An adiabatic reaction is expected only when the reaction is exothermic and no large energy barrier is present between the reactant and the product. In order to confirm the exothermicity of the reaction, the triplet energies of NN and QN were estimated by the measurement of the rate constants for the triplet energy transfer from various sensitizers to NN and QN by the similar pulse radiolysis technique. Although the precise consideration of the energy-transfer mechanism is under progress, the results shown in Table I make possible the estimation of the triplet energies of NN and QN, which are approximately 56 and 60 kcal/mol, respectively. Considering the strain energy of QN, which is estimated to be about 22 kcal/mol on the analogy to that of quadricyclane, the present cycloreversion of the triplet QN becomes exothermic by about 26 kcal/mol.

Now, let us consider the factors which control the reaction mechanism, adiabatic or biradicaloidal. In the case of a norbornadiene (N)-quadricyclane (Q) system, a 1,3-biradicaloidal species was estimated as the most stable common intermediate although the isomerization from Q to N is exothermic by 10 kcal/mol. The most distinguished difference between norbornadiene (N) and the naphthalene derivative (NN) is the conformation of the relaxed triplet state of the olefinic moiety. The most stable conformation of the triplet of simple olefins is twisted and the spin densities are localized at the olefinic double bond. Therefore, the olefinic double bond in the N triplet is also twisted and reactive to the other, proximately faced double bond giving a 1,3-biradical intermediate through the addition reaction. On the other hand, the naphthylethylene moiety of NN triplet is mainly planar at the relaxed state, thus the reactivity of the olefinic carbon atoms is reduced owing to the delocalization of the spin density to the naphthyl group. Thus, the NN triplet becomes the most stable form of the possible isomers.

Such a consideration of the conformation-reactivity relations of triplet olefins may lead to a better understanding of the potential energy surface of the reaction. Further investigation is in progress.

Acknowledgment. We are grateful to the members of the Radiation Laboratory of this institute for their running the linear accelerator. We are also indebted to the members of the Material Analysis Center of this institute for the analysis of the materials used.

Retinal and Rhodopsin Analogues Directed toward a Better Understanding of the H.T.-*n* Model of the Primary Process of Vision†

A. E. Asato, M. Denny, and R. S. H. Liu*

Department of Chemistry, University of Hawaii Honolulu, Hawaii 96822

Received February 10, 1986

Consideration of the effect of the medium (protein) on the direction of photoisomerization of polyenes has led to the proposal of a new mechanism for geometric isomerization,[1] which involves simultaneous rotation of two adjacent formal single and double bonds resulting in conformational as well as configurational isomerization. This process requires a small reaction volume, therefore it is particularly suitable for isomerizations in restricted cavities such as protein binding sites. Hence, it was shown that the process is compatible with all published experimental facts concerning the primary processes of vision[1] and bacteriorhodopsin.[2,3] This mechanistic process[1,2] has been dubbed H.T.-*n* (hula-twist at center *n*, also known as C.T.-n, concerted twist at center n).[1,2]

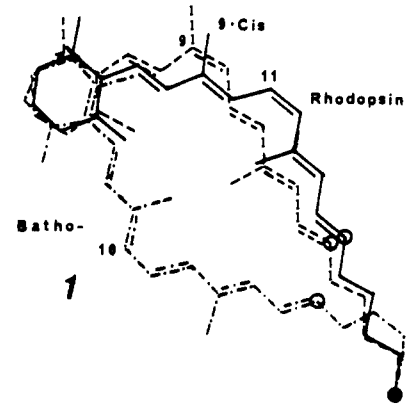
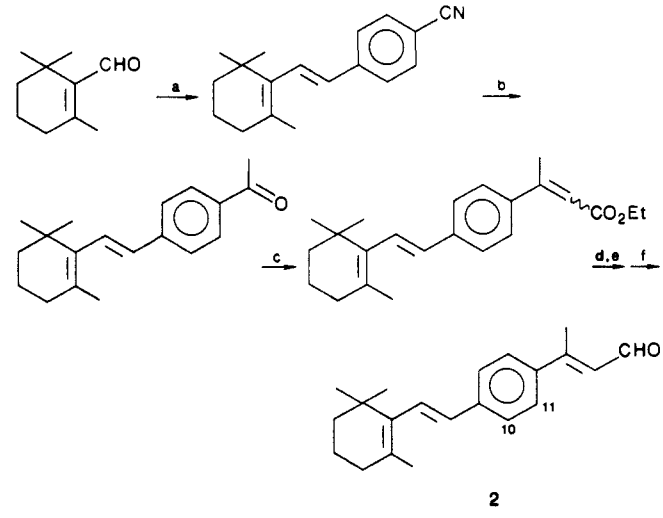


Figure 1. H.T.-*n* model for the primary processes of vision.[1,2] The 11-*cis*-retinylidene chromophore of rhodopsin (—) bonded to the butyl amine of Lys-296 via a protonated Schiff base linkage. The imino nitrogen is marked by a circle. Its photochemical conversion to bathorhodopsin (···), or the reverse, can be accomplished by the H.T.-11 process, i.e., concerted rotation of the 10,11- and the 11,12-bonds. The conversion of 9-*cis*-rhodopsin (---) to bathorhodopsin, or the reverse, can be accomplished by the H.T.-10 process, i.e., concerted rotation of the 9,10- and 10,11-bonds. It should be emphasized that only the substituent on carbon *n* is transposed from one side of the polyene chain to the other in such a H.T.-*n* process.

Scheme I



[a] (a) LDA in THF; *p*-cyanobenzylphosphonate; (b) MeMgCl/THF reflux; (c) $Me_3SiCH_2CO_2Et$, LDA/THF-hx; (d) DIBAL; (e) MnO_2; (f) preparative HPLC.

Some of the important consequences from applying the H.T.-*n* process to vision are summarized in Figure 1. The chromophore of the primary photoproduct bathorhodopsin has the all-trans,10-s-cis structure **1**. Photochemical interconversions of the 11-cis and the 9-cis chromophores by way of bathorhodopsin[4] proceed via the H.T.-11 and H.T.-10 processes. We have now carried out a study of several ring-fused retinal analogues designed to test these implications.

All analogues involve minor structural modifications, adding no more than two carbon atoms. First, the aromatic retinal

† Bioorganic Studies of Visual Pigment Analogues. 5. For previous paper in the series, see: ref. 9.

(1) Liu, R. S. H.; Asato, A. E. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 259-263.

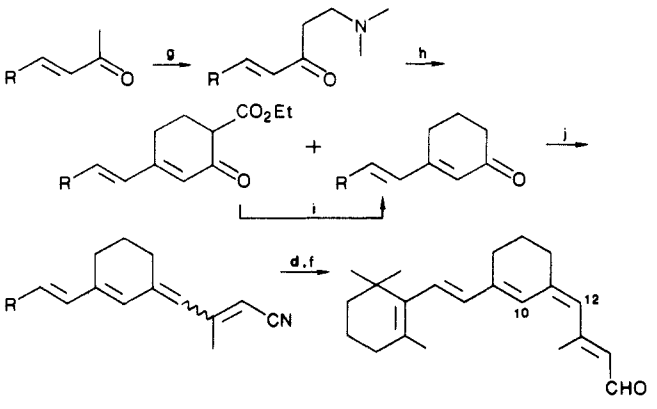
(2) (a) Liu, R. S. H.; Mead, D.; Asato, A. E. *J. Am. Chem. Soc.* **1985**, *107*, 6609-6614. (b) Liu, R. S. H.; Browne, D., *Acc. Chem. Res.* **1986**, *19*, 42-48.

(3) Recent vibrational spectroscopic studies reached opposite conclusions concerning the conformation of the retinyl chromophore in the primary photoproduct: (a) Smith, S. O.; Hornung, I.; van der Steen, R.; Pardoen, J. A.; Braiman, M. S.; Lugtenburg, J.; Mathies, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 967-971. (b) Gerwert, K.; Siebert, F. *EMBO J.* **1986**, *5*, 805-811.

(4) Yoshizawa, T.; Wald, G. *Nature (London)* **1963**, *197*, 1279-1286.

0002-7863/86/1508-5032$01.50/0

Scheme II

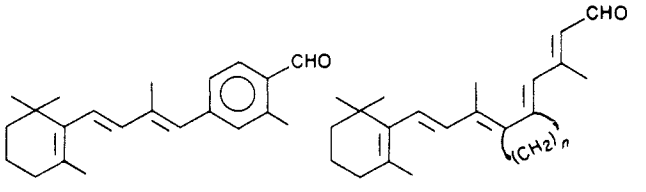


5

[a](g) $(CH_2O)_n$ + Me_2NH-HCl; (h) MeI; $CH_3COCH_2CO_2Et$, NaOMe/MeOH; (i) KOH/MeOH; HOAc; (j) C_5-phosphonate, NaH, DMF/THF; (d) DIBAL; (f) preparative HPLC; R = trimethylcyclohexenyl.

analogue **2**[5] was synthesized according to the reaction sequence of Scheme I. Incubation for 2 h at room temperature of an excess of the analogue with either digitonin or CHAPS solubilized bovine opsin did not yield any detectable amount of new pigments.[6] Since the shape of **2** is similar to that of the proposed chromophore of bathorhodopsin (**1**), this negative observation, obviously not to be considered a proof, is consistent with the suggestion that bathorhodopsin contains the all-trans,10-s-cis chromophore. This result, we might add, cannot readily be accounted for by any arguments based on the length requirement of the binding site.[7] For comparison, analogue **3**,[8] a model for 12-s-cis,all-trans retinal, a structure recently suggested for the chromophore of meta-I-rhodopsin,[9] also failed to interact with bovine opsin.

The instability of bathorhodopsin makes any attempt to prepare a corresponding visual pigment analogue impossible. Thus the merit of any elaborate effort to prepare other less accessible analogues containing the s-cis conformation, such as **4**, becomes questionable.



3 4

A more active approach is to examine effects of structural modification on the photochemical process. Hence, we have synthesized the ring-fused retinal analogue **5**[10] according to the reaction sequence shown. The 11-cis isomer[11] was isolated by preparative HPLC, which upon interaction with bovine opsin yielded a visual pigment analogue with an absorption maximum at 488 nm. The added fused ring negates the possibility of rotation of the C-11 end of the 11,12-double bond in its isomerization (hence shutting off the H.T.-11 process), while rotation of the C-12 end should be relatively unaffected. Its photochemical activity is, therefore, interesting (Scheme II).

Upon irradiation of the visual pigment analogue with visible light at room temperature in the presence of an excess amount of hydroxylamine, the pigment bleached readily. This result clearly cannot be accommodated by the H.T.-11 mechanism. While it is still consistent with the conventional one bond rotational process involving twisting of the C-12 end of the polyene chromophore, the result cannot be considered as a proof for such a mechanism in rhodopsin. In fact, upon reflection there is the added possibility that upon closing of the H.T.-11 channel in this analogue a new chemical pathway for dissipation of the excess electronic excitation energy might have been created. In addition to the one bond twist mechanism, the new pathway could be the H.T.-12 process. The latter, however, should produce a structurally different primary photoproduct (12-s-cis,all-trans instead of 10-s-cis,all-trans) and subsequent bleaching intermediates.[2b,4] Hence, detection and characterization of such intermediates[12] could be of primary importance for possible clarification of the specific mode of isomerization in the primary process of vision (assuming no substantial distortion of protein structure in this analogue). This experiment will be carried out in the laboratory of Professor Yoshizawa.[12]

Acknowledgment. The work was supported by a grant from the U.S. Public Health Services (AM-17806). Dr. V. J. Rao first suggested the use of compound **5** for examining the H.T.-n process.

(5) ^{1}H NMR ($CDCl_3$): δ 1.07 (s, CH_3-1,1), 1.77 (s, CH_3-5), 2.57 (s, CH_3-13), 6.77 (d, H_7), 6.36 (d, H_8), 6.43 (d, H_{14}), 7.46 (d, Ar 2 H), 7.53 (d, Ar 2 H), 10.17 (dd, CHO); $J_{7,8}$ = 16.4, $J_{10,11}$ = 7.3, $J_{14,15}$ = 7.9 Hz. The BR analogue of the same compound has been prepared: Koelling, E.; Gaertner, W.; Oesterhelt, D.; Ernst, L. *Angew. Chem.* **1984**, *96*, 76-78.

(6) After 23 h, a small amount (1.8%) of a pigment was detected, but such a small amount after a long incubation period is generally regarded as negative.

(7) (a) Matsumoto, H.; Yoshizawa, T. *Vision Res.* **1978**, *18*, 607-609. (b) Matsumoto, H.; Liu, R. S. H.; Simmons, C. J.; Seff, K. *J. Am. Chem. Soc.* **1980**, *102*, 4259-4262.

(8) ^{1}H NMR data for **3**: δ 1.05, 1.74, 2.09 and 2.67 (3 H each), 6.31 (d) and 6.21 (d) (1 H each for H_7 and H_8, $J_{7,8}$ = 15.6 Hz), 6.43 (s, H_{10}), 7.19 (s, H_{12}), 7.31 (d) and 7.77 (d) (1 H each, J = 7.5 Hz). The aldehyde was prepared from the corresponding ester. The latter was generously provided by Dr. M. Dawson: Dawson, M. I.; Hobbs, P. D.; Chan, R. L.; Chao, W.-R.; Fung, V. A. *J. Med. Chem.* **1981**, *24*, 583-592.

(9) Liu, R. S. H.; Matsumoto, H.; Asato, A. E.; Mead, D. *J. Am. Chem. Soc.* **1986**, *108*, 3796-37[illegible].

(10) Compound **5** has been synthesized independently by M. Sheves with the fused ring constructed by a totally different route. Private communication of M. Sheeves to R. S. H. Liu.

(11) ^{1}H NMR ($CDCl_3$): δ 6.31 (d, H_7), 6.12 (d, H_8), 6.60 (s, H_{10}), 5.73 (s, H_{12}), 6.04 (d, H_{14}), 10.05 ppm (d, H_{15}); $J_{7,8}$ = 16.2, $J_{14,15}$ = 8.2 Hz.

(12) Shichida, Y.; Yoshizawa, T. *Methods Enzymol.* **1982**, *88*, 333-354.

A Neutral Water-Soluble Aluminum Complex of Neurological Interest

Martin M. Finnegan, Steven J. Rettig, and Chris Orvig*

Department of Chemistry, University of British Columbia Vancouver, BC, V6T 1Y6 Canada

Received December 31, 1985

The involvement of aluminum in certain neurological dysfunctions has become the subject of considerable debate over the past decade.[1-4] Increased levels of aluminum in the brain have been observed in Alzheimer's disease[2,3] and dialysis encephalopathy,[4] conditions which result in progressive chronic dementia, among other symptoms. This controversy has included suggestions that Al intake should be drastically reduced[5] although it appears that very little Al is absorbed from the diet.[1] While it is generally agreed that elevated levels of Al are involved in the pathogenesis of Alzheimer's disease, there is little agreement on its role and no agreement on how it is delivered to the nuclei of brain cells.

To understand how aluminum arrives at its ultimate intracellular locus in human brain disease, more than a scant knowledge of its chemistry in aqueous solution at neutral pH is required. The extensive complicated hydrolysis chemistry of aluminum[6] has

* To whom correspondence should be addressed.

(1) For a review, see: Alfrey, A. C. *Adv. Clin. Chem.* **1983**, *23*, 69-91.

(2) Crapper, D. R.; Krishnan, S. S.; Dalton, A. J. *Science (Washington, D.C.)* **1973**, *180*, 511-513.

(3) Crapper, D. R.; Krishnan, S. S.; Quittkat, S. *Brain* **1976**, *99*, 67-80.

(4) Alfrey, A. C.; Legendre, G. R.; Kaehny, W. D. *N. Engl. J. Med.* **1976**, *294*, 184-188.

(5) Lione, A. *Food Chem. Toxicol.* **1983**, *21*, 103-109.

(6) Baes, C. F., Jr.; Mesmer, R. E. *The Hydrolysis of Cations*; Wiley-Interscience: New York, 1976; pp 112-123.

0002-7863/86/1508-5033$01.50/0