could be changed by mutation, and hence, the presence of a C-terminal aromatic residue may potentiate a protein conformation that is favorable for electron transfer but that is not reflected in the equilibrium binding energy. A more exciting possibility is that an extended π-electron system at putidaredoxin's C-terminus could serve as a mediator of the electron-transfer event. A similar role for aromatic mediation has been suggested for phenylalanine 82 in the cytochrome *c*/cytochrome *c* peroxidase system.[2e,g,i]

(14) Sligar, S. G.; Gunsalus, I. C. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 4, 1078-1082.
(15) Labeling was accomplished by the addition of 20 μL of an acrylodan-saturated 50/50 ethanol/water mixture to 50 mM HEPES buffer, pH = 6.8, at 4 °C for 5 min. Prendergast, F. G.; Meyer, M.; Carlson, G. L.; Iida, S.; Potter, J. D. *J. Biol. Chem.* **1983**, *258*, 12, 7541-7544.
(16) Eisenthal, R.; Cornish-Bowden, A. *Biochem. J.* **1974**, *139*, 715-720.
(17) This research was supported by grants from the National Institutes of Health (GM31756, GM33775, and HL25934). K.S.S. gratefully acknowledges an NIH Research Career Development Award.

Azulenic Retinoids and the Corresponding Bacteriorhodopsin Analogues. Unusually Red-Shifted Pigments

Alfred E. Asato,* Xiao-Yuan Li, Dennis Mead, G. M. L. Patterson, and R. S. H. Liu*

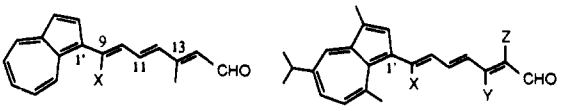
Department of Chemistry, University of Hawaii 2545 The Mall, Honolulu, Hawaii 96822

Received May 25, 1990

There has been extensive effort directed toward a better understanding of the red-shifted UV-vis absorption characteristics of visual pigments and bacteriorhodopsin (BR) analogues as distinguished from the absorption characteristics of the protonated Schiff bases (PSB). The proximity of a second point charge originating from the protein is believed to be important[1] although the medium and the extent of protonation are also suspected to have a significant effect on pigment absorption properties.[2] Less successful has been the search for extensively red-shifted pigment analogues. For rhodopsin, the most red-shifted analogue known is the 13-CF_3 analogue (545 nm),[3] and for BR, the most red-shifted analogues known are the cyanine dye analogues (662 nm)[4] and a minor equilibrium concentration of the 14-F analogue (680 nm).[5] We now report the preparation of BR analogues with long-wavelength absorption maxima beyond 750 nm.

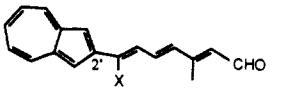
Azulene and guaiazulene retinoids **1**–**6** have been synthesized by following established procedures for olefination of the known acylated azulenes.[6] The methods gave mixtures of 13-cis and all-trans isomers which were separated by preparative HPLC and characterized by ^{1}H NMR spectroscopy.

While all these azulene retinal analogues were found to interact readily with bacterioopsin (BO), the absorption properties of the resultant pigments varied considerably with the long-wavelength band ranging from 520 (**2**) to 830 nm (**5**). Data are listed in Table I along with those of the protonated Schiff bases. As an example,



1 : X = H
2 : X = CF_3

3 : X = H, Y = CH_3, Z = H
4 : X = CF_3, Y = CH_3, Z = H
5 : X = H, Y = CF_3, Z = H
6 : X = H, Y = CH_3, Z = F



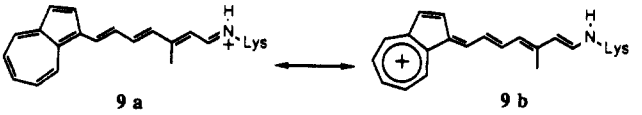
7 : X = H
8 : X = CH_3

spectra taken during formation of the 795-nm pigment of **6** are shown in Figure 1.

Two azulene-containing analogues (**7** and **8**) are known,[7] with the side chain originating from the 2'- rather than 1'-position as in **1**–**6**. The BR analogue of **7** has a long-wavelength absorption band centered at 475 nm[7a] while the phototaxis action spectrum of **8** in the algae *Chlamydomonas* centered at 472 nm.[7b] The lack of substantial red shifts is in complete contrast with the present data.

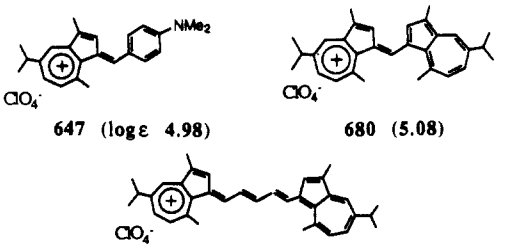
We note that the observed difference for the 1'- and 2'-substituted azulene analogues cannot be due to relative ordering of the two lowest azulene excited states that account for their unique colors. Symmetry consideration led to the conclusion that the 2'-substituted analogues would cause a red shift of the allowed S_2 band and the opposite for the 1'-substituted analogues.[8] This trend is contrary to the observed results. Neither would the large difference between the 1-substituted (to >800 nm) and the 2'-substituted azulenes (475 nm) likely be due to previously known factors alone, such as altered relative position of the second point charge. Instead, we offer the following additional explanation for the unusual red-shifted characteristics of several of the 1'-substituted azulene analogues.

The resonance hybrid of the protonated retinyl Schiff base can be represented by the imino (**9a**) and the enamino (**9b**) resonance structures. Because of the stability of the tropylium ion, we believe



9 a **9 b**

that, in the 1'-substituted azulene BR analogues, the enamino resonance structure should dominate, giving rise to the unusual red-shifted absorption characteristics. Consistent with this explanation are the absorption maxima reported for the following conjugated tropylium ions.[9]



647 (logε 4.98) **680** (5.08)

860 (5.49)

The seemingly disparate absorption properties of the above BR analogues can be rationalized by the relative importance of the two resonance contributing structures. The electron-donating alkyl

(1) (a) Derguini, F.; Dunn, D.; Eisenstein, L.; Nakanishi, K.; Odashima, K.; Rao, J. V.; Sastry, L.; Termini, J. *Pure Appl. Chem.* **1986**, *58*, 719. (b) Lugtenburg, J.; Muradin-Szweykowska, M.; Heeremans, C.; Pardoen, J. A.; Harbison, G. S.; Herzfeld, J.; Griffin, R. G.; Smith, S. O.; Mathies, R. A. *J. Am. Chem. Soc.* **1986**, *108*, 3104.
(2) Sandorfy, C.; Vocelle, D. *Can. J. Chem.* **1986**, *64*, 2251.
(3) (a) Mead, D.; Asato, A. E.; Denny, M.; Liu, R. S. H.; Hanzawa, Y.; Taguchi, T.; Yamada, A.; Kobayashi, N. *Tetrahedron Lett.* **1987**, *28*, 295. (b) Also private communication of Y. Shichida and Y. Kobayashi.
(4) Derguini, F.; Caldwell, C. G.; Motto, M. G.; Balogh-Nair, V.; Nakanishi, K. *J. Am. Chem. Soc.* **1983**, *105*, 646.
(5) Tierno, M. E.; Mead, D.; Asato, A. E.; Liu, R. S. H.; Sekiya, N.; Yoshihara, K.; Chang, C. W.; Nakanishi, K.; Govindjee, R.; Ebrey, T. G. *Biochemistry* **1990**, *29*, 5948.
(6) Liu, R. S. H.; Asato, A. E. *Methods Enzymol.* **1982**, *88*, 506.
(7) (a) Zarrilli, G. Ph.D. Thesis submitted to the Columbia University, 1984. (b) Nakanishi, K.; Derguini, F.; Rao, V. J.; Zarrilli, G.; Okabe, M.; Iden, T.; Johnson, R. *Pure Appl. Chem.* **1989**, *61*, 361.
(8) See, e.g.: Jaffe, H. H.; Orchin, M. *Theory and Applications of Ultraviolet Spectroscopy*; John Wiley & Sons, Inc.: New York, 1962; pp 337-341.
(9) Kirby, E. C.; Reid, D. H. *J. Chem. Soc.* **1960**, 494; **1961**, 3579.

0002-7863/90/1512-7398$02.50/0 © 1990 American Chemical Society

Table I. Absorption Properties of Azulene Retinoids and the Corresponding Analogues

analogue	λ_{max}, nm RCHO[a]	SB[b]	PSB[b]	BR	OS,[c] cm^{-1}
1, trans	446	430	541	644	2960
1, 13-cis	444	426	542	631	2600
2, trans	416	401	489	520	1220
3, trans	473	450	590	694	2540
4, trans	444	421	532	601	2160
4, 13-cis	442	418	510	596	2830
5, 13-cis	506	388	545	830	6300
6, trans	490	460	640	795	3050
6, 13-cis	465	450	638	795	3100
7, trans[d]				475	1170

[a] In hexane. [b] In ethanol. [c] Opsin shift; see footnote 10 for discussion. [d] Data from ref 7.

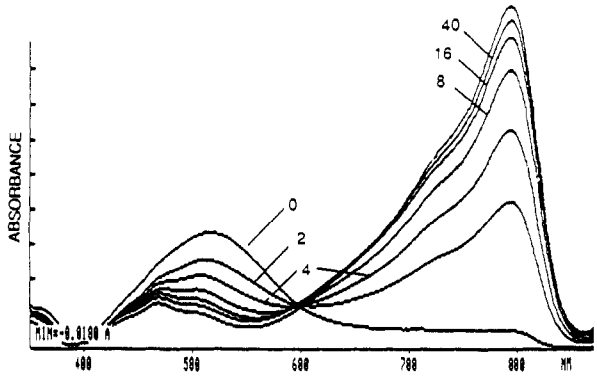


Figure 1. Formation of the 795-nm BR analogue from interaction of retinal analogue 6 with BO. Spectra were recorded immediately after mixing (0 min) and 2, 4, 8, 16, and 40 min and 18 h thereafter. The λ_{max} of the longest wavelength band is at 795 nm.

groups in guaiazulene pigments should stabilize the tropylium ion, making 3 more red-shifted than 1, and 4 more than 2 (more so than those in the free molecules). Electron-withdrawing substituents on the polyene chain (13-CF_3 and 14-F) should increase the electron density of the side chain, thus stabilizing the enamino structure giving the unusual red-shifts of 5 and 6. However, a substituent at C-9 (CF_3) introduces ring–chain steric interaction. The resultant conformational distortion would favor the imino structure, leading to the blue-shifted spectra of 2 and 4. The absence of a resonance structure containing the stable tropylium ion in 7 and 8 probably accounts for their blue-shifted spectra.

Furthermore, the relatively narrow long-wavelength band of these pigments is reminiscent of those in the cyanine dye analogues.[4] The increased planarity of the chromophore associated with the proposed resonance hybrid is expected to lead to a less diffused spectrum.

In summary, we believe that the current investigation has defined a new direction for preparing red-shifted BR and rhodopsin pigments. In progress are quantitative studies on the nature of the red shift of these and related pigments.[10]

Acknowledgment. This work was partially supported by grants from the U.S. Public Health Services (DK-17806) and the National Science Foundation (CHE-16500).

Supplementary Material Available: ^1H NMR data of azulene retinoids (1 page). Ordering information is given on any current masthead page.

(10) At the suggestion of a referee, we have included opsin shift data in Table I. The unusual entries from our compounds (2 and 5) are believed to be due to a different conformation of the free chromophore versus that in the protein. A twisted *S*-cis conformation is suspected for the CF_3-substituted compounds. This point is under active investigation. Results will be communicated separately.

Cine Substitution in Vinylstannane Cross-Coupling Reactions

Gilbert Stork* and Richard C. A. Isaacs[‡]

Department of Chemistry, Columbia University
New York, New York, 10027

Received February 27, 1990

We report the first examples of palladium(0)-catalyzed coupling of vinylstannanes with aryl halides[1] in which attachment of the aryl group occurs exclusively[2] adjacent to the trialkyltin-bearing carbon (cine substitution) instead of at the carbon that originally bore the tin substituent (ipso substitution).

Our interest in these coupling reactions arose because of our need for a general method for the synthesis of 6-arylnorbornenes 2, a task for which palladium cross-coupling chemistry seemed particularly well suited. We therefore examined vinyl derivatives (cf. 1) that would be expected to couple with aryl nucleophiles according to the protocol of Stille[2] (Scheme I). For this purpose, enol triflate 1, X = OTf, was converted to vinylstannane 1, X = $SnMe_3$, (Sn_2Me_6, LiCl, 2 mol % $Pd(Ph_3P)_4$, refluxing THF; 82%),[1c] which was then coupled with 1-bromonaphthalene (2 mol % $Pd(Ph_3P)_4$, catalytic 2,6-di-*tert* butyl-4-methylphenol, refluxing toluene)[1d] to give, in 83% yield, a product that showed a ^1H NMR spectrum [$CDCl_3$; δ 6.19 (d, 1 H, J = 2.8 Hz), 3.66 (s, 3 H), 1.52 (s, 3 H)] compatible with that expected for the desired product 2, Ar = 1-naphthyl, but which later work showed (vide infra) actually to be the product of cine substitution 3, Ar = 1-naphthyl.

Recent reports[3] that enol triflates undergo facile coupling with arylzinc reagents led us to examine this procedure as well. Indeed, treatment of enol triflate 1, X = OTf, with 1-naphthylzinc chloride in the presence of 2 mol % $Pd(Ph_3P)_4$ (THF, room temperature, 1 h) led to a smooth coupling reaction. To our surprise, however, the product, isolated in 94% yield [^1H NMR ($CDCl_3$): δ 6.37 (d, 1 H, J = 3.0 Hz), 2.78 (s, 3 H), 1.44 (s, 3 H)], was different from the isomeric (mass spectrum) product we had obtained from the tin coupling sequence. The similarities in the ^1H NMR spectra suggested that the two products were regioisomeric at C-5 and C-6. Our suspicion was confirmed by examination of the ^1H NMR spectra of the iodolactones obtained from these isomers.[4] This established that, in contrast to the zinc reaction which gave the expected coupling product 2, Ar = 1 naphthyl, the tin coupling sequence had led to the unexpected C-5 isomer 3, Ar = 1-naphthyl.

We have now shown by the following experiments (Scheme II) that the unexpected cine substitution leading to 3 takes place during the vinylstannane–aryl bromide coupling reaction. The enol triflate of *d*-camphor 4 gave a vinylstannane 5 with a vinyl *doublet* [δ 6.14 (d, J = 2.9 Hz)] in its ^1H NMR spectrum. Coupling of this stannane with bromobenzene gave a 91:9 mixture of isomers. The ^1H NMR spectrum of the major isomer 7 had a vinyl *singlet* at δ 6.02. In contrast, phenylzinc chloride coupling with 4 gave a *single* product 6, which had a vinyl *doublet* [δ 6.00

[‡] 1990–1991 N.I.H. National Research Service Awardee.

(1) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771. (c) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033. (d) McKean, D. R.; Parrinello, G.; Renaldo, A. F.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 422.

(2) During the preparation of this manuscript there appeared a report (Ennis, D. S.; Gilchrist, T. L. *Tetrahedron Lett.* **1989**, *30*, 3735) that palladium-catalyzed coupling of (1-bromovinyl)trimethylsilane with organozinc bromides gives mixtures of 1- and 2-substituted vinylsilanes. The possibility of directive influence of the trimethylsilyl group may, however, make this a special case.

(3) (a) McCague, R. *Tetrahedron Lett.* **1987**, *28*, 701. (b) Keenan, R. M.; Kruse, L. I. *Synth. Commun.* **1989**, *19*, 793.

(4) The iodolactone, mp 232–235 °C, corresponding to 3, Ar = 1-naphthyl [originating from methyl (2*S*)-(−)-2-*exo*-methyl-6-oxo-2-*endo*-bicyclo-[2.2.1]heptanecarboxylate, mp 48.5–49.5 °C, $[\alpha]^{24}_D$ −20.8 ° (*c* 3.2, EtOH)], showed an absorption in its ^1H NMR spectrum at δ 5.35 (d, $J_{1,6x}$ = 6.0 Hz), ascribed to the C6 exo hydrogen adjacent to the lactone oxygen. The iodolactone, mp 155–157 °C, derived from coupling product, 2, Ar = 1-naphthyl [originating from the (±)-oxobicycloheptanecarboxylic ester above, mp 62–63 °C], instead showed an absorption at δ 4.82 (d, $J_{5n,7s}$ = 2.6 Hz) ascribed to the C5 endo hydrogen α to the iodine. See: Ramey, K. C.; Lini, D. C.; Moriarty, R. M.; Gopal, H.; Welsh, H. G. *J. Am. Chem. Soc.* **1967**, *89*, 2401.

0002-7863/90/1512-7399$02.50/0 © 1990 American Chemical Society