cheeseman, T.Keith, G.A.Petersson, A.Montgomery, K.Raghavachari, M.A.Al-Laham, V.G.Zakrzewski, J.V.Ortiz, J.B.Foresman, C.Y.Peng, P.Y.Ayala, W.Chen, M.W.Wong, J.L.Andres, E.S.Replogle, R.Gomperts, R.L.Martin, D.J.Fox, J.S.Binkley, D.J.Defrees, J.Baker, J.J.P.Stewart, M.Head-Gordon, C.Gonzalez, and J.A.Pople, GAUSSIAN94, Rev. B.1, Rev. B.3, Gaussian, Inc.: Pittsburgh, PA 1995.

4 The IUPAC name for **1** is 1(3′methyl-1′butadienyl)-2,6,6-trimethylcyclohexene.

5 In three retinals computed in the meantime (*Angew. Chem*, submitted), the 6-s-trans conformations of the protonated Schiff bases still represent local minima, though they are higher in energy, 2.5 kcal/mol at the 6-31G** level, than their 6-s-cis counter-parts.

6 C.J.Simmons, R.S.H.Liu, M.Denny, and K.Seff, *Acta Cryst.*, **B37**, 2197 (1981).

7 G.S.Harbison, P.P.J.Mulder, H.Pardoen, J.Lugtenburg, J.Herzfeld, and R.J.Griffin, *J. Am. Chem. Soc.*, **107**, 4809 (1985).

8 R.F.Childs, G.S.Shaw, and R.E.Wasylishen, *J. Am. Chem. Soc.*, **109**, 5362 (1987).

9 G.S.Harbison, S.O.Smith, J.A.Pardoen, J.M.L.Courtin, J.Lugtenburg, J.Herzfeld, R.A.Mathies, and R.G.Griffin, *Biochemistry*, **24**, 6955 (1985).

10 A.Watts, *Biophys. Chem.*, **55**, 137 (1995).

11 M.Wada, M.Sakurai, Y.Inoue, Y.Tamura, and Y.Watanabe, *J. Am. Chem. Soc.*, **116**, 1537 (1994).

12 J.Hu, R.G.Griffin, and J.Herzfeld, *Natl. Acad. Sci. U.S.A.*, **91**, 8880 (1994).

13 A.R.de Lera, B.Iglesias, J.Rodriguez, R.Alvarez, S.Lopez, X.Villanueva, and E.Padros, *J. Am. Chem. Soc.*, **117**, 8220 (1995).