REGIOSELECTIVE PHOTOISOMERIZATION OF PENTAENALS. EFFECT OF METHYL SUBSTITUENTS.¹

P. Arjunan and R. S. H. Liu*

Department of Chemistry, University of Hawaii 2545 The Mall, Honolulu, Hawaii 96822, U.S.A.

Summary. The different photochemical behavior of a demethylated retinal analog versus its methylated homologs has been rationalized based on perturbation of the excited potential surface by the methyl substituents.

Photoisomerizations of retinal, 1, and its derivatives are known to be solvent dependent.² In a non-polar solvent, isomerization only takes place at the trisubstituted double bonds favoring the site with the smallest volume of reaction.³ In a polar solvent, the direction of reaction becomes less selective taking place at all four double bonds.⁴ The polar character of an excited polyene⁵ is also demonstrated in isomerization of negatively substituted aryldienes where the direction of isomerization appears to be controlled by dipolar character of the transition state borrowed from the more stable zwitterionic intermediate.⁶ The changed photochemical properties of demethylated retinals, e.g. the absence of 13-cis isomer during photoisomerization of 13-demethylretinal,⁷ could then be a reflection of the electronic and the steric effects exerted by the methyl group onto the excited chromophore. To test the importance of the role of the methyl substituents on the isomerization process, we have now prepared several pentaenals. We believe the result not only reinforce the ideas advanced earlier but also clarifies other aspects of regioselectivity in photoisomerization of polyenes.

9-(1'-Cyclohexenyl)-2.4,6,8-nonatetraenal, 2, was prepared by consecutive C₄ extensionof cyclohexenylcarboxylaldehyde by procedures analogous to those established in vitamin Asynthesis.⁷ Also prepared were the 6-methyl (3) and 7-methyl (4) homologs. Isomers wereisolated from synthetic or photo-mixtures by preparative hplc and the geometry characterizedby ¹H-nmr (Table 2). To examine the preferred direction of photoisomerization of each ofthe polyenes, the all-trans isomer was irradiated in hexane or acetonitrile, and thereaction followed by hplc until stationary states were reached. Photoproducts werecharacterized by comparison of retention times with authentic samples or by their uv-visabsorption spectra recorded on a diode array hplc detector. Results of such a study arelisted in Table 1.



Compound	Solvent ^b	irrd. time min	% conversion	2-cis	4-cis	6-cis	
2	Hexane	1	8		5	3	
-		5	13		8	5	
		20	14 [°]		10	4	
	CH3CN	1	4		4		
		2	8		8		
		5	47		37	10	
		10	53		39	14	
		20	58 [°]		42	16	
3~	Hexane	1	8	40	1	4	
		5	16 ^C	5	1	11	
		20 17 ^c 7 ^d		1	10		
	CH3CN	1	3		3		
		1.5	13		13		
		3	23		21	2	
		7	42 ^C		32	10	
4	Hexane	1	2.5	0.5	0.5	1.5	
~		1.5	9	2	2	5	
		5	30 [°]	7	5	18	
		20	29 [°]	7	5	17	
	CH₃CN	1	3			3	
		1.5	6		2	4	
		2	12		5	7	
		2.5	26	-1	12	14	
		4	35		16	19	
		10	66 [°]	~-	23	43	
		20	66 [°]		23	43	

Table 1. Photoisomerization of the all-trans isomer of pentaenals, $2 to 4^{a}$

a. Degassed solution of all-trans isomer (~0.01 M) was used. Corning 3-73 filter plus Hanovia Medium pressure Hg lamp. Analyzed: Altex ultrasphere Si column.
b. Commercial reagent solvents used without purification.
c. Photostationary state.
d. Overlapping peaks.

The most-interesting trend revealed by the data in Table 1 is the different behavior of the completely demethylated pentaenal 2 from the two methylated pentaenals. Compound 2 exhibited little sensitivity toward solvents of different polarity. Whether in hexane or in acetonitrile, the product mixture did not contain the 2-cis isomer and of the two product isomers, 4-cis was the major isomer in both solvents. But for the two methylated

pentaenals, there were noticeable changes of stationary state product distributions in the two solvents. Hence, for 3, the major isomer in hexane was the 6-cis isomer but in acetonitrile, the 4-cis; and for 4, the major isomer in hexane was the 6-cis isomer with 4-cis increased substantially in acetonitrile. Clearly, methyl substitution significantly affected the direction of photoisomerization.

The results are, however, compatible with the concepts introduced earlier. For compound 2, the absence of trisubstituted double bonds eliminates the possibility of substituent directed selected torsional relaxation. Hence, both in a non-polar and a polar solvent, the direction of isomerization was controlled by intrinsic characteristic of the excited polyene chromophore which apparently favored twisting at the central most double bonds of the polyene system. Steric relief, however, still played a role in the photochemistry of this demethylated pentaenal system appearing in the form of low trans to cis conversion in the photostationary state in hexane. The ensuing efficient cis to trans isomerization (relative to the unaccelerated trans to cis process) on account of 1.4-steric repulsion of a cis bond is expected to lead to a low conversion in the photostationary state. But in the dipolar acetonitrile where the more polarized excited polyene (leading to a lower π electron density) reduced the difference in reactivity between all double bonds, causing a higher conversion in the photostationary state.

The addition of a single methyl group to the polyene chain substantially altered the solvent insensitive photochemical characteristics. In nonpolarizing hexane, the reaction became regioselective at the trisubstituted double bonds; in the more polar acetonitrile, the reduced π electron density again diminished the role of selective decay at the trisubstituted centers as a criterion for selective twisting of the polyene system. Instead, the favored reaction sites were again at the more centrally located double bonds. There was, however, a noticeable difference in regioselectivity of the two pentaenals even though the methyl substituents were located at the same double bond. That the 6-cis isomer in 4 was more favored in acetonitrile than in 3 was consistent with the dipolar nature of an excited polyene.⁸ Stabilization of the transition state of the zwitterionic intermediate⁵ twisted at the 6,7 bond by the methyl group is possible only when it is located at C-7 and not at C-6.



The absence of the 8-cis isomer paralleled the observation of a low yield of the 7-cis isomer for retinal.^{2b} It probably merely reflected the remoteness of this bond to the electron withdrawing end group making it richer in electron density than other double bonds.

In summary, the present set of compounds lent support to the earlier suspicion that the methyl substituents have a profound effect on regioselective isomerization of retinal. The data also provided further evidence that the direction of twisting of the polar excited polyene, which determined its regioselective photoisomerization, resulted from a sensitive balance of many minor perturbations including the intrinsic steric and electronic effects and external factors such as relative ease of displacement of solvent molecules.³ It is our hope that a complete characterization of these effects and an understanding of their relative importance will allow prediction of direction of regioselective photoisomerization of all polyenes in the future.

Acknowledgement. This work was supported by grants from the National Science Foundation (CHE-16500) and the National Institutes of Health (DK-17806).

References

- 1. Photochemistry of Polyenes 25. For previous paper in the series, see ref. 6.
- 2. (a) A. Kropf and R. Hubbard, Photochem. Photobiol., <u>12</u>, 249-260 (1970).
 - (b) R. S. H. Liu and A. E. Asato, Tetrehedron, <u>40</u>, 1931-1969 (1984).
- 3. R. S. H. Liu, A. E. Asato and M. Denny, J. Am. Chem. Soc., 105, 4829-4830 (1983).
- 4. V. J. Rao, R. Fenstemacher and R. S. H. Liu, Tetrehedron Lett., 25, 1115-1118 (1984).
- 5. (a) L. Salem, Science, 191, 822-830 (1976).
 - (b) V. Bonancic-Koutecky, J. Am. Chem. Soc., 100, 396-402 (1978).
- 6. K. Muthuramu and R. S. H. Liu, J. Am. Chem. Soc., <u>109</u>, 6510-6511 (1987).
- 7. A. D. Broek, M. Muradin-Szweykowska, J. M. L. Courtin and J. Lugtenburg, Recl. Trav. Chim. Pays-Bas., <u>102</u>, 46-51 (1983).
- 8. R. S. H. Liu and A. E. Asato, Methods Enzymol., 88, 506-516 (1982).
- 9. R. Mathies and L. Stryer, Proc. Natl. Acad. Sci., 78, 2169-2173 (1976).

Table 2. 'H-nmr data of isomers of pentaenals 2 to 4^{a}

	Chemical shift (ppm) and coupling constants (Hz)															
Compound		<u>2H</u>		<u>3H</u>		<u>4H</u>		<u>5H</u>		<u>6H</u>		<u>7H</u>		<u>8H</u>		<u>9H</u>
	J <u>1,2</u>		J2.3		J3.4		J4.5		J5.6		J6.7		J7,8		J <u>8,9</u>	
all-trans-2	7 9	6.16	15 1	7.16	11 3	6.44	15.4	6.74	11 1	6.34	14 6	6.56	10.7	6.24	15.4	6.40
4-cis-2	7.5	6.17	10.1	7.62	10.0	6.18	10.1	6.48	10.0	6.79	14	6.52	10.0	6.27	15.1	6.40
6-cis-2	7.9	6.17	15.0	7.13	12.0	6.45	11	7.18	12.2	6.07	14	6.32	10.9	6.63	15	6.37
all-trans-3b	7.9	6.08	15.3	6.61	10	6.49	16	6.39	11		11	6.26	11	6.07	14.5	6.35
~ ?_cic_?	7.8	5 93	15.1	7 00	10.6	7 90	14.7	6 64				6 45	11.0	6 30	15.0	6 43
2-013-3	7.7	5.00	10		11	0.20	14.9	0.01				0.10	11.3	0.00	14.6	c. a.
6-cis-3	8.0	6.20	15.1	7.26	11.0	6.46	15.6	7.29				6.27	11.4	6.62	14.6	0.31
all-trans-4	8.0	6.19	15.1	7.24	11.4	6.49	14.4	7.10	10.6	6.27				6.77	15.9	6.48
6-cis-4	7.9	6.17	14.2	7.25	11.4	6.42	14.5	7.23	10.9	6.11				6.76	16.3	6.45

a. NM-300 spectrometer. Solvent CDCl₃ unless otherwise specified. b. In C_6D_6 . (Received in USA 12 November 1987)