Unusual Conformation and Photoisomerization of Retinochrome Analogues with 11-Methylretinals

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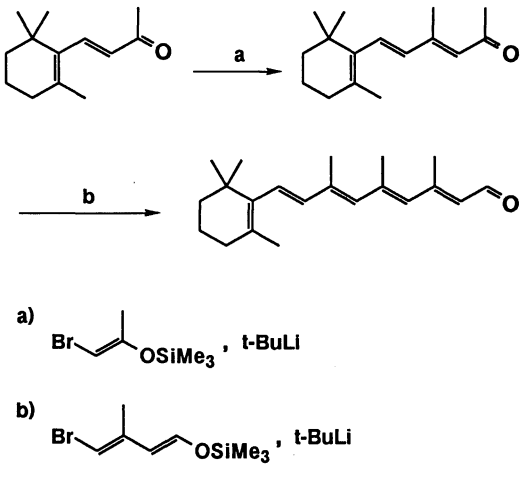
Three kinds of 11-methylretinals were synthesized for elucidating effect of methyl substitution on formation of retinochrome-analogues and their properties. The stable conformation of 11-methylretinal was found as 6,10,12-tri-*S*-cis conformation based on NOESY measurement. The formed retinochrome-analogues with 11-Me-, 11-Me-13-deMe- and 11-Me-9,13-dideMe-retinals showed their absorption maxima at 450, 470 and 470 nm, respectively. The enzymatic photoisomerization of their retinochrome-analogues gave the 11-cis isomers in 90-91 % regioselectivity. The CD spectra of 11-methylretinochrome exhibited the intense β-band with extremely weak α-band.

Retinochrome plays a complementary role in vision of cephalopods by comparison with rhodopsin which is effective in photoreception as a sensory pigment.[1] After photobleaching of rhodopsin, all-trans-retinal as a photoproduct can be photochemically reverted to 11-cis retinal with retinochrome-template.[2] Retinochrome is an enzyme involving regioselective photoisomerization of all-trans-retinal to 11-cis-retinal. A structural understanding of efficiency in the isomerization can be afforded by use of retinal analogues. One of candidates in the analogues is 11-methylretinal, which has energetically favored configuration in 11-cis isomer for avoiding steric hindrance in the all-trans isomer.

The synthesis of 11-methylretinal by conventional Wadsworth-Emmons[3] reaction was incapable to be accomplished because of steric repulsion between 9, 11, 13-methyl groups. The alternative to the reaction with silyl ethers made possible total synthesis of 11-methylretinals, as shown in Scheme 1.



Scheme 1.

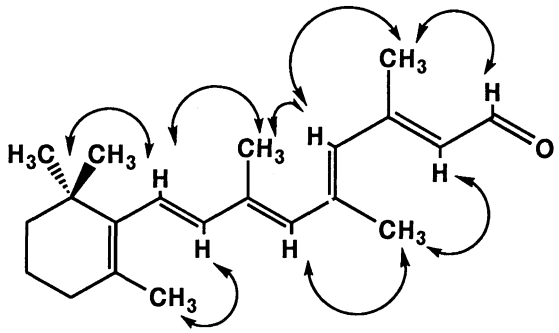
Table 1. Chemical shifts (δ/ppm) and coupling constants (J/Hz) of 11-methylretinals

	1,1'-Me	5-Me	9-Me	11-Me
all-trans	1.01	1.69	1.99	2.05
11-cis	1.02	1.07	2.00	1.78

13-Me	7H	8H	10H	12H
2.29	6.19	6.06	5.92	5.93
2.02	6.17	6.06	6.06	6.02

14H	15H	$J_{7,8}$	$J_{14,15}$
5.97	10.05	16.05	8.25
5.95	10.04	16.28	7.88

For determination of the structure of all-trans-11-methylretinal, the NMR spectoscopy provided a crucial tool. All the signals of protons and carbons in NMR spectra were assigned to the corresponding atoms in all-trans-11-methylretinal by means of COSY and COLOC methods as shown in Table 1. In particular, the detailed conformation was determined by NOESY to prefer 6,10,12-tri-*S*-cis to the all *S*-trans as figured in Scheme 2.



Scheme 2.

Formation of 11-methylretinochromes is apparently similar to reconstitution of native retinochrome with all-trans-retinal and aporetinochrome.[4] The addition of a methanolic solution of all-trans-11-methylretinal to digitonin solution of aporetinochrome afforded 11-methylretinochrome with absorption maximum at 450 nm. As a result, the conformation of *S*-cis in 11-methylretinal had no effect on the reconstitution of 11-methylretinochrome. The absorption maxima of the retinochrome-analogues and the protonated Schiff bases with their opsin shifts are listed in Table 2. Compared with the opsin shift of native retinochrome (2200 cm^{-1}), the low value for 11-methylretinochrome corresponds to

Table 2. Absorption maxima and opsin shifts of 11-methylretinochromes in UV-VR spectra

retinochrome analogues	λ_{SBH^+}/nm [a]	λ_{Ret}/nm [b]	$\Delta\nu$/cm^{-1} [c]
11-Me-Ret	426	450	1300
13-deMe-11-Me-Ret	440	470	1500
9,13-dideMe-11-Me-Ret	438	470	1600

[a]SBH^+ means protonated Schiff base with retinal analogue. [b]Ret means retinochrome analogue. [c]opsin shifts

the presence of *S*-cis conformation as referred in 3,7-dimethyl-2,4,6,8,10-dodecapentaenal.[5]

The retinochrome-analogues formed with 11-methylated retinal showed negligibly small α-band and intense β-band in CD spectra, whereas the α-band appeared in the retinochrome-analogue with 13-demethyl-11-methylretinal (λ_{max}/nm=485) or 9,13-didemethyl-11-methylretinal (λ_{max}/nm=475) as well as that in the native retinochrome.[6] Although this phenomenon has not been reported so far in the retinal proteins with simply alkyl-substituted retinal analogues, it is suggestive that 10- or/and 12-*S*-cis conformation can cause intense α-band in retinochrome.[7] In spite of the weak α-band, irradiation of 11-methylretinochrome quantitatively gave 11-cis-11-methylretinal in 90% selectivity together with 13-cis and all-trans isomers in 5% regioselectivity, respectively.[8] In conclusion, the selectivity in the photochemical trans-cis isomerization of 11-methylretinochrome is independent of the presence of α-band in the CD spectrum or the *S*-cis conformation.

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