Stereospecific Thermal Rearrangement of the Four Labile Isomers of Retinal. Activation Parameters and FT-IR Data

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We have determined enthalpy and entropy of activation and FT-IR spectra of the four thermally labile isomers of retinal (11,13-dicis, 7,11,13-tricis, 9,11,13-tricis, and all-cis). The data are in agreement with the postulated Kluge–Lillya mechanism of isomerization, involving consecutive 6e-electrocyclization reactions for the stereospecific reactions.

Introduction

Following successful synthesis of the 7,11,13-tricis and all-cis isomers, all 16 possible geometric isomers of retinal are now known.[1] Of these, 12 are stable at room temperature and four undergo facile stereospecific rearrangements. Thus, Wald and co-workers reported in the fifties of the ready conversion of 11,13-*dicis*-retinal to 13-*cis*-retinal,[2] and more recently, similar rearrangements of 9,11,13-*tricis*-,[3] 7,11,13-*tricis*-[4] and *all-cis*-retinal to, respectively, the 9,13-dicis, 7,13-dicis and 7,9,13-tricis isomers[1,5] have also been reported.

In a study of dienals and dienones, Kluge and Lillya showed that the thermal rearrangement of some of the dicis isomers to the monocis involved the intermediacy of α-pyrans.[6] Thus, the mechanistic pathway for the stereospecific reaction was believed to involve two consecutive steps of 6e-electrocyclization.[6a] They suggested that the same mechanism might be involved in the 11,13-*dicis*- to 13-*cis*-retinal conversion reported by Wald et al. earlier.[2] The same pathway was also assumed for other retinal isomers.[4,5]

Accurate kinetic data necessary for calculation of activation parameters as corroborative evidence for the postulated mechanism are, however, lacking. Thus, the 11,13-dicis and 9,11,13-tricis isomers of retinal were reported to have approximate half-lives of 2 h at 40 °C,[7] and the activation energies for 7,11,13-tricis and all-cis were both reported to be about 22 kcal/mol.[1] We have now determined accurate kinetic data for thermal isomerization of all four isomers and calculated the enthalpy and entropy of activation. Mechanistic implications of these data are discussed along with the infrared and other spectral data of these compounds.

Experimental Section

Materials. 7,11,13-Tricis, 9,11,13-tricis, and all-cis isomers of retinal were prepared by direct irradiation of the corresponding 13-trans isomers,[8] which were prepared in a general reaction scheme that led to all 16 possible geometric isomers of vitamin A, or in the case of 9,11-dicis from a photostationary-state mixture.[9] 11,13-*dicis*-Retinal was also isolated from the irradiated mixture. All isomers were purified by preparative HPLC at 4 °C (with the unit situated in a chromatography refrigerator) immediately before use. Their structures were verified by the ^{1}H-NMR[1,3] (GE QE-300) and UV–vis spectra[1,3] (PE-λ5).

Methods. The thermal isomerization reactions were carried out in an UV–vis cell situated in a thermostated cuvette cell holder of a PE-λ5 absorption spectrometer. The temperature of the solution was determined by an immersion thermocouple thermometer. The progress of the reaction was monitored by the increase of absorbance at the absorption maximum of the product isomer (usually around 360 nm). Four runs at temperatures ranging from 20 to 50 °C were conducted for each isomer, reaching conversions for more than three half-lives. The reaction mixture was then allowed to convert completely to the product isomer in order to determine final absorbance, A_∞. For lower temperature runs, this involved warming the solution to 40 °C for 10 h before cooling to the original temperature for recording the final spectrum. Changes in absorbance, expressed as ln $(A_\infty - A_t)$ is a measure of fraction of conversion (ln x). They were used for calculation of rates of isomerization. The data are listed in Table I.

The infrared spectra were recorded on a Nicolet-740 FT-IR spectrometer (resolution, 1 cm^{-1}; 100 scans). Samples were deposited on a sodium chloride plate by evaporation of a hexane solution of the freshly collected retinal isomer. Immediately after recording the spectra, the sample was redissolved in hexane and analyzed by HPLC to determine the extent of isomerization. In

Table I. Rate Constants of Isomerization of the Four Labile Isomers of Retinal at Various Temperatures and the Calculated Enthalpy and Entropy of Activation

isomers	T (°C)	k^a (m^{-1}) × 10^3	$\Delta H^\ddagger$ (kcal/mol)	$\Delta E^{\ddagger\,b}$	$\Delta S^\ddagger$ (cal/deg mol)
11,13-dicis	50.3	27.0	22.4 ± 0.7	23.0	−4.7 ± 1.7
	39.8	8.68			
	30.5	2.55			
	21.2	0.784			
9,11,13-tricis	49.8	29.3	21.2 ± 0.6	21.8	−8.5 ± 1.0
	39.8	8.84			
	30.6	3.45			
	21.1	1.08			
7,11,13-tricis	49.3	33.8	21.5 ± 0.4	22.1	−6.8 ± 1.3
	39.5	11.5			
	30.6	4.42			
	21.1	1.19			
all-cis	49.8	28.7	23.1 ± 0.2	23.6	−2.3 ± 0.5
	39.5	8.44			
	30.6	3.02			
	21.3	0.789			

^{a} ±0.2–0.9%. ^{b} $\Delta H^\ddagger + RT$

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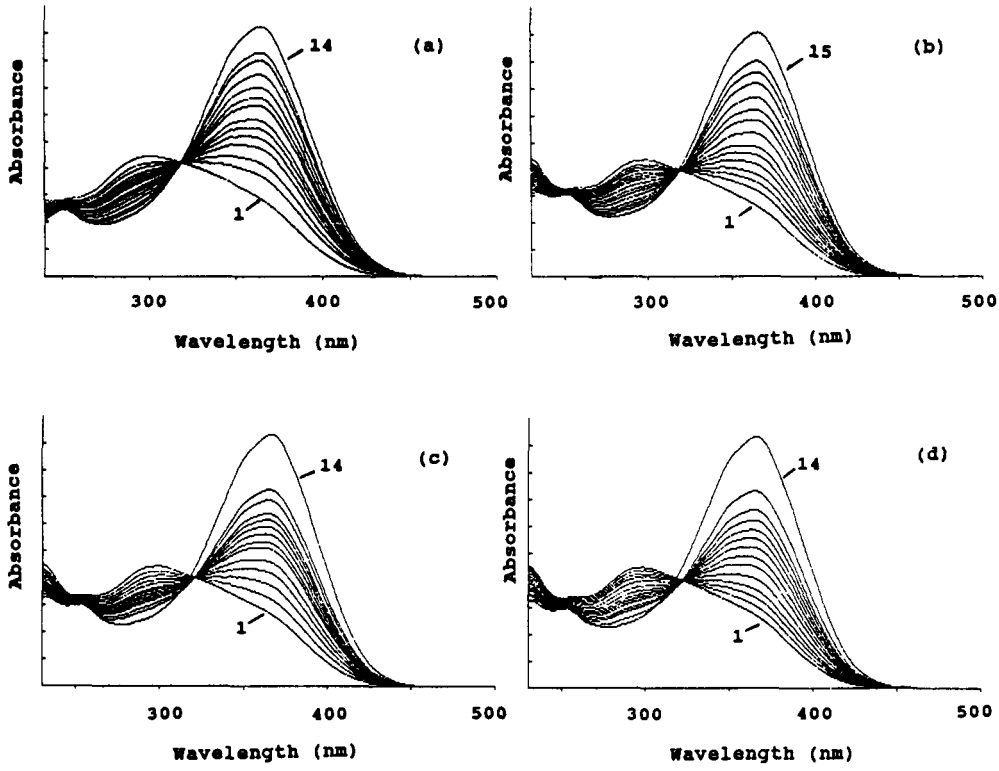


Figure 1. UV–vis absorption changes during conversion of 11,13-*dicis*-retinal to 13-*cis*-retinal in methylcyclohexane at (a) 50.3 °C, spectra taken at the following intervals: 0 (curve 1), 5, 8, 12, 15, 18, 21, 27, 31, 37, 46, 60, 72 m, and ∞ (curve 14); (b) 39.8 °C, at 0 (curve 1), 10, 16, 22, 30, 38, 46, 60, 76, 90, 110, 140, 170, 210 m, and ∞ (curve 15); (c) 30.5 °C, at 0 (curve 1), 60, 90, 120, 160, 180, 210, 240, 270, 300, 375, 450, 540 m, and ∞ (curve 14); and (d) 21.0 °C, at 0 (curve 1), 60, 120, 180, 270, 385, 490, 610, 720, 840, 1020, 1200, 1320 m, and ∞ (curve 14). The last entry of each after warming overnight at 40 °C.

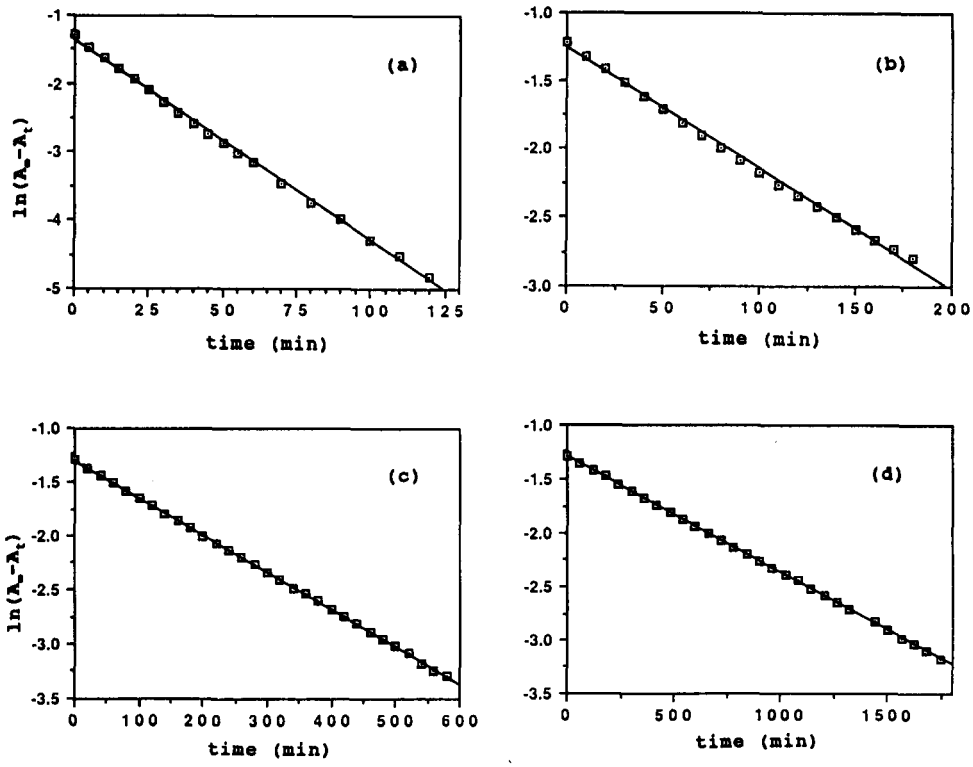


Figure 2. Change of absorbance ln $(A_\infty - A_t)$ vs time at 359 nm during thermal reaction of 9,11,13-*tricis*-retinal at (a) 49.8, (b) 39.8, (c) 30.6, and (d) 21.1 °C.

no instances did rearranged products constitute more than 5% of the sample.

Results and Discussion

The course of thermal isomerization of 11,13-*dicis*-retinal is shown in Figure 1 as a representative example. The presence of a well-defined isosbestic point as well as the linearity of the plots for three half-lives clearly reflects the unimolecular nature of the reaction. The plotted kinetic data for 9,11,13-*tricis*-retinal are shown in Figure 2 as a representative example. Similar plots for the remaining isomers are available in the supplementary material. The

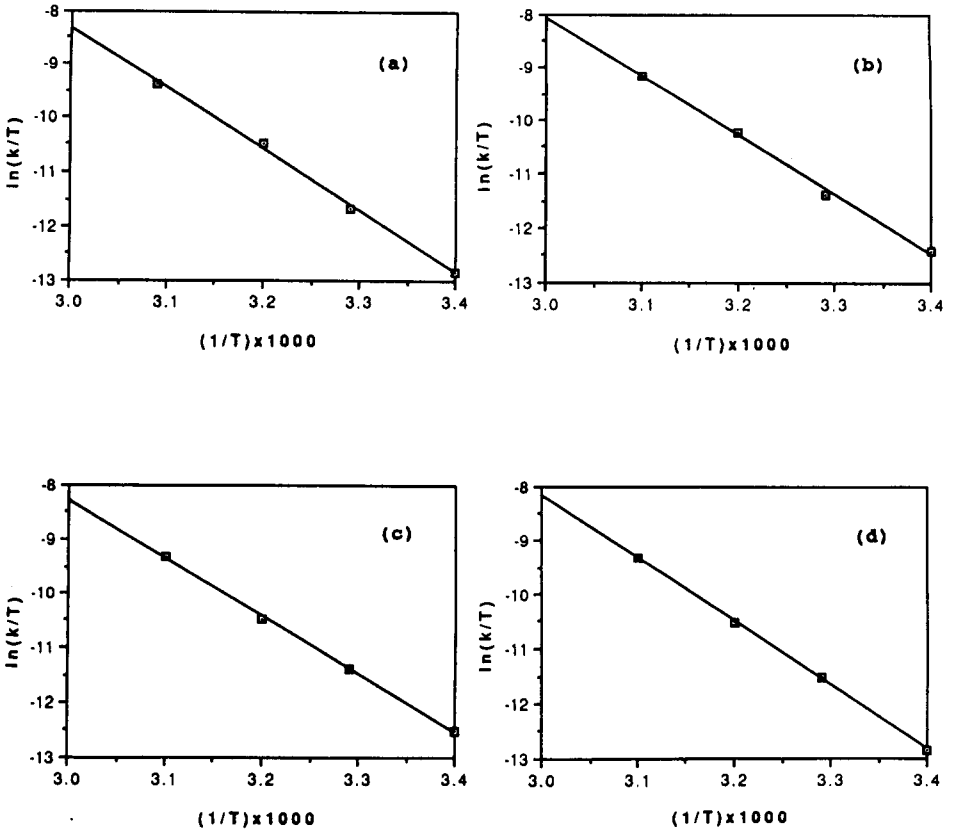
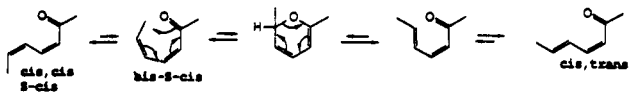


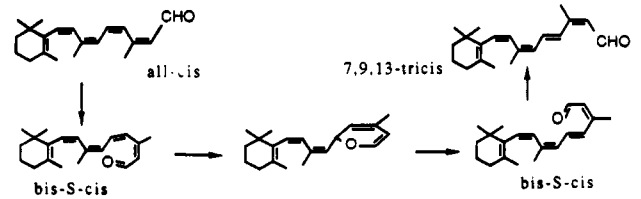
Figure 3. Plots of ln (k/T) vs $1/T$ for determination of enthalpy and entropy of activation for isomerization of (a) 11,13-*dicis*-retinal, (b) 7,11,13-*tricis*-retinal, (c) 9,11,13-*tricis*-retinal, and (d) *all-cis*-retinal.

calculated rate constants are listed in Table I. Then, from the slopes and intercepts of the ln (k/T) vs $1/T$ plots (Figure 3), activation parameters ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$) for each of these four cases were calculated. They are also listed in Table I.

The central feature of the Kluge–Lillya mechanism for isomerization of dicis dienals or dienones to the central cis isomers[6] is the involvement of the intermediate α-pyrans. Implied in such a mechanism is that the bis-*S*-cis conformers of the dicis isomers must be readily accessible.



When this mechanistic pathway is incorporated into isomerization of the 11,13-dicis isomers of retinal, e.g., *all-cis*-retinal, the following scheme is obtained:



The activation parameters obtained for these four isomers (Table I) appear to be in support of such a mechanism. First, the current values of activation energy of 7,11,13-*tricis*- and *all-cis*-retinal are close to those reported.[1] All four values of activation enthalpy fall within the narrow range of 21.2–23.1 kcal/mol suggesting a common mechanism. These values (after adding 0.6 kcal/mol for RT to $\Delta H^{\ddagger}$ for comparison) are closer to that (E_a = 20 kcal/mol) determined for cyclization of *cis*-β-ionone to its stable α-pyran rather than that of ring opening of the α-pyran back to *cis*-β-ionone (E_a = 27 kcal/mol).[10] This suggests that the rate-determining step for the isomerization reaction of the retinal isomer is formation of the α-pyran rather than its ring opening. Values for the entropy of activation for all four cases are negative, implying the involvement of a similar, more highly organized transition state. This is in agreement with the above reaction scheme in which conversion to the bis-*S*-cis conformer should be entropically activated. That the all-cis value is least negative is also in agreement with its expected, more highly twisted conformation that is structurally closer to the bis-*S*-cis form necessary for α-pyran formation. (However, it should be noted that the presence of a similarly substituted dicis geometry does not guarantee facile isomerization to the monocis. For example, 7,9-dicis C_{15}-aldehyde is known to be stable.[11] In this case, steric bulk at C-6 apparently forbids participation of the 8-*S*-cis conformation necessary for the Kluge–Lillya mechanism for the isomerization process.)

In agreement with these kinetic data was the earlier conclusion from molecular mechanics calculations[1] which showed that the relative energy difference of the bis-*S*-cis and the mono-*S*-cis conformer could indeed account for the different reactivity of the isomers of dienals. The highly blue-shifted UV–VIS absorption maximum of these isomers (287, 289, 302, 302 nm for all-cis, 7,11,13-tricis, 9,11,13-tricis, and 11,13-dicis, respectively)[1,7] are also in agreement with a highly twisted chromophore. In fact, Okamura et al. reasoned that the absorption maximum of 9,11,13-tricis is close to that of a tetraene, i.e., the presence of a substantial twist at the 12,13-bond.[7] Additional supporting evidence for the Kluge–Lillya mechanism is the possible existence of several stable α-pyrans for structurally

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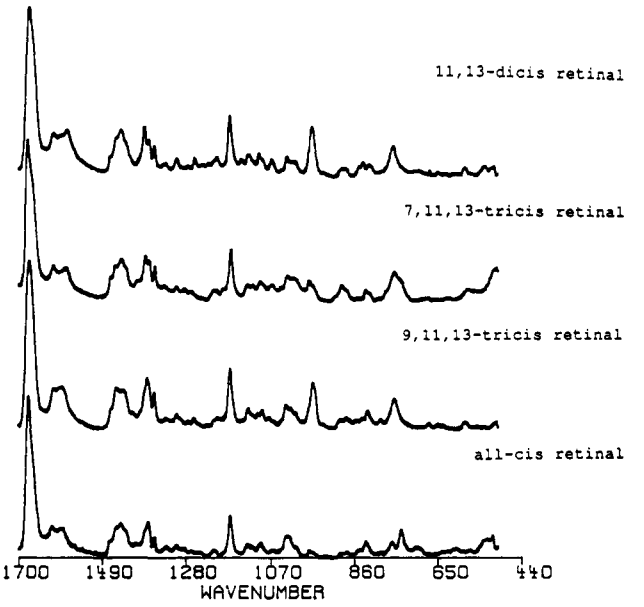

Figure 4. Partial FT-IR spectra (1700–440 cm^{-1}) of the four labile isomers of retinal.

modified dienals[9,10] and the corresponding nitrogen analogues,[12] indicating close energy of the ring-closed form.

We have recorded the FT-IR spectra of all poly-cis isomers of retinal. The partial FT-IR spectra of the four labile isomers are shown in Figure 4. In a detailed analysis of the vibrational spectra (Raman and resonance Raman) of commonly available retinal isomers (all-trans, 13-cis, 11-cis, and 9-cis), including a large number of isotopically labeled retinals, Mathies, Lugtenburg, and co-workers identified several important regions that are informative of the polyene structures.[13] We have now analyzed IR signals in some of these regions of the four labile isomers. The key signals are listed in Table II.

Signals of the double-bond region (1550–1650 cm^{-1}) of these four isomers are different from other commonly available retinal isomers. For all previous cases, one medium-intensity peak appears near 1580–1590 cm^{-1} while a shoulder appeared at a lower wavenumber. The main peak is believed to be due to combined stretching signals of C_7=C_8, C_9=C_{10}, and C_{11}=C_{12} and the more delocalized C_{13}=C_{14} signal appearing at a lower wavenumber.[13] For all these hindered isomers, a doublet appears in this region centering around 1580–1595 and 1612–1616 cm^{-1}. The loss

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Table II. Partial Assignment of IR Signals (cm^{-1}) of the Four Labile Isomers of Retinal

	isomer			
assignment	11,13-dicis	7,11,13-tricis	9,11,13-tricis	all-cis
C=O stretch	1676	1679	1676	1677
C=C stretch				
11,12 + 13,14	1613	1615	1612	1616
7,8 + 9,10	1580	1582	1595	1593
C–C stretch	1171	1170	1171	1170
HOOP, trans 7,8	966	none	964	none
11,12	none	none	none	none
HOOP, cis 7,8	none	740	none	743
11,12	761	760	759	765

of a shoulder near 1570, the decrease in intensity of the peak near 1585, and the appearance of a peak near 1614 cm^{-1} are consistent with the notion of substantial twisting near the C_{11}–C_{15} portion of the molecule with the consequence of the C_{11}=C_{12} and C_{13}=C_{14} double bonds being less conjugated with the remaining portion of the polyene system (thus ethylene-like). The C–C single bond region, on the other hand, is characterized by the appearance of a single medium-intensity peak near 1170–1171 cm^{-1}, which is based on the assignment of the all-trans isomer[12] should correspond to overlapping signals of C_8–C_9, C_{10}–C_{11}, and C_{12}–C_{13}.

We might also mention that knowledge from other known retinal isomers[13] makes signals in the HOOP band region (hydrogen-out-of-plane bending region) readily assignable. The 960 cm^{-1} band due to $H_{7,8}$ for isomers with the 7-trans geometry only appears in the 11,13-dicis and 9,11,13-tricis isomers while disappearance of similar signals in 7,11,13-tricis and all-cis is accompanied by doubling of the cis HOOP bands near 740–760 cm^{-1}.

In conclusion, activation parameters for thermal isomerization of the four hindered 11,13-dicis isomers of retinal, their FT-IR data, and earlier reported UV–VIS absorption data are in agreement with the Kluge–Lillya mechanism for isomerization of these isomers. The requisite, intermediate α-pyrans via the bis-*S*-cis conformers are more accessible due to steric crowding of the multiple cis linkages in these polyene systems.

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Supplementary Material Available: Kinetic plots for determining rate constants of isomerization of the 11,13-*dicis*-, 7,11,13-*tricis*-, and *all-cis*-retinal in the same form as those in Figure 2 (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.