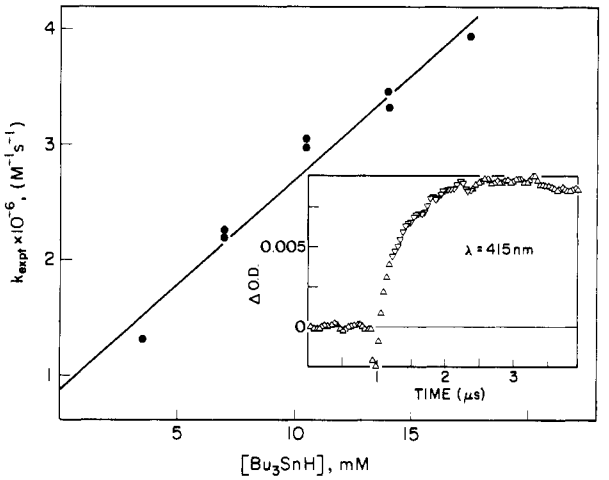

Figure 2. Experimental pseudo-first-order rate constant for the formation of $Bu_3Sn\cdot$ as a function of substrate concentration. (Insert) Trace obtained for [Bu_3SnH] = 0.007 M. The negative signal observed at the beginning of the buildup is due to luminescence, presumably originating from trace impurities.

Consistent with the mechanism of reactions 1-3, we observe that the transient signals are produced in a pseudo-first-order process following excitation (see insert in Figure 2). A plot of the pseudo-first-order rate constant (k_{expt}), derived from the buildup of the signal, as a function of [Bu_3SnH] yields k_2 from the slope while the intercept is determined by the lifetime of *tert*-butoxy in this solvent (Figure 2).[12] From this plot, we obtained $k_2 = 1.9 \times 10^8$ M^{-1} s^{-1} at 22 °C with di-*tert*-butyl peroxide as solvent. An analysis of the second-order decay traces mentioned before yields $2k_3/\epsilon l = 1.1 \times 10^7$ s^{-1} which, taking $2k_3 \sim 1.4 \times 10^9$ M^{-1} s^{-1},[3] and taking into consideration the optical path (l), leads to an estimate of the extinction coefficient as $\epsilon_{400} \sim 450$ M^{-1} cm^{-1}.

The rate constant for the reaction of *tert*-butoxy radicals with Bu_3SnH can also be obtained by using the method employed in earlier studies,[11,14] using diphenylmethanol as a probe. In this method, one monitors the kinetics of the formation of diphenylhydroxymethyl radicals as a function of the concentration of added reagent. The method is quite accurate because the intense signal from $Ph_2\dot{C}OH$ makes detection quite easy. This approach led to $k_2 = 2.2 \times 10^8$ M^{-1} s^{-1} at 22 °C in a 1:2 (v/v) mixture of benzene/di-*tert*-butyl peroxide as solvent. While the excellent agreement of the rate constant obtained by this method with the value obtained by direct detection (Figure 2) is not in itself definitive proof for the assignment given above, it certainly supports our conclusion that the species detected is the $Bu_3Sn\cdot$ radical. Similar experiments with Bu_3SnD (using diphenylmethanol as a probe) led to a kinetic isotope effect $k_H/k_D = 1.23 \pm 0.15$. The low value obtained is not unusual for fast exothermic reactions,[15] though in this particular case the involvement of charge transfer in the transition configuration could conceivably contribute to the low value observed.

The similarities in the behavior of alkoxy radicals and n-π^* ketone triplets have been widely documented in the literature;[16] in order to compare the behavior of these two species in the case of tin-hydrogen bonds, we examined the reaction of benzophenone triplets with Bu_3SnH. A kinetic study led to a rate constant for triplet quenching by the tin hydride of 2.9×10^8 M^{-1} s^{-1}, quite similar to the value observed in the case of *tert*-butoxy radicals. The transient spectrum immediately after triplet decay is consistent with a 1:1 mixture of $Ph_2\dot{C}OH$ and $Bu_3Sn\cdot$. A slower process, which is believed to reflect the addition of $Bu_3Sn\cdot$ to benzophenone, has also been detected and is currently under study. The rate constant measured for benzophenone is ca. three times smaller than the values reported for acetone[2b] and acetophenone;[19] at this point, it is not clear whether the difference simply reflects the sum of the errors of the various measurements (this seems unlikely) or whether it is the result of the higher triplet energy in the case of acetone and acetophenone.[2b,19]

The radical $Bu_3Sn\cdot$ is efficiently scavenged by oxygen.[17] From a study of the radical lifetimes in the presence of different oxygen concentrations, we obtained $k_{O_2} = 1.8 \times 10^9$ M^{-1} s^{-1} in benzene at 22 °C.[18] Finally, we have carried out a few preliminary experiments with hexabutylditin in the hope of monitoring reaction 4. Our results indicate that reaction 4 involves another inter-

$$t\text{-BuO}\cdot + Bu_6Sn_2 \rightarrow t\text{-BuOSn}Bu_3 + Bu_3Sn\cdot \quad (4)$$

mediate in addition to the stannyl radical; our spectroscopic evidence requires that this intermediate be produced by reaction of *tert*-butoxy with the ditin compound. Two explanations are possible; in one, the intermediate (that has a spectrum different from $Bu_3Sn\cdot$) would correspond to a pentacoordinate tin radical produced by radical addition at one of the tin centers. Such a radical would be similar to phosphoranyl and boranyl radicals detected in other S_H2 processes.[20] The other possibility is an electron-transfer process leading to the ditin radical cation which could then cleave to yield $Bu_3Sn\cdot$.

The mechanism of reaction in the case of the ditin compounds and the possibility of using laser photolysis to examine the reactions of tin radicals with halogen donors are currently under study.

Acknowledgments. Thanks are due to S. E. Sugamori for his technical assistance.

(12) A detailed kinetic treatment can be found in earlier papers.[11,13]
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(15) For example: Law, K. Y.; de Mayo, P.; Wong, S. K. *J. Am. Chem. Soc.* **1977**, *99*, 5813-5815. Johnston, H. S. "Gas Phase Reaction Rate Theory"; Ronald Press: New York, 1966; p 242.
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(18) The peroxide-benzene mixture was saturated with O_2/N_2 mixtures, and the tin substrate was added immediately before the experiment. The sample was stirred between pulses to avoid local depletion of oxygen.
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(21) Issued as NRCC-18219.

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Model Approach to Retinal Pigments. Remarkable Red Shift Due to Proximal Ammonium Ion

Sir:

The retinal pigments have attracted strong attention from chemists, especially because of the significant effect of such an apoprotein as opsin upon the physicochemical behavior of the chromophore, Schiff base of retinal. Absorption maxima of the bacteriorhodopsin or rhodopsins, for example, are spread over a wide range (432-575 nm) of wavelengths, depending on the nature of the proteins, suggesting that the tight binding of the chromophore to the protein affords electrostatic destabilization of the ground state and/or stabilization of the excited state of the chromophore[1] and special medium effects due to the high polarizability of the protein residue(s)[2] or conformational twisting

(1) (a) Sulkers, M.; Lewis, A.; Lemley, A. T.; Cookingham, R. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 4266. (b) Mathias, R.; Stryer, L. *Ibid.* **1976**, *73*, 2169.

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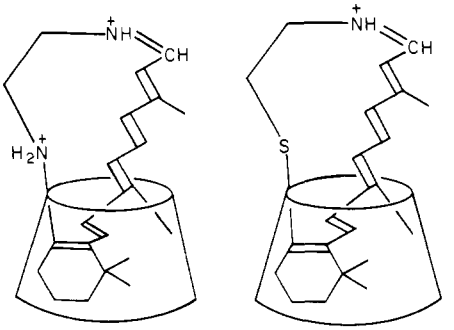
Table I. Absorption Maxima of Retinal Pigment Models

compd	λ_{max}, nm		
	aq	org	aq, CD inclusion
1	497	476[b]	
2	445	460[b]	
3	471	470[a,b]	444
4[a]	450	450[a]	430
5	486	488[b,c]	
6	455	453	432

[a] In MeOH. [b] In ethylene glycol. [c] Because of its very rapid hydrolysis, the electronic spectra were taken by means of a stopped-flow, rapid-scanning spectrophotometer.

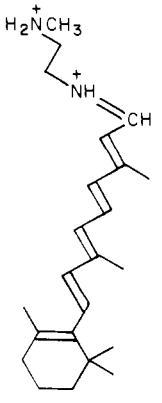
of the chromophore.[3] However, none of these effects are observable separately in the real retinal pigments, and some systematic model approach should be warranted.[4]

Cyclodextrins show the unique characteristic of strong hydrophobic binding in water,[5] providing for a conformationally stable (not destroyed by thermal motion) environment and a significant recognition site in multirecognition systems.[6] In the first successful application of cyclodextrins to the retinal pigment problem, a remarkable red shift (λ_{max} 497 nm) such as that for native rhodopsin was observed for **1** in aqueous solution.[7] Now



1

2



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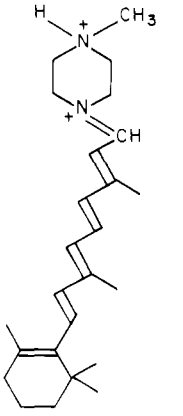
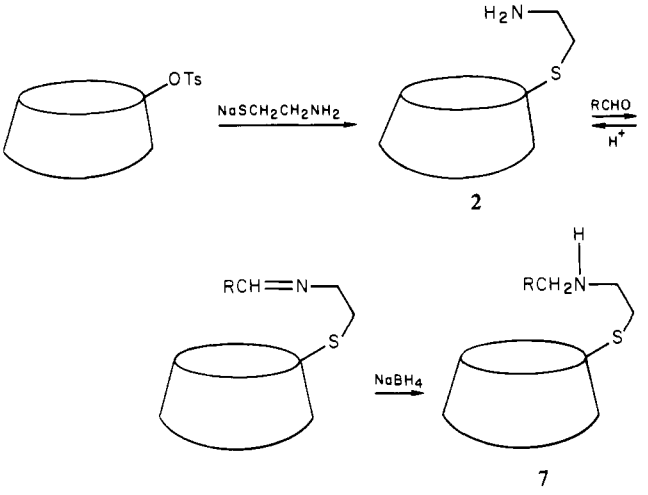


5

we report that the ammonium ion in proximity to the protonated azomethine group of the chromophore causes the remarkable red shift.

Treatment of $H_2NCH_2CH_2SH$ (30 mmol) with β-cyclodextrin tosylated at the primary position (1 mmol) in 50 mL of aqueous ethanol (pH 12) at 60 °C for 16 h gave ω-aminoethyl β-cyclodextryl sulfide, (**2**) in 75% yield. NMR (D_2O–NaOD) signals



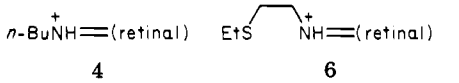
RCHO = retinal

centered at δ 5.4, 4.2, and 3.2 and other spectra are satisfactory. The structure of the Schiff base of **2** was ascertained by the isolation of retinylaminocyclodextrin (**7**) after treatment with $NaBH_4$.

As previously reported,[7] **1** shows a remarkable red shift. In marked contrast to **1**, the corresponding sulfur analogue (**2**) does not show such a remarkable red shift in aqueous solution at the same pH, demonstrating that the twist induced by the double-tight binding (the hydrophobic binding and the Schiff base formation) of the chromophore can not be the sole origin of the red shift (Table I).

In order to gain further insight into this red shift, the cisoid diammonium analogue (**5**) was prepared. Thus, *N*-methylpiperazinium dichloride (0.1 mmol) was treated with retinal (0.1 mmol) in 2 mL of absolute methanol at room temperature for 4 h to give the *N'*-methylpiperazinium chloride of retinal (**5**). The IR (KBr) spectrum of **5** showed the absorptions at 1650, 1550, 1450, 1245, 1110, and 970 cm^{-1}.

Comparison of absorption maxima of **1**–**5** (see Table I) allows the following conclusions to be drawn: (a) Electrostatic destabilization of the ground state causes a red shift as is seen from **3** (transoid N^+) – **4** (none) = +20 nm and **5** (cisoid N^+) – **4** (none) = +36 nm. (b) Inclusion into the CD cavity in aqueous solution



4 **6**

causes a blue shift as is seen from **3**·CD – **3** (free) = –27 nm, **4**·CD – **4** (free) = –20 nm, and **6**·CD – **6** (free) = –23 nm. Average = –23 nm. (c) Tight binding via double recognition (Schiff base formation and inclusions in CD) causes red shift as is seen from **1** and **2**. For compound **1**, expected λ = 476 (organic) – 23 (inclusion) = 453, and Δ**1** = observed λ (aqueous) – expected λ = +44 nm, where a reasonable assumption was made that λ in water was practically the same as λ in an organic solvent for a free chromophore. For compound 2, expected λ = 460 (organic) – 23 (inclusion) = 437, and Δ**2** = observed λ (aqueous) – expected λ = +8 nm, where Δ**2** may be due to the twist, although small, induced in the chromophore by the tight binding but Δ**1** seems to be more complex. A part of the red shift induced in **1** seems to be the electrostatic destabilization of the ground state, the magnitude of which is estimated in (a). The simplest assumption is that the transoid destablization (+20 nm) must induce a considerable twist (from molecular model) of the chromophore due to the double-tight binding. Thus, the following simple estimation is made—Δ**1** = +44 nm = +20 (transoid effect) + 24 nm (induced twist). However, the actual situation does not seem to be so simple, and most probably, some conformational change takes place from

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(3) (a) Honig, B.; Warshel, A.; Karplus, M. *Acc. Chem. Res.* **1975**, *8*, 92. (b) Yoshizawa, T.; Wald, G. *Nature (London)* **1963**, *197*, 1279.
(4) A remarkable effect of CO_2^- was also pointed out; Sheves, M.; Nakanishi, K.; Honig, B. *J. Am. Chem. Soc.* **1979**, *101*, 7086.
(5) Bender, M. L.; Komiyama, M. "Chemistry of Cyclodextrin"; Springer-Verlag: New York, **1978**.
(6) (a) Tabushi, I.; Kuroda, Y.; Shimokawa, K. *J. Am. Chem. Soc.* **1979**, *101*, 1614. (b) Breslow, R.; Overman, L. E. *Ibid.* **1970**, *92*, 1075. (c) Tabushi, I.; Shimizu, N.; Sugimoto, T.; Shiozuka, M.; Yamamura, K. *Ibid.* **1977**, *99*, 7100.
(7) Tabushi, I.; Kuroda, Y.; Shimokawa, K. *J. Am. Chem. Soc.* **1979**, *101*, 1614.

Table II. Effect of Solvent and Counteranion

compd	λ_{max}, nm MeOH	λ_{max}, nm $CHCl_3$ (1% EtOH)
3 (transoid)	470 (Cl^-)	496 (Cl^-)
	471 (ClO_4^-)	510 (ClO_4^-)
5 (cisoid)	480 (Cl^-)	500 (Cl^-)
	478 (ClO_4^-)	526 (ClO_4^-)

transoid to some intermediary state between transoid and cisoid to reduce the serious twist involved in transoid by the sacrifice of the electrostatic effect.

Also an environmental effect seems to be operating to some extent, which we conclude by considering that in **1** the two N^+ interact in a somewhat hydrophobic environment which may enhance the interaction energy. The effect of solvent was investigated together with the effect of a counteranion to ascertain this mechanism (Table II). In such an apolar solvent as $CHCl_3$, the red shift became very significant as expected, especially for the cisoid chromophore, and this red shift was more significant when the cation was more "naked" (see Table II). This enormous enhancement of the electrostatic interaction in a less polar medium is also seen in the specific phase transfer of a hydrophilic anion by a lipophilic ammonium ion.[8]

Thus, a conclusion may be drawn that a moderate red shift is observed for the protonated Schiff base with a proximal ammonium ion, and the shift is further enhanced either (i) when the system has a loose counteranion and especially is embedded into the less polar environment or (ii) when the system is restricted in its motion by the binding and both the electrostatic destabilization and the unfavorable twist of the conjugated chromophore are operating. Interestingly, the latter mechanism is important even in aqueous solution and without any loose counteranion.

The present situation combined with the electrostatic stabilization of the excited state by a proximal anion[4] seem to be closely correlated with bacteriorhodopsin[9] and rhodopsin. An attempted a priori general estimation of the red shift is now under way.

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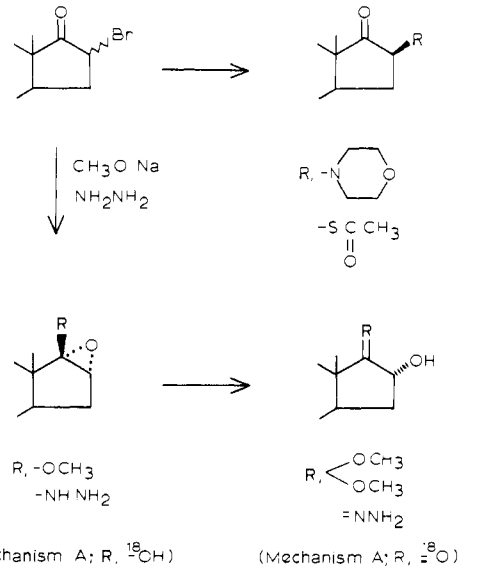
Controlled Alkaline Hydrolysis of 16-Bromo-17-keto Steroids without Ketol Rearrangement and Its Reaction Mechanism

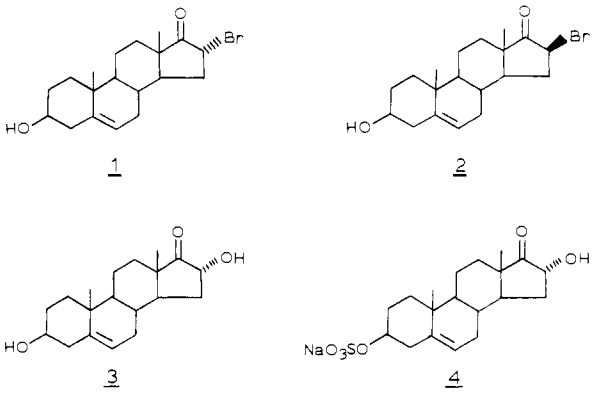
Sir:

From the observations[1,2] on the relative stability of steroidal 16,17-ketols toward alkali hydroxide and the unsuccessful attempts to isolate thermodynamically unstable 16-hydroxy 17-ketone, it has been considered impossible to isolate the ketol by hydrolysis of 16-bromo 17-ketone. Two types of reactions of 16-bromo 17-ketone with other nucleophiles have been known, the direct displacement of bromine with amines[3] and thioacetate,[4] leading

Scheme I



to formation of the 16β-substituted steroids, and the attack of methoxide ion[2,5] and hydrazine[6] at the 17-carbonyl function, leading to 16α-hydroxy derivatives via 16α,17α-epoxide intermediates (Scheme I). We wish to report the controlled stereospecific alkaline hydrolysis, with pyridine as a buffer,[7] of 16α-bromo 17-ketone **1** to 16α-hydroxy 17-ketones **3** and **4** and elucidation of the reaction mechanism by use of deuterium- and ^{18}O-labeling experiments. The isotope experiments showed the mechanism to be nucleophilic displacement of bromine of the 16β-bromo isomer **2** by hydroxide ion and refutes the putative 16α,17α-epoxide mechanism.



The dynamic aspects of equilibrium between the bromo ketones **1** and **2**[8] and of production of the 16α-hydroxy 17-ketone **3** are shown in Table I.[9] Treatment of **1** with 0.012 equiv of NaOH in aqueous pyridine at room temperature did not cause any change,

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(2) Hassner, A.; Catsoulacos, P. *J. Org. Chem.* **1966**, *31*, 3149.
(3) (a) Hewett, C. L.; Savage, D. S. *J. Chem. Soc. C* **1966**, 484. (b) Hassner, A.; Catsoulacos, P. *J. Org. Chem.* **1967**, *32*, 549.
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(6) Catsoulacos, P.; Hassner, A. *J. Org. Chem.* **1967**, *32*, 3723.
(7) When MeOH, EtOH, and dioxane were used as a solvent, the formation of the rearranged product, 3β,17β-dihydroxy-5-androsten-16-one, together with the ketol **3** were observed in 5–20% yield with 1.2 equiv of NaOH and 2-h reaction time.
(8) The 16α-bromo 17-ketone **1** was prepared according to the paper: Numazawa, M.; Osawa, Y. *Steroids* **1978**, *32*, 519. Upon a fractional crystallization of the mother liquor of **1**, the 16β-bromo isomer **2** was obtained; mp 171–173 °C.
(9) The bromo ketones **1** and **2** and the ketol **3** were quantified by the peak areas corresponding to both the C-16 proton and the C-18 angular methyl of ^1H NMR spectra of the reaction mixtures without isolation. ^1H NMR ($CDCl_3$): **1** δ 0.90 (s, 3 H), 4.57 (t, 1 H); **2** δ 1.09 (s, 3 H), 4.14 (t, 1 H); **3** δ 0.96 (s, 3 H), 4.37 (t, 1 H).

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