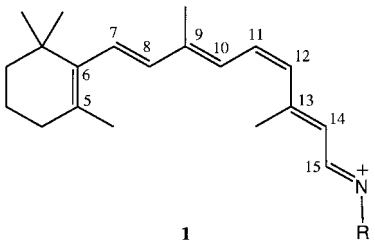
[8] a) E. W. Randall, D. Shaw, *J. Chem. Soc. A* **1969**, 2867 – 2872; b) J. Chatt, G. J. Leigh, D. M. P. Mingos, *ibid.* **1969**, 1674 – 1680.
[9] S. Ritter, U. Abram, *Inorg. Chim. Acta* **1995**, *231*, 245 – 248.
[10] See for example: a) G. W. Kabalka, N. M. Goudgaon, Y. Liang, *Synthetic Commun.* **1988**, *18*, 1363 – 1369; b) G. W. Kabalka, Z. Wang, *ibid.* **1990**, *20*, 231 – 237.
[11] A radical pathway may also contribute for some substrates: G. W. Kabalka, Z. Wang, *Organometallics* **1989**, *8*, 1093 – 1095.
[12] G. M. Sheldrick, SHELXL93. In *Crystallographic Computing 6*. (Eds.: P. Flack, P. Parkanyi, K. Simon), IUCr/Oxford University Press, Oxford, UK, **1993**.

Absolute Sense of Twist of the C12 – C13 Bond of the Retinal Chromophore in Rhodopsin—Semiempirical and Nonempirical Calculations of Chiroptical Data**

Volker Buß,* Klaus Kolster, Frank Terstegen, and Rainer Vahrenhorst

The protonated Schiff base of 11-*cis*-retinal, 11-*cis*-retinal PSB (**1**), is the light-sensitive chromophore of rhodopsin, the



1

photoreceptor that is responsible for dim-light vision of vertebrates. Photochemical isomerization of **1** to the all-*trans* isomer triggers the visual transduction process, which eventually results in the excitation of the visual nerve and the liberation of all-*trans*-retinal from the protein.[1] To understand this process on a molecular basis, the conformation of the retinal chromophore and its interaction with neighboring groups inside the protein-binding pocket have been studied by a variety of methods, mostly spectroscopic and including circular dichroism (CD) spectroscopy.[2]

All retinals are chiral (point group C_1), a consequence of the distorted geometry about the C6 – C7 bond of the β-ionone ring. In addition, steric hindrance from the C13 methyl group may cause the C13 – N16 fragment in **1** to rotate about the C12 – C13 bond into a more stable geometry. In the absence of other sources of chirality, retinal conformations in which the dihedral angles are twisted in the opposite direction are enantiomers and cannot be distinguished. In the chiral environment of the protein pocket, discrimination between the enantiomers takes place and the chromophore becomes optically active, leading to two well-resolved positive CD absorptions in the visible (480 nm) and near-UV (340 nm) region. These absorptions are called the α and the β band, respectively.[3] It has long been assumed, on the basis of spectroscopic studies of conformationally locked retinal analogues,[4] that the α- and β-bands derive their rotatory strengths from the twist about the C12 – C13 and the C6 – C7 bonds, respectively.

Recently, in a study of artificial pigments formed from bovin opsin with several 11,12-dihydroretinal derivatives, the absolute sense of twist of the C12 – C13 bond was derived from CD exciton chirality theory,[5] a method that cannot be applied to the native chromophores with their through-conjugated π systems. In view of the importance of the absolute configuration of the retinal chromophore for modeling the binding site in rhodopsin, we computed the chiroptical properties of 11-*cis*-12-s-*trans*-retinal PSB directly with the best methodologies available. The results prove that a positive long-wavelength CD absorption of this compound corresponds to a positive twist about the C12 – C13 s-*trans* bond.

The starting point for every calculation of chiroptical properties is a reliable three-dimensional molecular structure. The only known crystal structure of a retinal PSB has an all-*trans*-configured chromophore, including *trans* C11 – C12 and C6 – C7 bonds.[6] This configuration corresponds to the dark-adapted state of bacteriorhodopsin[7] but not to rhodopsin, in which the conformation is twisted 6-s-*cis*-11-*cis*-12-s-*trans*. The crystal structure of 11-*cis*-retinal is of no use either as the chromophore is twisted from 12-s-*cis*.[8] Computational resources are now sufficient to treat molecules as large as retinal in a rigorous manner. We have recently reported the completely optimized geometry of *N*-methyl-11-*cis*-12-s-*trans*-retinal PSB (**1**, R = Me) employing ab initio (RHF/6-31G**) and density functional theory (DFT) methodologies (B3LYP/6-31G**).[9] According to these calculations the whole chromophore is planar except for the C6 – C7 dihedral angle. This structure agrees with results of other calculations of comparable sophistication,[10] and with the exception of the rotation about the C12 – C13 bond, is our basis for the calculation of chiroptical properties.

From resonance Raman spectroscopy[11] it is known that the C12 – C13 bond is twisted significantly from s-*trans* as a consequence of steric and/or electronic interactions with the protein environment, a factor that we have not taken into account in our calculations. We arbitrarily assigned values of $+160^\circ$ and -160° to this dihedral angle (180° corresponds to a planar s-*trans* conformation) and have combined each of these with the two possible orientations of the cyclohexene ring. Calculations of the excited states of these geometries were performed with three different theoretical models: CNDO/S including configuration interaction of 100 singly excited states (model 1); the nonempirical method CIS from the GAUSSIAN 94 package[12] using the same basis set as for the

[*] Prof. Dr. V. Buß, Dr. K. Kolster, Dipl.-Chem. F. Terstegen, Dipl.-Chem. R. Vahrenhorst
Fachgebiet Theoretische Chemie der Universität-GH Duisburg
D-47048 Duisburg (Germany)
Fax: (+49) 203-379-2772
E-mail: theobuss@uni-duisburg.de

[**] This work was funded by the Deutsche Forschungsgemeinschaft (R.V.), Land Nordrhein-Westfalen (F.T.), and the Fonds der Chemischen Industrie.

  1433-7851/98/3713-1893 $ 17.50+.50/0

geometry optimization augmented by diffuse functions, that is 6-31 + G**, (model 2); and the nonempirical method CASSCF/CASPT2 from the MOLCAS-4 package[13] (model 3). This last set of calculations was too demanding on computational resources, and so the saturated residue of the cyclohexene ring (C1 to C4) was substituted by two hydrogen atoms. The basis set of density matrix averaged atomic natural orbitals (ANO-L[14]) consisted of 3s2p functions for the heavy elements and 2s for the hydrogen atoms. The active space chosen contained 12 electrons in 11 orbitals, all of local π symmetry. The results of the calculations are summarized in Table 1.

All three methods identify the excited state of lowest energy as the strongly allowed ^1B_u state (approximate symmetry label according to the C_{2h} point group of an all-*trans*-configured polyene) consisting mainly of the HOMO–LUMO excitation of the conjugated π system. This excited state is polarized approximately along the long axis of the molecule and has high oscillator strength. The energies of this state differ considerably between the models. Of the two nonempirical methods used, the results of perturbational calculations are closest to the experimental wavelength at 480 nm for the α band. This agreement is at least partly accidental since all the factors assumed to be responsible for the special long-wavelength shift that the chromophore undergoes in the protein pocket (the opsin shift) are not considered in these calculations. The CIS calculations deviate by more than 130 nm from the experimental value, no doubt a consequence of the very limited configuration interactions, which considers only singly excited states. The parametrized semi-empirical method is intermediate in its accuracy. The origin of the β band is more difficult to ascertain. So far our calculations have not yielded converging results for the higher excited states of **1**.

Table 1. The calculated wavelength λ, oscillator strength f, and rotatory strength R of the lowest excited state of **1** as determined by three different methods for four different combinations of dihedral angles Θ_{6-7} and Θ_{12-13}.

Θ_{6-7}	Θ_{12-13}	Method[a]	λ [nm]	f	R [D μ_B]
−60°	160°	1	440	1.4	0.4
		2	351	1.96	2.6
		3	483	2.35	1.1
58°	−160°	1	443	1.5	−0.43
		2	354	1.97	−2.3
		3[b]	–	–	–
−60°	−160°	1	439	1.5	−0.98
		2	351	1.98	−1.79
		3	483	2.35	−1.06
58°	160°	1	443	1.5	0.98
		2	354	1.99	2.0
		3[b]	–	–	–

[a] 1: CNDO/S; 2: GAUSSIAN 94/CIS; 3: MOLCAS4/CASPT2. [b] Not calculated because of close enantiomeric relationship to conformation above.

Regardless of these differences all three models yield positive rotatory strengths R for the lowest excited state independent of the orientation of the β-ionone ring (the sign of Θ_{6-7}), provided the dihedral angle at the C12–C13 bond is positive. The calculated rotatory strength is negative when this angle is negative. The absolute value of R depends, like the oscillator strength, on the method of calculation; the magnitude is, however, in the range of the experimentally observed value of about 0.5 D μ_B.[3]

There is a simple physical picture which supports the correlation between the sign of Θ_{12-13} and the sign of the α band. Figure 1 shows 11-*cis*-12-s-*trans*-retinal PSB with a negative dihedral angle Θ_{6-7} and a positive dihedral angle Θ_{12-13}. The electric transition moment μ_e that is directed along the chromophore lies in the plane of the central fragment but has a small, though critical, perpendicular component in the direction of the twisted C13–N16 fragment. The magnetic transition moment μ_m is caused mainly by the circular charge movement along the chromophore and is almost perpendicular to the central chromophore fragment, but also in the direction of the C–N$^+$ fragment. The resulting rotatory strengths computed as the scalar product of the two is thus positive (the angle between the two moments is 87.9° according to CNDO/S and 87.7° according to CIS calculations). Changing the sign of Θ_{12-13} inverts the perpendicular component of the electric transition moment but leaves the magnetic moment unchanged, with the result that the rotatory strength changes sign.

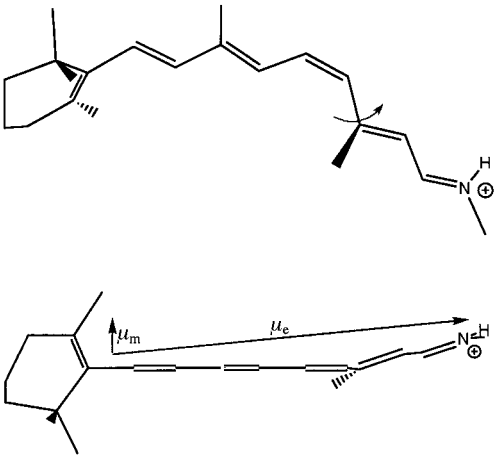


Figure 1. Side view (top) and plan view (bottom) of the twisted conformer of **1**. The geometry corresponds to that of the first entry of Table 1. For an explanation of the electric and magnetic transition moments, μ_e and μ_m, respectively, see the text.

Is there a flaw in our treatment in that we started with a chromophore that was calculated to be planar except for the twisted C6–C7 bond? We believe not. In principle, torsion about any bond of the chromophore could be the origin of the observed CD spectrum. We have concentrated on the C12–C13 bond for two reasons. Firstly, the location of the bond close to the center of the chromophore is crucial. Our calculations show (and intuition suggests) that terminal torsion, for example about the C6–C7 bond, results only in minor perturbation of the long-wavelength absorption. Secondly, the C12–C13 bond is especially prone to distortion because of steric hindrance between the C13 methyl group and the C10 hydrogen atom. The planar minimum-energy geometry is realized only in the protonated species where the

  1433-7851/98/3713-1894 $ 17.50+.50/0

system can gain maximal benefit from resonance stabilization. In the deprotonated species, the system relaxes into a geometry which is twisted in this region, albeit slightly.[9] In rhodopsin, the chromophore is certainly not deprotonated. However, according to two photon spectroscopic measurements the binding site of rhodopsin is neutral;[15] that is the charge balanced by a negatively charged counter ion, most probably the carboxylate group of glu 113, which interacts with the chromophore in the C12–C13 region[16] and may cause not only partial fixation of the double bond but also additional steric distortion.

Received: February 5, 1998 [Z 11439 IE]
German version: *Angew. Chem.* **1998**, *110*, 1997–2000

Keywords: chirality · circular dichroism · retinal · rhodopsin

[1] T. Yoshizawa, G. Wald, *Nature* **1963**, *197*, 1279.
[2] a) H. Shichi, *Biochemistry of Vision*, Academic Press, New York, **1983**; b) *Biophysical Studies of Retinal Proteins* (Eds.: T. G. Ebrey, H. Frauenfelder, B. Honig, K. Nakanishi), University of Illinois Press, **1987**; c) "Photophysics and Photochemistry of Retinal Proteins": *Israel J. Chem*. **1995**, *35* (special issue).
[3] a) F. Crescitelli, W. F. H. M. Mommaerts, T. I. Shaw, *Proc. Nat. Acad. Sci. USA* **1966**, *56*, 1729; b) A. S. Waggoner, L. Stryer, *Biochemistry* **1971**, *10*, 3250.
[4] a) M. Ito, A. Kodama, K. Tsukida, Y. Fudaka, Y. Shichida, T. Yoshizawa, *Chem. Pharm. Bull.* **1982**, *30*, 1913; b) A. Wada, M. Sakai, Y. Imamoto, Y. Shichida, M. Yamauchi, M. Ito, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1773.
[5] Q. Tan, J. Lou, B. Borhan, E. Karnaukhova, N. Berova, K. Nakanishi, *Angew. Chem*. **1997**, *109*, 2190; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2089.
[6] B. D. Santarsiero, M. N. G. James, M. Mahendran, R. F. Childs, *J. Am. Chem. Soc.* **1990**, *112*, 9416.
[7] W. Stöckenius, R. A. Bogomolni, *Ann. Rev. Biochem.* **1982**, 587.
[8] R. Gilardi, I. Karle, J. Karle, W. Sperling, *Nature (London)* **1971**, *232*, 187.
[9] a) F. Terstegen, V. Buss, *J. Mol. Struct. (Theochem)* **1996**, *369*, 53; b) F. Terstegen, V. Buss, *J. Mol. Struct. (Theochem)* **1998,** *430*, 209.
[10] R. D. J. Froese, I. Komaromi, K. S. Byun, K. Morokuma, *Chem. Phys. Lett.* **1997**, *272*, 335.
[11] R. H. Callender, A. Doukas, R. Crouch, K. Nakanishi, *Biochemistry* **1976**, *15*, 1621.
[12] 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, J. A. Pople, GAUSSIAN 94. Rev E.1, Gaussian Inc., Pittsburgh, PA, **1995**.
[13] K. Andersson, M. R. A. Blomberg, M. P. Fülscher, G. Karlström, R. Lindh, P.-Å. Malmqvist, P. Neogrády, J. Olsen, B. O. Roos, A. J. Sadlej, M. Schütz, L. Seijo, L. Serrano-Andrés, P. E. M. Siegbahn, P.-O. Widmark, MOLCAS-4, Lund University (Sweden).
[14] P.-O. Widmark, P.-Å. Malmqvist, B. O. Roos, *Theor. Chim. Acta* **1990**, *79*, 291.
[15] R. R. Birge, L. P. Murray, M. B. Pierce, H. Akita, V. Balogh-Nair, L. A. Findsen, K. Nakanishi, *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 4117.
[16] M. Han, B. S. Decker, S. O. Smith, *Biophys. J.* **1993**, *65*, 899.

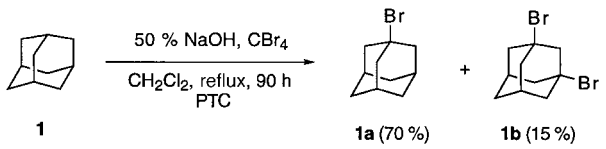
Selective C–H Activation of Aliphatic Hydrocarbons under Phase-Transfer Conditions**

Peter R. Schreiner,* Oliver Lauenstein,
Igor V. Kolomitsyn, Suad Nadi, and Andrey A. Fokin

Dedicated to Professor Paul von Ragué Schleyer

The selective activation of aliphatic hydrocarbons,[1] is mostly achieved with electronically unsaturated transition metal complexes,[2–6] superacids,[32] or enzymatic processes.[7, 8] In this paper we present a highly unusual C–H activation of aliphatic hydrocarbons by phase-transfer catalysis (PTC) in mixed aqueous/organic solvents.

When treated with tetrabromomethane and sodium hydroxide under standard PTC conditions (catalyst: triethylbenzylammonium chloride), adamantane **1**[9] gives 1-bromo- (**1a**) and 1,3-dibromoadamantane (**1b**) in 85 % conversion and 70 % yield [Eq. (1); Table 1]. The dibromide **1b** can also



(1)

be obtained from **1a** under the same conditions but with longer reaction times, which indicates a stepwise incorporation of bromine into the adamantane core. Although the synthesis of polybromoadamantanes[10] is straightforward,[11–15] we have chosen **1** as a model for studying tertiary C–H bond activations.[1]

We arrived at these reaction conditions in the course of derivatizing adamantane **1** to its bridgehead substituted analogues[9, 10] by dibromocarbene (from $HCBr_3$/50 % $NaOH/CH_2Cl_2$/PTC, 16 h, reflux) insertion into the bridgehead C–H bond. Apart from the desired dibromomethyladamantane (**1c,** 33 %),[16] we also found **1a** (41 %), **1b** (16 %), and traces of 2-bromoadamantane (**1d**) (2 %). Since isolated **1c** does not form **1a** or **1b** under the same reaction conditions, we surmized that it is not the reaction of $:CBr_2$ with **1** that yields the bromoadamantanes. Rather, we reasoned that the halogen may be transferred from CBr_4. This compound is known to equilibrate with $HCBr_3$ under the reaction conditions used.[17, 18]

The transformation is highly regiospecific for the bridgehead position of **1** (the methyl groups of methyladamantanes

[*] Dr. P. R. Schreiner, O. Lauenstein
Institut für Organische Chemie der Universität
Tammannstrasse 2, D-37077 Göttingen (Germany)
Fax: (+49) 551-399-475
E-mail: pschrei@gwdg.de
Prof. Dr. A. A. Fokin, I. V. Kolomitsyn, S. Nadi
Department of Organic Chemistry, Kiev Polytechnic Institute
Pr. Pobedy, 37, 252056 Kiev (Ukraine)

[**] The dedication honors the seminal contributions of Paul von Ragué Schleyer to adamantane chemistry. This work was supported by the Fonds der Chemische Industrie (Liebig-Fellowship for P.R.S.), the Deutsche Forschungsgemeinschaft, and the Fundamental Research Foundation of the Ukraine. P.R.S. is grateful to Prof. A. de Meijere for his support. Critical comments from Dr. J. Belzner were highly appreciated.

  1433-7851/98/3713-1895 $ 17.50+.50/0