On the Amine-Catalyzed Isomerization of Vitamin A Aldehydes

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The thermal, nonphotochemical isomerization of vitamin A aldehydes plays a central role in vertebrate and invertebrate vision as well as in light-driven proton pumping in certain halophilic bacteria. In vertebrate vision, 11-*cis*-retinal bound to opsin via a protonated Schiff base (rhodopsin) is photochemically isomerized to its all-trans congener, which then is hydrolyzed to form *all-trans*-retinal and opsin.[1] In order for rhodopsin regeneration to occur, *all-trans*-retinal, or a derivative thereof, must be thermally isomerized to its 11-cis congener. In certain halophilic bacteria, a photochemical transformation of the all trans to the 13-retinylidine Schiff base (probably in the protonated form), coupled with a thermal back reaction, is of importance in the proton pumping cycle.[2] Therefore, the mechanism(s) by which the retinals and their Schiff bases are thermally interconverted is of great importance.

Model systems informative of how the isomerization reaction might proceed at ambient temperature are of great interest. This is because 11-*cis*-retinaldehyde is thermally isomerized with an activation energy of ca. 25 kcal/mol.[3] A lowering of the activation energy by only approximately 5 kcal/mol would allow the isomerization reaction to proceed at room temperature in the absence of enzymatic catalysis. An important question here is how to achieve this stabilization of the transition-state complex and thereby effect the rapid isomerization of the retinals. One possibility, of course, is Schiff base formation. A relatively recent article reported that Schiff base formation between 13-*cis*-retinaldehyde and *n*-butylamine occurred rapidly and that smooth isomerization of the Schiff base occurred at room temperature.[4] It was also reported that the rate was strongly catalyzed by added triethylamine ($t_{1/2}$ = 7 s) and that acid catalysis led to a variety of competing pathways not including double-bond isomerization.[4] We have reinvestigated the problem and obtained results quite opposite to those reported in the article mentioned above.[4] We found that unprotonated retinal Schiff bases are thermally isomerized very *slowly* at room temperature, a process made *slower* by the addition of base. Moreover, the isomerization of the retinal Schiff bases is markedly *accelerated* by HCl.

Initial experiments were performed according to the published method.[4] *n*-Butylamine was allowed to react with 13-*cis*-retinaldehyde in chloroform and the solution was followed spectrophotometrically at 25 °C (Figure 1). The spectral changes observed were similar to those reported, although a greater OD increase was observed at 363 nm in the previous publication.[4] The ultraviolet/visible spectral changes, however, have nothing to do with isomerization as reported, and indeed Schiff base formation does not occur in 10 min but instead required at least 5 h to go to completion. The spectral changes occurring here are those for the conversion of the aldehyde to the Schiff base and have nothing to do with double-bond isomerization. This was shown in the following way: 40 mL of a solution of 14 μM 13-*cis*-retinal in chloroform that had been passed through an alumina column was made 100 mM in *n*-butylamine at 25 °C. The extent of Schiff base formation was determined by adding excess trifluoroacetic acid to an aliquot of the solution and measuring its ultraviolet/visible spectra. The protonated Schiff base absorbs at 450–460 nm, and the hydrogen-bonded starting aldehyde absorbs at

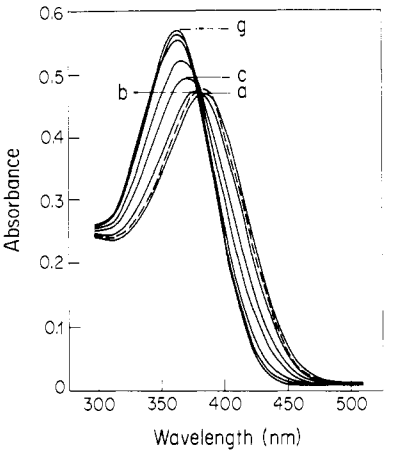

Figure 1. UV spectra showing the reaction between 13-*cis*-retinal (14 μM) and *n*-butylamine (100 mM) at 25 °C in chloroform: 13-*cis*-retinal (----); subsequent curves indicate 13-*cis*-imine formation. Time after addition of amine (min): (a) 1, (b) 52, (c) 122, (d) 183, (e) 271, (f) 324, (g) 381.

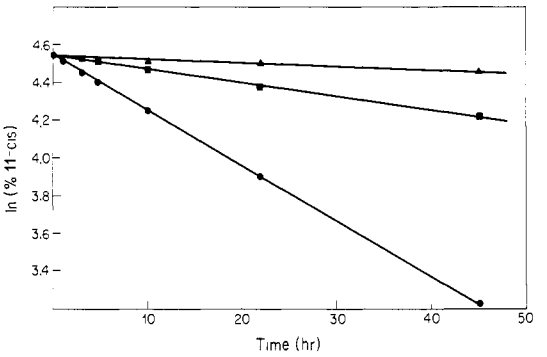

Figure 2. Inhibition of 11-*cis*-imine isomerization by amines. A solution of 11-*cis*-imine (12 μM) in heptane was divided three ways and heated at 65 °C. The isomerization (●) was inhibited by 50 mM *n*-butylamine (▲) and by 50 mM triethylamine (■). For each time point, an aliquot (1 mL) of the solution was removed from the reaction vessel, and the imines converted to oximes for HPLC analysis.

380–400 nm, where the starting aldehyde absorbs at approximately 382 nm under these conditions. The extent of isomerization was determined by forming the oximes under standard conditions and subjecting the oximes to separation by high-performance liquid chromatography using a LiChrosorb Silica 60 column (Merck, Inc.) and 12% diethyl ether/*n*-hexane as the eluant.[5] Formation of the oximes from the Schiff base occurs with stereochemical integrity.[5] It should be noted that retinal Schiff bases themselves cannot be chromatographed on silica columns since they are protonated and are readily broken down to the retinaldehydes. Under the conditions already described, Schiff base formation required approximately 5 h to go to completion; moreover a period of 4 days was required for the isomerization to proceed to 50% completion.

Further studies were conducted with 11-*cis*-retinaldehyde both because this isomer is relevant to vision and because its isomerization reactions are easily followed kinetically, there being only 0.1% 11-*cis*-retinaldehyde at equilibrium as opposed to 23% 13 cis.[6] When 12 μM 11-*cis*-retinaldehyde was mixed with 100 mM *n*-butylamine, a period of 6 h was required for complete conversion to the Schiff base at 25 °C. However, even after 32 h, no isomerization was evident as judged by HPLC of the retinal oximes. It was of some interest to learn the actual rate of thermal isomerization of the unprotonated retinal Schiff bases and compare it to the rate of retinaldehyde isomerization. At 12 μM, the

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first-order rate of 11-*cis*-retinaldehyde isomerization was measured to be 2.4×10^{-6} s^{-1} at 65 °C in *n*-heptane. Under the same conditions the rate for the preformed *n*-butylamine Schiff base of 11-*cis*-retinaldehyde, prepared by stirring a 5% excess of *n*-butylamine with the aldehyde in dry ether followed by solvent evaporation, was 8.0×10^{-6} s^{-1} (Figure 2). Therefore Schiff base formation by itself does enhance the thermal isomerization of the retinaldehydes by approximately a factor of 3 under the conditions shown. However, this acceleration is not nearly what would be required to enable the isomerization reactions to proceed at room temperature, even after Schiff base formation was completed.

The effects of added bases on the isomerization rates of the Schiff bases was also investigated. The rates of isomerization of the *n*-butylamine Schiff base of 11-*cis*-retinaldehyde was measured in *n*-heptane in the presence and absence of either added *n*-butylamine or triethylamine (Figure 2). The addition of the amines led to a slowing down of the rate of isomerization, with the *n*-butylamine being more effective than the triethylamine in this regard (Figure 2). The isomerization rate constant in the presence of 50 mM *n*-butylamine was 4.9×10^{-7} s^{-1},, and in the presence of 50 mM triethylamine, it was 2.0×10^{-6} s^{-1}. In separate experiments we also found that, as would be anticipated, triethylamine markedly decreased the rate of isomerization of the *n*-butylamine Schiff base of 13-*cis*-retinal in chloroform. The preformed Schiff base (12 μM) was isomerized at 65 °C in chloroform passed through alumina with a first-order rate constant of 1.5×10^{-5} s^{-1}. The addition of 100 mM triethylamine slowed down the rate to 1.7×10^{-6} s^{-1}. The inhibitory effect of the added amines is probably due to the neutralization of trace amounts of acid catalysts in the medium. Finally, as expected, it was also found that acid catalysis rapidly brought the retinal Schiff bases into equilibrium. The half-life for the isomerization of 9.8 μM 11-*cis*-retinaldehyde Schiff base in chloroform by approximately 10 mM HCl is 7 min at 25 °C.

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Registry No. 13-*cis*-Retinaldehyde, 472-86-6; 11-*cis*-retinaldehyde, 564-87-4; butylamine, 109-73-9; 13-*cis*-retinaldehyde butylamine Schiff base, 51847-39-3; 11-*cis*-retinaldehyde butylamine Schiff base, 52647-48-0; *all-trans*-retinal, 116-31-4; triethylamine, 121-44-8.

Diastereoselective Addition of Electrogenerated Trichloromethyl and Dichloro(methoxycarbonyl)methyl Anions to α-Branching Aldehydes[1]

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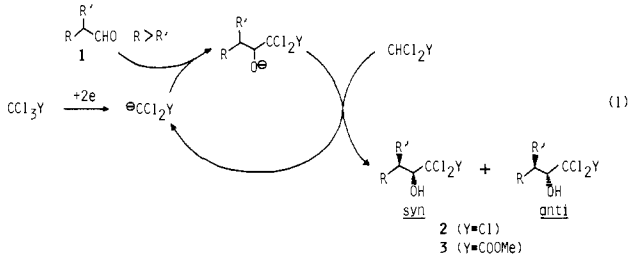
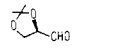
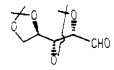
Previously we have reported a new electroreductive anionic chain reaction, in which aldehydes were converted into 1,1,1-trichloro-2-alkanols (**2**) with high current efficiency (eq 1).[2] The



(1)

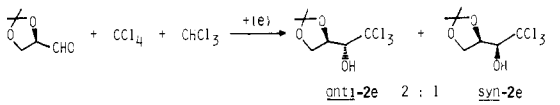
stereoconfiguration of products was classified by using "syn" and "anti" according to the definition of Masamune.[3] Similarly to

Table I. Diastereomeric Ratios and Yields of **2** and **3**

	1	**2**, Y = Cl[a] syn:anti	yield, %[c]	**3**, Y = COOMe[b] syn:anti	yield, %[c]
a	R = Et; R' = Me	67:33[d]	89	90:10[d]	42
b	R = *i*-Pr; R' = Me	89:11[d]	76	~100:0[d]	25
c	R = *t*-Bu; R' = Me	~100:0[d]	49		
d	R = Ph; R' = Me	86:14[d]	60	~100:0[d]	36
e		33:67[e]	66	<5:95[f]	63
f		40:60[e]	52	<5:95[f]	55
g	R = *n*-Pr, R' = OAc	45:55[g]	76	17:83[g]	63

[a] Aldehyde:CCl_4:$CHCl_3$ = 1:1:10. [b] Aldehyde:CCl_3COOMe:$CHCl_2COOMe$ = 1:1:2. [c] Isolated yield based on aldehyde. [d] See ref 13. [e] See ref 15. [f] See ref 16. [g] See ref 17.

2, methyl 2,2-dichloro-3-hydroxyalkanoates (**3**) were obtained in reasonable yields by the electroreduction of mixtures of aldehydes, methyl trichloroacetate, and methyl dichloroacetate (eq 1).[4] In our continuing study on the utilization of **2** in organic synthesis, we have found that the electrogenerated trichloromethyl anion adds to 2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde with moderate diasteroselectivity (eq 2).[8] This result prompted us to



(2)

anti-2e 2 : 1 syn-2e

investigate the diastereoselectivity of addition of electrogenerated trichloromethyl and dichloro(methoxycarbonyl)methyl anion to various aldehydes branching at the α-position.

A general procedure of the reaction is as follows: A solution of tetraethylammonium *p*-toluenesulfonate in 60 mL of DMF was placed in a divided cell equipped with carbon-rod electrodes. To the catholyte was added 0.01 mol of carbon tetrachloride, 0.1 mol of chloroform, and 0.01 mol of aldehydes. The catholyte was electrochemically reduced with a constant current of 0.1 A. After 0.02*F* of electricity was passed (5.33 h), the product was isolated by distillation or column chromatography. All the products gave satisfactory results in elemental and spectroscopic analyses.

The yield and diastereoselectivity are summarized in Table I. In the reaction with trichloromethyl anion, the aldehydes **1a–d** mainly yield syn isomers (R > R'), whereas the main products obtained from aldehydes **1e–g** are called anti isomer, since the main chain is the carbon chain. The ratio of syn/anti of **2a–c** increased in the order of bulkiness of α-substituent R (*t*-Bu > *i*-Pr > Et). No anti isomer was formed in the reaction of **1c**. The stereochemistry of the addition of trichloromethyl anion to aldehydes has not been known so far, but tribromomethyl anion generated by rather complex methods has been known to show similar stereoselectivity.[9]

The noteworthy results in the present study are that the addition of dichloro(methoxycarbonyl)methyl anion to α-branching aldehydes always shows excellent stereoselectivity. Since dichloro(methoxycarbonyl)methyl anion is hardly generated by the

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(4) (a) Products **3** have also been obtained by the reaction of aldehydes with alkyl trichloroacetates using Grignard reagents[5a] or Zn[5b] or with alkyl dichloroacetate using a strong base.[6] In these methods, however, low temperature is necessary, and in the latter case, only limited types of esters and aldehydes are usable. (b) It has been reported that dichloro(ethoxycarbonyl)methyl anion, cathodically generated from ethyl trichloroacetate, adds to cyclic ketones to yield ring-expanded products.[7]
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