measurements of $1/\tau_2$ were carried out on a Durrum stopped-flow spectrophotometer. Determinations of $1/\tau_1$ and initial rate measurements were carried out on a Gilford Model 2000 spectrophotometer. All relaxation times reported in Tables I, II, and IV represent averages of three (in a few cases two) determinations.

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The Kinetics of Carbonium Ion Formation from Anhydroretinol

Vernon C. Bulgrin* and George L. Lookhart

Contribution from the Department of Chemistry, University of Wyoming, Laramie, Wyoming 82071. *Received February 22, 1974*

Abstract: The initial stages of the reaction between anhydroretinol and anhydrous hydrogen chloride in 1,2-dichloroethane were studied using stopped-flow spectrophotometry. The results are explained in terms of a five-step mechanism, involving two carbonium ions, with the anhydroretinylic cation forming much more rapidly than the more stable retinylic cation. Evidence is presented indicating that the former cation may be a precursor of the latter.

Highly conjugated polyenes when treated with acid generally give rise to absorption maxima in the visible region. These absorptions have been attributed to charge transfer or to carbonium ion formation. Wasserman[1] showed by conductance measurements that, in the case of protonic acids, carbonium ions are present, and presumably are responsible for the color observed.

The carbonium ions from *all-trans*-retinol and related compounds have been of particular interest because their spectral properties are similar to those of visual pigments, and they may be meaningful as models of visual pigments. Blatz and Pippert[2] showed the retinylic cation (Figure 1,II) to be the only cation observed on protonating *all-trans*-retinyl acetate or retinol; their results also demonstrated that λ_{max} of the cation is only a weak function of solvent and independent of the nature and concentration of the protonic acid. Protonation of anhydroretinol (I) gave rise to a longer wavelength absorption, which was assigned to the anhydroretinylic cation (III) by Blatz on the basis of protonation at the C_{15} position.[3] (Protonation at the other most likely point of attack, C_4, would give rise to the retinylic cation.) Symmetry considerations also favored the assignment of the longer wavelength absorption to the anhydroretinylic cation. Baumgartner[4] observed both cations to form when anhydroretinol is protonated by HCl in 1,2-dichloroethane. It could not be determined which of the cations formed first.

A kinetic study of the rate of formation of carbonium ions from anhydroretinol was undertaken, in order to establish the mechanism of the reaction, to ascertain the relative rates of formation of the cations, to indicate the relative ease of protonation at the C_4 and C_{15} positions of anhydroretinol, and to give some indication as to the relative stabilities of the two cations.

The reaction was studied at 10.0, 21.2, and 30.0°, using HCl as protonating agent in 1,2-dichloroethane solvent. Only the initial (up to several minutes) portion of the reaction was studied in detail, since it has been shown by Sorenson,[5] Deno,[6] and Blatz[7] that cyclization and polymerization of such carbonium ions take place at longer times. In all of the studies, a very large excess of HCl was used in order to achieve first-order kinetics. The concentration of HCl was varied to obtain the HCl dependency.

Results and Discussion

Typical action spectra taken on the Cary 14R at −30° are shown in Figure 2. During the time period of these observations (0.5–4 min), it appears that the first-formed anhydroretinylic cation (~620 nm) is decreasing slightly with time, while the retinylic cation (~580 nm) is increasing.

Typical reaction profiles from the stopped-flow data are shown in Figure 3, which also illustrates the effect of temperature. The data are plotted as absorbance *vs.* log time for convenience. Allowing for some overlap in the spectra of the two cations, there appear to be four regions in time corresponding to four rate processes. These are labeled ϕ_1, ϕ_2, ϕ_d, and ϕ_3, with overlap in rates occurring between ϕ_2 and ϕ_d. ϕ_2 and ϕ_3 were assigned to the formation of anhydroretinylic and retinylic cations, respectively, ϕ_1 to the formation of a precursor which absorbs rather broadly over the 580–620-nm region, and ϕ_d to a process involving the disappearance of the anhydroretinylic cation. The ϕ_2, ϕ_d, and ϕ_3 assignments were made after comparing the stopped-flow data with the Cary 14 action spectra. The time scale of the action spectra suggests a correspondence with processes occurring in the ϕ_d–ϕ_3 region of the stopped-flow data. The ϕ_1 assignment, that of a reaction leading to a precursor to the carbonium ions,

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[1] A. Wasserman, *J. Chem. Soc.*, 245 (1954).

[2] P. E. Blatz and D. L. Pippert, *J. Amer. Chem. Soc.*, **90**, 1296 (1968).

[3] The numbering system is that used in the carotenoid literature.

[4] N. R. Baumgartner, Ph.D. Dissertation, University of Wyoming, 1969.

[5] T. S. Sorenson, *Can. J. Chem.*, **43**, 2744 (1965).

[6] N. C. Deno, C. U. Pittman, and J. O. Turner, *J. Amer. Chem. Soc.*, **87**, 2153 (1965).

[7] P. E. Blatz and D. L. Pippert, *Tetrahedron Lett.*, 1117 (1966).

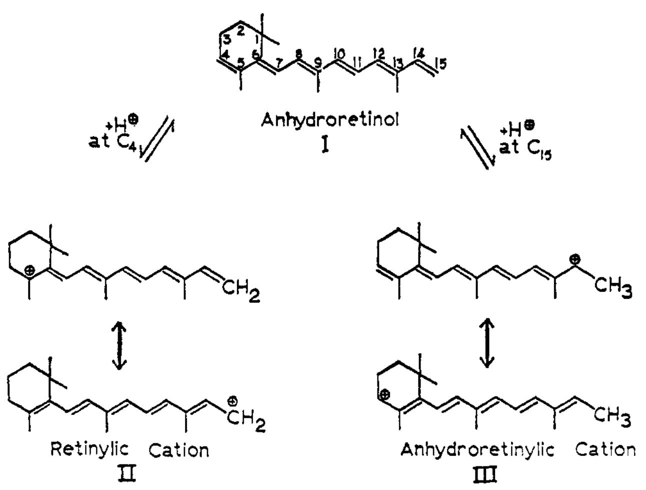

Figure 1. Carbonium ions from anhydroretinol.

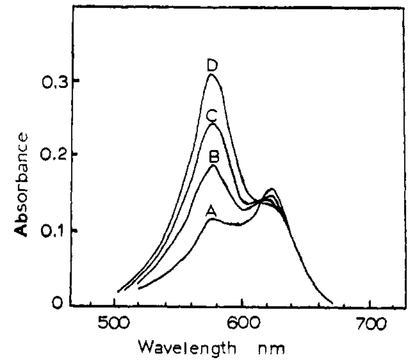

Figure 2. Action spectra, Cary 14R, −30°. Anhydroretinol concentration, 8 × 10^{-4} *M*; HCl concentration, about 0.01 *M*. Curves A, B, C, and D taken at 0.5, 1, 2, and 4 min, respectively.

was more difficult, but was made on the basis that the process was observable at both 580 and 620 nm with identical rate constants within the experimental error of about ±10%. A detailed analysis of each region was then made.

ϕ_1 Region. The time scale of the ϕ_1 reaction was such as to push the stopped-flow instrument to the limit of its capabilities. Nevertheless, good first-order plots were obtained from both the 580- and 620-nm data, with the first-order rate constants at the two wavelengths agreeing at each temperature and HCl concentration to within 10% or less. Plots of reciprocal rate constants ϕ_1 *vs.* reciprocal HCl concentration are linear (Figure 4), consistent with a two-step process

$$\mathrm{A} + \mathrm{HCl} \underset{\text{fast}}{\overset{K}{\rightleftharpoons}} \mathrm{C} \underset{\text{slow}}{\xrightarrow{k_1}} \mathrm{AHCl}$$

where A is anhydroretinol, C an intermediate of unknown structure, and AHCl an anhydroretinol–HCl species absorbing rather weakly and broadly over the 580–620-nm region. It is assumed that in the AHCl species, taken to be the immediate precursor to the anhydroretinylic cation, the HCl molecule is attached at the C_{15} end of the anhydroretinol molecule, perhaps as a π complex as discussed later. In the mechanism above, k_1 is the reciprocal of the intercepts in Figure 4; the ratio of the intercept to the slope gives *K*. Values of k_1 and *K* are given later.

ϕ_2–ϕ_d Region. First-order rate constants were determined from the 620-nm data in this region, where overlap of two rate processes occurs. The method for separating the two rate constants ϕ_2 and ϕ_d is well known. It involves obtaining ϕ_d (the smaller rate constant) from the slope of a plot of ln ($A - A_\infty$) *vs.* time at longer times as shown in Figure 5a. Here, *A* is the observed absorbance at time *t* and A_∞ the absorbance (very nearly constant) at the completion of the ϕ_d process. The straight line is extrapolated back to zero time, and values of A_{calcd} were obtained for the early (ϕ_2) part of the region. Plots of ln ($A - A_{\text{calcd}}$) *vs.* time are linear, as shown in Figure 5b, with slopes equal to negative ϕ_2.

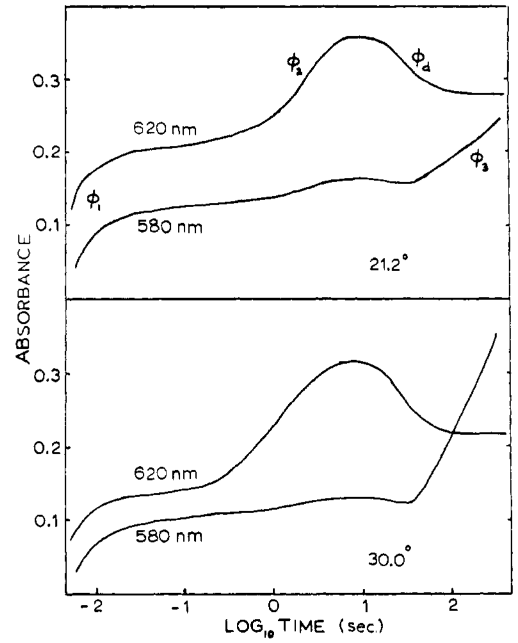

Figure 3. Reaction profile, stopped-flow data. Anhydroretinol concentration, 7.45 × 10^{-4} *M*; HCl concentration, 0.0144 *M*.

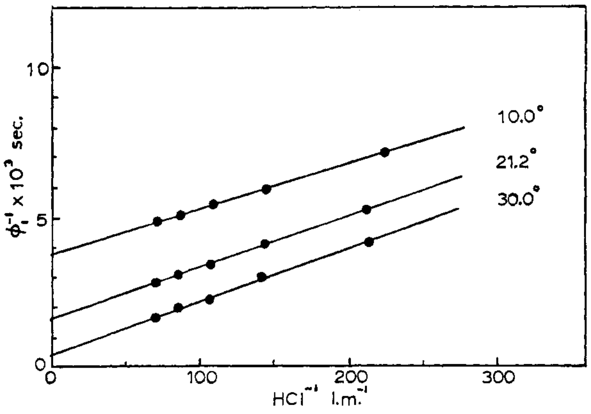

Figure 4. Reciprocal first-order rate constant, ϕ_1 *vs.* reciprocal HCl. Intercepts are k_1^{-1}; slopes/intercepts are *K*.

Figure 6 shows plots of ϕ_2 *vs.* the concentration of HCl at the three temperatures studied, demonstrating a first-order HCl dependency. The slope of each line is k_2, the rate constant for the reaction of the AHCl complex with HCl to give the anhydroretinylic cation. In the solvent used the anhydroretinylic cation probably exists as an ion pair with chloride, *i.e.*, $\mathrm{AH^+Cl^-}$. Thus, the formation of the anhydroretinol cation from anhydroretinol requires two HCl molecules. This is in

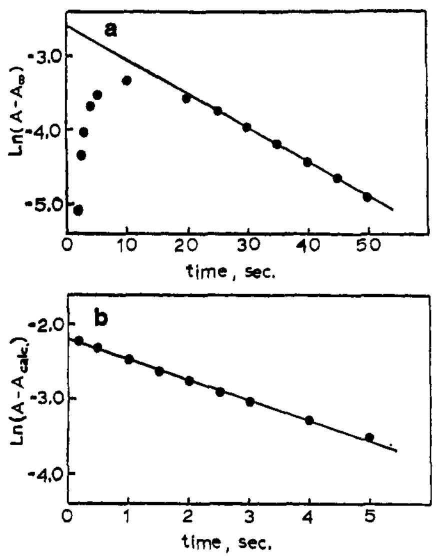

Figure 5. First-order plots in ϕ_2–ϕ_d region. Figure 5b corresponds to first 5 min of 5a.

agreement with the observation that in hydrohalogenation of olefins,[8] involving formation of carbonium ions, two molecules of HCl are required to form the carbonium ion intermediate, the first leading to the formation of an HCl π complex to the olefin (as in the ϕ_1 step of this reaction), the second removing the Cl^- ion as (presumably) HCl_2^- (as in the ϕ_2 step of this reaction). In the anhydroretinol reaction, however, it is possible to observe, spectroscopically, the formation of the carbonium ion, because of the conjugated polyene system leading to an absorption in the visible region.

The ϕ_d rate constants obtained were found to be nearly independent of HCl concentration. For example, although there appeared to be a slight increase in ϕ_d with HCl, at 30°, for example, the average deviation of ϕ_d for all five HCl concentrations over a threefold change was only $\pm 5\%$. Therefore, ϕ_d was taken to be k_d, the HCl-independent rate constant for the disappearance of the anydroretinylic cation, possibly *via* cyclization or polymerization as mentioned earlier.

It appears that a suitable mechanism describing the ϕ_1, ϕ_2, and ϕ_d regions is

$$A + HCl \underset{}{\overset{K}{\rightleftharpoons}} C \xrightarrow{k_1} AHCl \xrightarrow{k_2 HCl} AH^+Cl^- \underset{k_{-d}}{\overset{k_d}{\rightleftharpoons}} P$$

where P is a cyclization or polymerization product. Evidence for the reversibility of the last step is presented later.

ϕ_3 Region. A relatively slow zero-order process was found from the 580-nm data in this region, plots of absorbance *vs.* time giving very good straight lines. Figure 7 shows plots of ϕ_3 *vs.* the hydrogen chloride concentration, the resulting straight lines indicating a first-order dependency. The slope of each line is k_3, the rate constant for the formation of the retinylic cation (III). Zero-order kinetics under the conditions of the experiment (large excess of HCl) would be expected if the precursor of the retinylic cation were in very nearly a steady-state concentration, or if the process were photochemical. The latter was ruled out by the observation that the rate of growth of the 580-nm peak was the same whether irradiation in the stopped-flow spectrophotometer was continuous or intermittent. An approximate steady state in the anhydroretinylic cation in this region is indicated by the Cary action spectra (Figure 2). Therefore, one conclusion is that the retinylic cation is formed by attack of HCl at the C_4 position of the anhydroretinylic cation, with subsequent or simultaneous elimination of a proton from C_{15}. Alternatively, the precursor to the retinylic cation could be an earlier intermediate such as C or AHCl. No way has been found to distinguish between these alternatives, although the latter would seem to require a higher degree of reversibility in the mechanism than is observed. A third possibility is that the precursor is the unknown reaction product P of the anhydroretinylic cation.

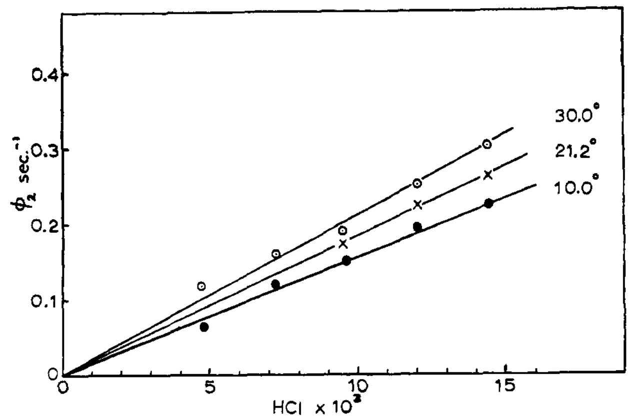

Figure 6. Plot showing first-order HCl dependency for ϕ_2.

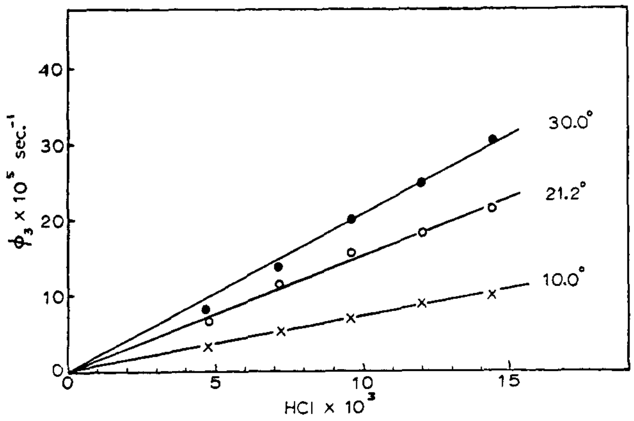

Figure 7. Plot showing first-order HCl dependency for ϕ_3.

A mechanism which is consistent with the experimental observations is

$$\begin{tikzcd}
A + HCl \arrow[r, shift left, "K"] & C \arrow[l, shift left] \arrow[r, "k_1"] & AHCl \arrow[r, "k_2(HCl)"] & AH^+Cl^- \arrow[r, shift left, "k_d"] \arrow[d, "k_3(HCl)"] & P \arrow[l, shift left, "k_{-d}"] \\
 & & & RH^+Cl^- &
\end{tikzcd} \quad (1)$$

The constants for this mechanism, as well as the thermodynamic parameters, are given in Table I.

Why the retinylic cation appears to be formed primarily by HCl attack on the anhydroretinylic cation rather than on anhydroretinol is not understood at this time. The latter case would be expected to give first-order kinetics rather than the zero order observed.

The necessity for reversibility of the k_d step is indicated from the observed near steady state in AH^+Cl^- and the accompanying zero-order formation of RH^+Cl^-.

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(8) F. R. Mayo and C. Walling, *Chem. Rev.*, 27, 351 (1940).

Table I. Constants[a] and Thermodynamic Parameters[b] for the Mechanism in Eq 1

Constant[a]	Temp, °C 10.0	 21.2	 30.0	$\Delta H°$, kcal	$\Delta S°$, cal mol^{-1} deg^{-1}
K	250	90	39	−19.3	−57
				$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, cal mol^{-1} deg^{-1}
k_1	260	640	1500	15.7	85
k_2	15.7	18.4	21.1	4.9	43
$k_d + k_{-d}$	0.026	0.045	0.054	6.3	35
k_3[c]	0.0074	0.0154	0.0210	9.8	44

[a] K in l. mol^{-1}; k_1 and k_d in sec^{-1}; k_2 and k_3 in M^{-1} sec^{-1}. [b] All ln (K or k) *vs.* T^{-1} plots gave good straight lines except for the $\phi_d(= k_d + k_{-d})$ plot which showed curvature, as might be expected for the sum of two rate constants. [c] Thermodynamic parameters for k_3, although listed here, have no absolute significance in that the k_3 determined is a product of a second-order rate constant times an extinction coefficient times a cell path length times the concentration of a steady-state precursor.

It is also likely that the k_1, k_2, and k_3 steps are to some degree reversible. The major evidence in support of this is the fact that anhydroretinol is prepared (albeit in very small yields) by action of HCl on retinol or retinyl acetate. Preliminary stopped-flow experiments following the protonation of retinol indicate that only one carbonium ion, the retinylic cation, is present in observable quantity early in the reaction; Cary data, however, indicate a small amount of the anhydroretinylic cation is present in the later stages. Thus, it appears that the retinylic cation is capable of being converted to anhydroretinol, probably *via* the anhydroretinylic cation. The stopped-flow data on retinol cannot directly confirm this, however, because of the difficulty of observing a small amount of anhydroretinylic cation (620 nm) in the presence of a very large amount of retinylic cation (590 nm), due to the (small) amount of overlap in the peaks.

The zero-order formation of the retinylic cation, coupled with the near steady-state in anhydroretinylic cation in this (ϕ_3) time region, seems to be rather compelling evidence that the anhydroretinylic cation is a necessary intermediate in the formation of retinylic cation from anhydroretinol. That two molecules of HCl are required to form the anhydroretinylic cation is consistent with the generally accepted mechanism of hydrohalogenation of olefins. Other aspects of the reaction are more difficult to explain, for example, the nature of the intermediate C, and the apparent lack of direct protonation of anhydroretinol to give retinylic cation.

It is concluded, however, that direct protonation of anhydroretinol at the C_{15} position is kinetically favored over protonation at C_4. Conversely, the retinylic cation is ultimately formed in much larger quantity than the anhydroretinylic, and therefore appears to be more stable than the latter. The mechanism proposed also explains why the yields of anhydroretinol obtained on protonating retinol or retinyl acetate are always very low.

Experimental Section

Polyenes. *all-trans*-Retinyl acetate was obtained in crystalline form from Sigma Chemical Co. in vacuum-sealed 100-g ampoules. After opening the ampoules, the crystals were dried under vacuum for 3 hr and stored under dry nitrogen at −30° in total darkness. *all-trans*-Anhydroretinol was prepared from retinyl acetate by a modication of the procedure of Shantz;[9] 10 g of retinyl acetate was dissolved in 500 ml of anhydrous ethanol, and 250 ml of an approximately 3% solution of HCl in anhydrous ethanol was added. The reaction mixture was neutralized after 5 min with a saturated aqueous solution of sodium bicarbonate. This time of reaction was selected, by monitoring the uv spectrum at 1-min intervals, as that giving the maximum concentration of the desired material. The mixture was extracted with low-boiling petroleum ether; the extracts were combined, washed with water, dried over anhydrous $MgSO_4$, and reduced in volume. This was followed by twice chromatographing under N_2 in dim red light on a 4 × 30 cm column packed with 6% water-deactivated Woelm neutral alumina, using petroleum ether as eluent. The second band through the column was the *all-trans*-anhydroretinol. The first and third (minor) bands have been ascribed to cis isomers.[10] The fractions with the proper relative peak heights[11] were combined, reduced in volume (under dry nitrogen) to near oil, and stored in total darkness at −30°. After 3 days, crystallization was complete; the yellow-orange crystals were dissolved in a small amount of petroleum ether; after reduction in volume, crystallization was complete in 24 hr at −30°. The crystals were rinsed with a small amount of very cold petroleum ether, dried under vacuum for 8 hr, and stored under dry nitrogen in the dark at −30°. The yield was 500 mg of yellow-orange crystals melting at 75.5–76.5°. Solutions of the crystals in 1,2-dichloroethane showed the characteristic triple peaks at 356, 375, and 398 nm, with relative peak heights of 0.68, 1.00, and 0.90, respectively. The molar absorptivity for the 375-nm peak was found to be 7.83×10^4 (±0.53, average deviation for 16 preparations). Oroshnik[12] reported a value of 7.8×10^4 in ethanol. Solutions of anhydroretinol in 1,2-dichloroethane were found to be stable for up to a week if stored in the dark under dry nitrogen at −30°.

Solvents. 1,2-Dichloroethane was washed several times with concentrated sulfuric acid, then with water, a saturated solution of sodium bicarbonate, and water again. After successively drying with anhydrous $MgSO_4$ and P_2O_5, it was distilled under dry nitrogen from P_2O_5. Petroleum ether was purified in a similar manner. The solvents, after purification, were stored in glass under dry nitrogen.

Hydrogen Chloride Solutions. Solutions of hydrogen chloride in 1,2-dichloroethane were prepared by passing anhydrous HCl from Matheson Gas Products through Drierite and then through the solvent. The solution was analyzed titrimetrically and used as a stock solution for preparing the standard HCl solutions used in the rate determinations.

Action Spectra. The action spectra shown in Figure 3 were obtained on the Cary 14R in the following way. Two milliliters of an 8.5×10^{-4} M solution of anhydroretinol in 1,2-dichloroethane was placed in one of two matched 10-mm Suprasil quartz cells, pure solvent in the other. The cells were cooled to −30° and a small amount of HCl solution (constituting a large excess of HCl) was added to the first. The spectrum was rapidly scanned repetitively until the peaks began to disappear.

Rate Determinations. The rate of the reaction was studied using a Durrum-Gibson D-110 stopped-flow spectrophotometer, equipped with a 20-mm path length Kel-F cell and Kel-F flow components. Temperature was maintained at 10.0, 21.2, and 30.0° to within ±0.1° by means of a thermostated bath, using anhydrous ethanol as circulating liquid. The flow system, including all syringes, was thoroughly rinsed with dry acetone, anhydrous ethanol, and purified anhydrous 1,2-dichloroethane. The concentration of anhydroretinol used was 7.45×10^{-4} M (after mixing in the stopped-flow apparatus); concentrations of HCl used (after mixing) were 0.0048, 0.0072, 0.0096, 0.0120, and 0.0144 M. For each concentration at each temperature, the reaction was followed at 580 nm and repeated at 620 nm, corresponding to the absorption peaks of the retinylic and anhydroretinylic cations, respectively. All runs were made in dim red light.

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(9) E. M. Shantz, J. D. Cawley, and N. D. Embree, *J. Amer. Chem. Soc.*, **65**, 901 (1943).

(10) R. C. Christensen and B. E. Kohler, *Photochem. Photobiol.*, **18**, 293 (1973).

(11) E. M. Shantz, *J. Biol. Chem.*, **182**, 515 (1950).

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