carbons. Even when correction is made for the slightly longer CH bond length expected for the aldehyde carbon compared to the other olefinic carbons (1.11 *vs.* 1.08 Å, which would account for a 20% increase in the T_1), the T_1 of 15C is still long. 15C must have a shorter correlation time than the rest of the chain carbons, which implies some oscillatory motion about the 14–15 single bond.

We now turn to consideration of the isotropy of the tumbling of retinal in solution. A reasonable assumption is that one of the principal diffusion axes is the axis of the chain. For *all-trans*-retinal, all of the relaxation vectors for the protonated chain carbons are perpendicular to this axis, so it is impossible to determine from these T_1's the relative rates of rotation about this axis compared to an axis perpendicular to the chain. The situation is more informative for 13-*cis*-retinal, which has a bend at the end of the chain. We assume that one of the principal diffusion axes is the axis of the chain from 7C to 13C, but now the relaxation vector of 14C makes a 30° angle with the main axis. We now use the formula of Woessner[37] as transcribed by Noggle[38] for the rotational correlation time in the case of anisotropic motion in a symmetric-top molecule

$$\tau_c(\theta) = \frac{(3\cos^2\theta - 1)^2}{24D_\perp} + \frac{3\sin^2\theta\cos^2\theta}{5D_\perp + D_\parallel} + \frac{{}^3/_4\sin^4\theta}{2D_\perp + 4D_\parallel}$$

where $\tau_c(\theta)$ is the correlation time of a carbon whose CH bond makes an angle θ with the major rotational axis, $D_\parallel$ is the diffusion constant for rotation about this axis, and $D_\perp$ is the diffusion constant for rotation about an axis perpendicular to the main axis. While we do not know the correlation times, we do know that T_1 (90°) = 2.43 (the average value for protonated chain T_1's 7C to 12C) and T_1 (30°) = 1.52 (T_1 of 14C). Under the extreme narrowing condition, one can now obtain the ratio of $D_\parallel$ to $D_\perp$ by taking the ratio of $\tau_c(90°)/\tau_c(30°) = T_1(30°)/T_1(90°)$. One obtains $D_\parallel = 4.6D_\perp$. Presumably something approximating this ratio also obtains in *all-trans*-retinal, where the mean T_1 of the protonated carbons 7C–14C is 2.31, close to the T_1 (90°) of 13-*cis*-retinal, 2.43. It is noteworthy that the T_1 of 15C in 13-*cis*-retinal is also longer than would be predicted if it had the same correlation time as 14C, again implying some oscillatory motion about the 14–15 bond.

Acknowledgments. The authors would like to acknowledge the financial support of the National Institutes of Health (Grant GM-17190) and the National Science Foundation (Predoctoral Fellowship to R. R.), the gift of 11-*cis*-retinal from Paul Brown, and a helpful conversation with Professor Alan G. Marshall.

(37) D. E. Woessner, *J. Chem. Phys.*, 37, 647 (1962).
(38) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect," Academic Press, New York, N. Y., 1971, p 27.

Carbon-13 Magnetic Resonance Investigation of Retinal Isomers and Related Compounds

Ralph S. Becker,[1a] Stefan Berger,[1b] Don K. Dalling,[1c] David M. Grant,*[1c,d] and Ronald J. Pugmire[1c]

Contribution from the Department of Chemistry, University of Utah, Salt Lake City, Utah 84112, Department of Chemistry, University of Houston, Houston, Texas 77004, and Contribution No. 4920 from Gates and Crellin Laboratories, California Institute of Technology, Pasadena, California 91109. *Received January 14, 1974*

Abstract: Carbon-13 chemical shift and relaxation data are reported for the *all-trans*-retinal as well as several isomeric and related species. The results demonstrate that *all-trans*-, 13-*cis*-, and 9-*cis*-retinal, as well as the related all-trans- and 9-cis 15-carbon aldehydes, exist as essentially planar structures in the polyene portion of these molecules. However, 11-*cis*-retinal, the chromophore of the visual pigment rhodopsin, is not planar along the entire polyene chain but exists as an intermediate structure. Both chemical shift and relaxation data indicate substantial segmental motion about the C-12, C-13 bond. Woessner's equations for the effect of anisotropic motion on spin relaxation are used to confirm structural details of the rigid parts of these molecules and failure of these expressions to correlate relaxation data can be used to characterize segmental motion of molecular moieties.

The solution conformation of retinal isomers is of value in understanding the mechanism by which the chromophore 11-*cis*-retinal serves as the visual pigment when attached to the protein opsin through an imine linkage. The structures of *all-trans*- and 11-*cis*-retinal have been determined by X-ray crystallography[2,3] in the solid state and proton nmr studies[4–7] have been used to study their conformations in solution.

(1) (a) University of Houston; (b) California Institute of Technology; (c) University of Utah; (d) on leave at California Institute of Technology, 1973–1974, as Sherman Fairchild Distinguished Scholar.

(2) T. Hamanaka, T. Mitsui, T. Ashida, and M. Kakudo, *Acta Crystallogr., Sect. B*, 28, 214 (1972).
(3) R. D. Gilardi, I. L. Karle, and J. Karle, *Acta Crystallogr., Sect. B*, 28, 2605 (1972).
(4) D. Patel, *Nature (London)*, **221**, 826 (1969).
(5) D. Patel and R. G. Schulman, *Proc. Nat. Acad. Sci. U. S.*, **65**, 31 (1970).
(6) B. Honig, B. Hudson, B. D. Sykes, and M. Karplus, *Proc. Nat. Acad. Sci. U. S.*, 68, 1289 (1971).
(7) R. Rowan, A. Warshel, B. D. Sykes, and M. Karplus, *Proc. Nat. Acad. Sci. U. S.*, in press.

We wish to report chemical shift and spin-relaxation analysis of the carbon-13 nmr (cmr) data on *all-trans*-(IV), 13-*cis*- (V), 11-*cis*- (VI), and 9-*cis*-retinal (VII), as well as the all-trans (II) and 2-cis (III) isomers of 5-[2,6,6-trimethyl-1-cyclohexen-1-yl]-3-methyl-2,4-pentadienal (hereafter referred to as all-trans- and 9-cis-C_{15} aldehydes) and β-cyclocitral (I).

Experimental Section

The compounds treated herein were obtained for the most part through standard commercial sources. Compounds II, III, and VI were gifts from Hoffman LaRoche Chemical Co. The samples were dissolved in dioxane and sealed in 10-mm glass tubes after being degassed by application of several freeze–pump–thaw cycles. Data were obtained on a Varian XL-100-15 nmr spectrometer by use of Fourier transform techniques. Decoupling was accomplished using a Hewlett-Packard 1505A frequency synthesizer and an ENI Model 310 power amplifier.

Results and Discussion

A. Chemical Shifts. The cmr chemical shift values for the compounds studied are given in Table I and the correlation diagram for the data is presented in Figure 1. For each compound studied, off-resonance techniques[8,9] established the identity of the quaternary, methyne, methylene, and methyl carbons while the individual protonated carbons were assigned by a combination of single frequency proton decoupling[8,9] and use of the correlation diagram. In compounds II and III the protonated olefinic carbons assignments were made by single frequency proton decoupling as mentioned above. Carbons 5, 6, and 9 were assigned as given in Table I by comparison with the chemical shift changes observed in small model compounds. Compound I exhibits the large downfield shifts which result at both ends of a double bond when an aldehyde is attached. The aliphatic carbons in I, II, and III were assigned by analogy with the corresponding positions in vitamin A acetate reported by Roberts, *et al.*,[10] coupled with use of the correlation diagram.

Two major changes occur in the chemical shift values of III as compared to those of II. Removal of the interaction between C-9a and the C–H bond at C-11 results in an 8.3 ppm downfield shift while the resonance position at C-8 moves upfield −7.9 ppm as a result of this isomeric change (see Table II). This latter shift arises from a γ type[11,12] of interaction between C-8 and C-11. The aldehyde carbon resonance which moves upfield only slightly (−1.4 ppm) is sterically perturbed by C-9a in II and C-8 in III, reflecting the fact that the two seemingly different environments produce very similar chemical shifts. The resonance position of C-7 moves downfield (1.2 ppm) and C-10 moves upfield (−1.0 ppm) while no other significant shifts are observed. The origin of the shifts at C-7 and C-10 are not presently understood but similar effects are noted at the corresponding positions in comparing IV and V and IV and VI (see Table II).

The resonance positions of the aliphatic carbons in

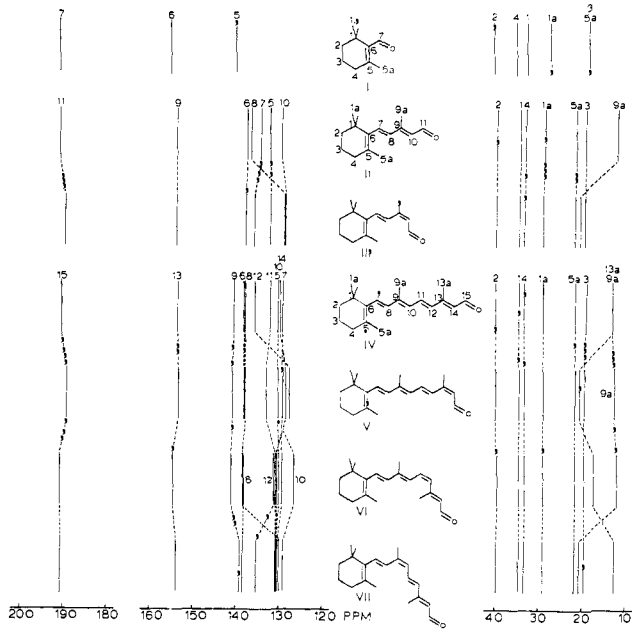

Figure 1. Correlation diagram for carbon-13 chemical shifts of isomeric retinals and related compounds. The numbering systems of β-cyclocitral (I) and the 15-carbon compounds (II and III) have been altered to conform to that of the retinals for the sake of comparing chemical shifts.

all-trans-retinal are nearly identical with those reported in vitamin A acetate.[10] Carbons C-11 and C-14 were unequivocally assigned by single frequency decoupling whereas C-7, C-12 and C-8, C-10 were assigned pairwise as a consequence of the small separation in the pmr frequencies of the pairs. Individual assignments of these pairs were made by means of the correlation diagram. Assignments of C-5 and C-13 were made by analogy to the shifts in the C_{15} aldehydes. Confirmation of the assignments at C-6 and C-9 cannot be unambiguously extracted from the correlation diagram but the correct assignment is rendered straightforward by examination of the T_1 data. The chemical shift assignment in V, VI, and VII were made by single frequency decoupling (some pairwise as above) in combination with the correlation diagram.

A comparison of the chemical shift changes observed in compounds IV through VII reflects trends similar to those noted for II and III. In V and VII the resonances of both C-13a and C-9a, respectively, move downfield 8.0 ppm when compared to those of corresponding carbons in IV, demonstrating the consistent upfield shift experienced by a methyl involved in a cis-1,4 interaction. Similar results were noted by Collins for the methylethylenes.[13] As expected, the resonance positions of C-13a in IV and VII and those of C-9a in IV, V, and VI are unchanged because the isomeric changes do not alter their environments. One also observed upfield shifts of −8.0 ppm in V and −7.8 ppm in VII for C-12 and C-8, respectively, as a result of inclusion of a cis bond and, once again, the shift changes are similar to the analogous changes observed between II and III (−7.9 ppm at C-8). As noted previously, consistent chemical shift changes are also observed for carbons which do not experience major variations in steric environment but which are located in

(8) R. J. Pugmire, D. M. Grant, M. J. Robins, and R. K. Robins, *J. Amer. Chem. Soc.*, **91**, 6381 (1969).
(9) F. J. Weigert, Ph.D. Thesis, California Institute of Technology, 1968.
(10) M. Jautelat, J. B. Grutzner, and J. D. Roberts, *Proc. Nat. Acad. Sci. U. S.*, **65**, 288 (1970).
(11) E. G. Paul and D. M. Grant, *J. Amer. Chem. Soc.*, **86**, 2984 (1964).
(12) B. V. Cheney and D. M. Grant, *J. Amer. Chem. Soc.*, **89**, 5315 (1967).
(13) S. W. Collins, Ph.D. Thesis, University of Utah, 1971.

Table I. Carbon-13 Chemical Shifts[a] of Isomeric Retinals and Related Compounds

Compd	Position 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15(CHO)	1a	5a	9a	13a
β-Cyclocitral[c] (I)	33.2	40.9	18.9	35.6	140.5	155.5	*b*								191.2	27.8	18.9		
All-trans-C_{15} aldehyde[c] (II)	34.5	39.9	19.4	33.3	132.2	137.6	134.6	136.7	153.9	129.6	*b*				190.9	28.9	21.6	12.2	
9-Cis-C_{15} aldehyde[c] (III)	34.5	39.8	19.4	33.4	132.1	137.7	135.8	128.8	153.8	128.6	*b*				189.5	29.0	21.7	20.5	
all-trans-Retinal (IV)	34.6	40.0	19.5	33.4	130.3	138.2	129.2	137.8	140.5	130.3	132.1	135.6	153.6	129.7	190.4	29.0	21.6	12.5	12.5
13-*cis*-Retinal (V)	34.6	40.0	19.5	33.4	130.3	138.1	129.2	137.8	140.8	130.4	133.0	127.6	153.4	128.5	189.2	29.0	21.6	12.6	20.5
11-*cis*-Retinal (VI)	34.6	39.6	19.5	33.3	130.0	138.1	129.3	138.3	141.1	126.6	130.9	131.2	154.6	130.5	190.8	29.0	21.6	11.9	17.4
9-*cis*-Retinal (VII)	34.5	39.8	19.5	33.3	130.2	138.4	130.2	130.0	139.1	129.0	130.7	135.2	153.9	130.6	190.7	29.0	21.8	20.5	12.4

[a] In ppm as measured from internal dioxane and converted to the TMS scale according to $\delta_{TMS}(ppm) = \delta_{dioxane} + 67.2$ ppm. [b] For ease of comparison, the chemical shifts for these carbons are listed in the CHO column (C-15). [c] The numbering system of this compound has been altered to conform to that of retinal for the sake of comparing chemical shifts.

Table II. Chemical Shift Changes[a] ($\Delta\delta$) of Isomeric Retinals and Related 15-Carbon Aldehydes Relative to the All-Trans Parent Compounds

Compd	Position 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15(CHO)	1a	5a	9a	13a
δ(III) − δ(II)	0.0	−0.1	0.0	+0.1	−0.1	+0.1	+1.2	−7.9	−0.1	−1.0					−1.4	+0.1	+0.1	+8.3	
δ(V) − δ(IV)	0.0	0.0	0.0	0.0	0.0	−0.1	0.0	0.0	+0.3	+0.1	+0.9	−8.0	−0.2	−1.2	−1.2	0.0	0.0	−0.1	+8.0
δ(VI) − δ(IV)	0.0	−0.4	0.0	−0.1	−0.3	−0.1	+0.1	+0.5	+0.6	−3.7	−1.2	−4.4	+1.0	+0.8	+0.4	0.0	0.0	−0.6	+4.9
δ(VII) − δ(IV)	−0.1	−0.2	0.0	−0.1	−0.1	+0.2	+1.0	−7.8	−1.4	−1.3	−1.4	−0.4	+0.3	+0.9	+0.3	0.0	+0.2	+8.0	−0.1

[a] In ppm.

Table III. T_1 Relaxation Times in Seconds of Isomeric Retinals and Related Compounds

Compd	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15(CHO)	1a, 1a′	5a	9a	13a
I	23.1	2.2	2.6	1.8	34.6	28.0	4.8									1.9	9.5		
II	9.9	0.76	0.54	0.67	12.6	20.1	1.42	1.51	17.0	1.63	1.87					0.84	3.0	4.2	
III	9.5	0.52	0.38	0.56	11.4	18.5	1.02	1.23	13.9	0.82	1.08					0.64	2.1	2.2	
IV	4.4	0.32	0.16	0.28	5.1	8.4	0.45	0.44	5.4	*a*	0.42	0.50	5.5	0.50	0.57	0.46	1.4	1.9	1.9
V	4.8	0.37	0.29	0.38	6.5	8.2	0.56	0.63	5.2	*a*	0.52	0.54	5.3	0.26	0.37	0.48	1.7	2.3	1.6
VI	4.0	0.28	0.27	0.38	6.7	7.1	0.55	0.58	5.2	0.59	0.55	0.51	6.8	0.88	0.78	0.46	1.7	2.6	2.3
VII[b]	9.6	0.4	0.6	0.5		8.8	1.1	1.0	7.5	0.8	0.8	0.8		0.8	0.6	0.6	1.8	1.4	1.9

[a] This peak lies under peak 5 with a longer relaxation time. Peak 10 decays out rapidly thereby allowing C-5 to be studied. [b] Due to very low concentration of this difficult to obtain compound, these values lack accuracy and must be considered to be tentative.

analogous positions at or near sites of isomeric structure changes (*i.e.*, compare the $\Delta\delta$ values given in Table II for C-11 and V and C-7 in VII and III which move downfield; in addition, C-14 in V and C-10 in VII and III move upfield). The aldehyde carbons in II, IV, VI, and VII exhibit little variation in chemical shift reflecting similar local chemical environments and suggest that, since the polyene portion of IV is locked,[7] little rotation occurs around the C-14, C-15 bond in the other compounds. On the other hand, the aldehyde carbon moves upfield -1.2 ppm in V as it did in III, as discussed earlier, and this perturbation is undoubtedly due to a γ-steric interaction which also produces the upfield shift at C-12. In VII, an anomalous upfield shift occurs at C-9 (-1.4 ppm) which may be due to distortion in the C-8, C-9 or C-10, C-11 bond. With this one exception, the chemical shifts in IV, V, and VII as well as II and III are consistent and suggest that the polyene chains of II, III, V, and VII are essentially planar. These results are in agreement with uv[14] and pmr[7] data.

However, evidence given in ref 6 and 14 indicates that the 11-*cis*-retinal does not have a planar polyene chain, but the angular distortion occurs about the C-12, C-13 bond. The cmr data for 11-*cis*-retinal exhibit three major anomalies: the chemical shift changes at C-10, C-12, and C-13a. One cannot invoke the same arguments previously used to explain the intermediate upfield shift at C-10 because the C_{10}–H$\cdots$methyl interaction is different from the previously discussed γ interactions present in III, V, and VII. Regardless of which rotameric form (s-cis or s-trans about the C-12, C-13 bond) is assumed by 11-*cis*-retinal, it is expected that carbon C-10 should experience an upfield steric shift arising from interaction with either C-14 or C-13a so that the data for this carbon do not contribute to the resolution of the problem of rotameric conformation. The -4.4 ppm upfield shift observed at C-12 is considerably larger than the $\Delta\delta$ values observed at analogous positions in 13-*cis*-retinal (C-14; -1.2 ppm) and 9-*cis*-retinal (C-10; -1.3 ppm). The cause of this large change is not understood at this time. In the case of C-13a, a $+8$ ppm shift would be expected if the molecules were predominatly in the distorted s-cis form which would eliminate one cis-1,4 interaction at C-13a, and the methyl chemical shifts in V and VI would be similar. The steric chemical shift parameters are not known for the δ interaction resulting from conformations like that found in the s-trans form and hence it is not possible to accurately predict the contribution which this rotameric form would make to the C-13a chemical shift. However, such an interaction is not likely to be the same as the γ interaction noted in V. If a significant amount of the s-cis form exists at the experimental temperature (15°) one should expect to observe an upfield shift at C-14 due to steric interaction with C-10. Rather, a small downfield shift ($+0.8$ ppm) is observed.

Sykes, *et al.*,[7] propose an equilibrium between distorted s-cis and distorted s-trans structures at 32° and suggest that s-trans is preferred at $-47°$ while Becker and coworkers[14] report that considerable s-cis is favored at 25° with s-trans predominating at $-196°$. The cmr data reported herein, especially at C-10 and C-13a, do not indicate that either s-cis or s-trans is the predominant conformation. This uncertainty led to a study of the carbon-13 relaxation times because of their potential for characterizing possible segmental motion in the region of the C-12, C-13 bond in the important 11-*cis*-retinal isomer.

B. T_1 Relaxation Times. The T_1 values for the compounds studied in this work are given in Table III. With the exception of compound I and some of the "freely" rotating methyls the T_1's for proton-bearing carbons are of the order of 1 sec or less. In this range it is reasonable to assume that the proton carbon-13 dipolar term dominates the T_1 relaxation[15,16] and no attempt was therefore made to evaluate the nuclear Overhauser enhancement (NOE) factors. Furthermore, the relative NOE of the rapidly rotating methyls and of the carbons without directly bonded protons would indicate that spin–rotation or other relaxation mechanisms do not make significant contributions to these carbons. We, therefore, analyzed all data solely with theoretical expressions appropriate for dipole–dipole relaxation.

Several general observations are now appropriate. The T_1 values at corresponding positions decrease as one moves from the 10-carbon aldehyde (I) to the 15-carbon molecules (II and III) and on to the 20-carbon retinals (IV–VII). This trend, of course, may be rationalized in terms of the greater mass and bulk of the larger molecules. This increase in size leads to a decrease in the overall rotational diffusion with a concomitant reduction in T_1. Within the retinal series there is a slight increase in T_1 noted at most positions for the cis isomers over that of the trans molecule. This variation may be explained once again in terms of more rapid rotational motion in the slightly less extended cis isomers. Comparison of the T_1's for II and III indicates the reverse feature holds for the 15-carbon aldehydes as the T_1's in the cis compound now are slightly less than in the trans isomer. As the X-ray structural data are not presently available for these two species, no attempt is made to rationalize this apparent anomaly on structural grounds.

The great variety of methyl T_1 values clearly infers a significant range in internal methyl rotation rates. It is to be noted that methyls at C-1a in every case are the shortest of the methyl carbons manifesting larger internal rotation barriers. The remaining methyls at C-5a, C-9a, and C-13a each have T_1's which are 3 to 5 times greater than the value at C-1a and C-1b. This suggests considerably greater internal rotation rates for the polyene backbone methyls. As barriers for methyls attached to sp^2 *vs.* sp^3 carbons are generally lower, these results were to be expected. Attention is also focused on the shortening of T_1 at the 9a methyl when the trans–cis isomers II and III and IV and VII are compared. In each of these instances the symmetry of the barrier changes from sixfold to a dominant threefold with an apparent increase in magnitude leading to greater restriction of internal rotation. An analogous reduction of T_1 at the C-13a methyl for the IV–V trans–cis pair is also noted. In none of these cases is the

(14) A. H. Schaeffer, W. H. Wadell, and R. S. Becker, *J. Amer. Chem. Soc.*, **96**, 2063 (1974).

(15) A. Allerhand, D. Doddrell, and R. Komorski, *J. Chem. Phys.*, **55**, 189 (1971).

(16) J. R. Lyerla, Jr., and D. M. Grant, *MTP (Med. Tech. Publ. Co.) Int. Rev. Sci.: Phys. Chem., Ser. One*, **4**, 155 (1972).

Table IV

C-5, C-6, C-7, C-8 dihedral angle	Rotational diffusion constants[a] (10^9 per sec^{-1}) R_1	R_2	R_3	Standard deviations in fit of $1/T_1$	Moments of inertia for principal axes, amu Å^2 I_1	I_2	I_3
40°	19.3 ± 10.8	1.1 ± 0.8	<0.9	0.357	589	6433	6831
50°	15.4 + 4.4	1.2 ± 0.6	<0.6	0.258	601	6443	6788
60°	11.7 ± 1.9	1.3 ± 0.5	<0.5	0.206	613	6452	6744
70°	8.8 ± 1.0	1.4 ± 0.9	<0.8	0.209	629	6463	6674
80°	8.0 ± 1.2	1.7 ± 1.1	<0.9	0.216	641	6470	6610

[a] Whenever error limits exceed a magnitude of T_1 then the value is reported as $<(R + \Delta R)$ to avoid the implication of negative rotational diffusion constants.

reduction of motion comparable to that observed for the two C-1a methyls where methyl–methyl interactions augment the normal threefold barriers associated with two adjacent sp^3 carbon atoms.[17] The T_1 at the C-13a methyls in VI increases compared with IV even though corresponding C-1a values remain the same. This increase indicates that the motion of the C-13a methyl has *not* been restricted as might be expected if the s-trans (conformation designation of the C-12 C-13 bond) configuration were dominant in the 11-*cis*-retinal structure. The slight increase at C-9a and C-5a in VI compared with IV also suggests that other minor conformation variations noted by X-ray data in the solid state probably also exist in the skeletal structure between C-5 and C-11 in the liquid samples of these two isomers.

The observation of shorter T_1 values for carbons with C–H bonds lying in a direction more parallel to the long axis in these rod shaped molecules (one C–H bond at C-3 in species II through V and the C–H bonds at C-10, C-11 in III and at C-14, C-15 in V) suggests the importance of anisotropic rotational diffusion in these molecules. The shorter T_1 values at C-10, C-11 (especially C-10) in III and C-14, C-15 in V, thus, substantiate the planarity of these molecules about the cis double bond. Although the T_1 at C-12 is also the shortest ethylenic carbon in VI the shortening is not as pronounced as is noted in III (at C-10, C-11) and V (at C-14, C-15) with cis formation. Furthermore, a significant increase is noted at C-14, C-15 in the VI isomer whereas just the opposite trend might have been anticipated for an all planar 11-*cis*-retinal as the C–H bond vectors in this molecule would otherwise have been parallel at C-12, C-14, and C-15. The principal axes in the 9-*cis*-retinal compared with the all-trans isomer obviously will no longer lie in the same general directions relative to the six-member ring and, therefore, it is not possible to make comparisons for this compound. Furthermore, the low concentration available to us prevented the data refinement of VII which was given to I through VI and the 9-*cis*-retinal values presented herein must be considered to be tentative at this time.

To test the above qualitative conclusions the equations of Woessner[18] for the effect of anisotropic diffusion on T_1 were used to calculate rotational diffusion constants in these systems. The non-linear least-squares computer program used to acquire anisotropic rotational diffusion constants in compounds when redundancy in data is available is described in detail by Berger, *et al.*[19] As the inverse moment of inertia ellipsoid roughly characterizes the molecular shape of these aldehydes, this tensor was diagonalized to provide the principal axis[20] system for the rotational diffusion tensor. X-Ray structural data[1,2] on *trans*- and 11-*cis*-retinal were used to construct the carbon–oxygen skeletal structure of these two molecules. Idealized C–H bond distances (1.09 Å) and angles, however, were employed to fix the position of the hydrogens as the sixth-power dependence of dipolar relaxation on the ^{13}C–^1H distance was too sensitive for the rather crude X-ray data given for proton positions. This feature emphasizes the strength of relaxation techniques over other structural methods for fixing proton positions in a molecule. To explore the possibility that the dihedral angle about the C-6, C-7 bond may vary between the solid and liquid states, the calculation was undertaken for a variety of angles. The results of the T_1 fit are given in Table IV for C-5, C-6, C-7, C-8 dihedral angles in the ranges of 40 to 80°. As rotation about the C-6, C-7 bond does not greatly affect either of the moment of inertia components (see Table IV position 2 for the overall shape), it is understandable that the results of these five calculations are similar. It is interesting to note that all five calculations show a high degree of anisotropic diffusional motion, with R_2 and R_3 almost equal to each other, while R_1 is about an order of magnitude larger. The fastest motion is about the long axis of the molecule having the greatest cylindrical symmetry and the lowest moment of inertia. As the various R values in each column of Table IV become larger so do the corresponding errors, so that in almost every instance the values with the errors included overlap a common value.

In the 11-*cis*-retinal the C-5, C-6, C-7, C-8 dihedral angle was also varied about the 40° X-ray value but no significant difference was noted in the standard deviation of fit. Thus, our predicted T_1 values are for the 40° conformation. Because of its similarity with the all-trans isomer, the 13-*cis*-retinal was arbitrarily assigned the same 60° dihedral angle at C-5, C-6, C-7, C-8 as used in the trans isomer. The unavailability of any structural data on the 9-*cis*-retinal and the C_{15}

(17) D. M. Grant, R. J. Pugmire, R. C. Livingston, K. A. Strong, H. L. McMurray, and R. M. Brugger, *J. Chem. Phys.*, 52, 4424 (1970).

(18) D. E. Woessner, *J. Chem. Phys.*, 37, 647 (1962).

(19) S. Berger, F. R. Kreissl, D. M. Grant, and J. D. Roberts, submitted for publication.

(20) It is acknowledged that the moment of inertia and rotational diffusion tensors for an asymmetric molecule will not in general have the same principal axes system. However, in these molecules the molecular backbones are in every case carbon with only one terminal oxygen and no other heavy atoms. Thus, both mass and shape effects important in rotational diffusion will be characterized to a large extent by the principal axes of the moment of inertia tensor and, for want of a better approximation, these principal axes are used here for rotational diffusion.

aldehydes prevents a significant dynamical treatment of these molecules at this time.

Table V gives the comparison between predicted and experimental T_1's for IV through VI. Those experimental values given in parentheses were *not* used in the non-linear least-squares analysis to obtain the rotational diffusion constants given in Table V. Figure 2 contains a log–log plot of predicted *vs.* experimental T_1's to graphically illustrate the degree of fit obtained for the various types of carbons. A log–log plot is required to reveal the relative errors in T_1 data which span almost two orders of magnitude. Plots of T_1 or $1/T_1$ compress the data for either the proton-bearing or quaternary carbons, respectively, and obscure the scatter of one of these two groups of carbons. The significance of deviations of methyl carbons from the perfect agreement line is emphasized by this method of plotting as log–log plots are notorious for yielding straight lines. The considerable internal motion present in methyl groups led to discrepancies of an order of magnitude in the predicted *vs.* experimental values as observed in Table V and exhibited in Figure 2. For this reason the T_1 data of all methyl carbons were not included in the minimization process as the Woessner equation presumes a rigid structure. A comparison of found *vs.* predicted values for T_1 in methyl carbons gives a crude measure of the barrier to methyl rotation. Very large barriers completely restricting internal motion on the rotational diffusion time scale will result in good agreement between predicted and experiment, while a ninefold discrepancy can be found in methyl tops which are rotating very rapidly compared to overall rotational diffusion.[21] The great scatter in methyl carbons in Figure 2 indicates that the methyl rotation barriers vary considerably between different CH_3 groups. The methyls with relaxation times below 1 sec and lying closest to the perfect agreement line are attached at C-1 in every instance.

Table V. Predicted and Experimental Relaxation Times in Three Retinal Isomers[a]

Atom	*trans*-Retinal Exptl	*trans*-Retinal Pred	13-*cis*-Retinal Exptl	13-*cis*-Retinal Pred	11-*cis*-Retinal Exptl	11-*cis*-Retinal Pred
1	4.40	3.41	4.76	4.84	4.01	4.68
2	0.32	0.29	0.37	0.39	0.28	0.29
3	0.16	0.16	0.29	0.25	0.27	0.30
4	0.28	0.26	0.38	0.37	0.38	0.33
5	5.12	3.05	6.50	4.21	6.65	5.14
6	8.43	9.59	8.21	12.82	7.12	11.01
7	0.45	0.46	0.56	0.62	0.55	0.56
8	0.44	0.47	0.63	0.62	0.58	0.55
9	5.35	6.02	5.16	7.26	5.18	6.10
10	...	0.47	...	0.62	0.59	0.58
11	0.42	0.51	0.52	0.63	0.55	0.56
12	0.50	0.49	0.54	0.63	0.51	0.47
13	5.54	5.83	5.26	6.06	6.85	6.46
14	0.50	0.56	0.26	0.30	(0.88)	0.57
15	0.57	0.66	0.37	0.35	(0.78)	0.57
1a		0.15		0.21		0.22
	(0.46)		(0.46)		(0.46)	
1a′		0.16		0.24		0.22
5a	(1.43)	0.31	(1.62)	0.34	(1.72)	0.25
9a	(1.90)	0.16	(2.25)	0.23	(2.62)	0.23
13a	(1.92)	0.16	(1.57)	0.23	(2.29)	0.23
Std dev	0.206		0.254		0.200	
R_1, sec^{-1}	$11.7 \pm 1.9 \times 10^9$		$11.3 \pm 2.8 \times 10^9$		$4.6 \pm 1.6 \times 10^9$	
R_2, sec^{-1}	$1.3 \pm 0.5 \times 10^9$		$2.2 \pm 0.8 \times 10^9$		$2.3 \pm 0.7 \times 10^9$	
R_3, sec^{-1}	$<0.5 \times 10^9$		$<0.7 \times 10^9$		$0.9 \pm 0.5 \times 10^9$	

[a] Parentheses indicate data not included in analysis.

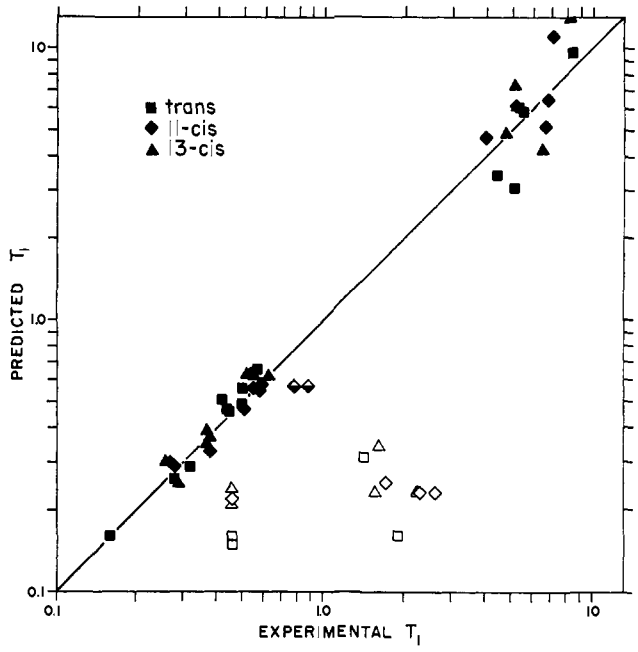

Figure 2. A log–log plot of predicted *vs.* experimental T_1 for *trans*-retinal, 13-*cis*-retinal, and 11-*cis*-retinal. The log–log plot provides an estimate of relative deviations in data over a range of almost two orders of magnitude. Significant negative deviation of the predicted values from the perfect correlation line is indicative of segmental motion of these carbons. These carbons, primarily methyls, were not included in the data fitting program and are indicated by open symbols. The two half-filled diamonds are for C-14 and C-15 in 11-*cis*-retinal.

The fairly large scatter noted for quaternary carbons appearing in the upper right hand corner of Figure 2 reflects the greater errors intrinsic in these carbons which relax through long-range ^{13}C–^{1}H interactions. Furthermore, as the least-squares minimization was executed on reciprocal T_1's or relaxation rates, it is the larger rate constants or shorter T_1's which are more accurately determined that fortunately weight the calculation of the rotational diffusion constants. The correlation of more than 40 T_1's ranging from 0.16 to 8.21 sec, a better than 50-fold range, with one model and three rotational diffusion constants for each molecule however must be considered to be unusually good when proper account is given to the very high power (sixth order) dependence of spin–spin interactions on distance. In addition, methyl segmental motion will decrease the efficiency of some long-range interactions and intermolecular interactions can increase relaxation rates of quaternary carbons more than proton bearing carbons where relaxation is essentially dominated by directly bonded hydrogens.

With the exception of CH_3 groups the correlation of carbons bearing protons, shown in the lower left portion of Figure 2, is of course very satisfactory. Based on this unusually good fit of such carbon atoms the C-14, C-15 carbons in 11-*cis*-retinal are indicated by half-filled diamonds do stand out as unique. This failure to fit the data at C-14, C-15 in VI provides evi-

(21) K. F. Kuhlmann and D. M. Grant, *J. Chem. Phys.*, **55**, 2998 (1971).

dence for significant internal or segmental motion in this very important 11-cis isomer. When viewed in combination with the chemical shift data on VI, a good picture of the "dynamical" structure is provided. The rapid segmental motion indicated for the C-13a, C-14, C-15 moiety from relaxation data arises presumably from the inability of the molecule to assume the normal planar, conjugated structure. These data would warn against the use of a static conformation for the 11-*cis*-retinal at least on the nanosecond time scale important in the reorientational motion of these molecules.

We believe this use of T_1 and chemical shift data to elicidate both structural and dynamical features of a moderate sized molecule emphasizes the importance of utilizing both techniques in concert. The two types of data have been shown here to provide complimentary information useful in molecular studies of both structure and motion.

Acknowledgment. This work was supported by the National Institutes of Health under Grants RR-574-03, GM 08521, and RO1-EY-00875. The computer program used in interpreting T_1 values in molecules undergoing anisotropic diffusion was developed for another purpose in conjunction with Professor J. D. Roberts at California Institute of Technology, and we appreciate his encouragement of this work. He is supported by the National Institutes of Health (GM 11072) and National Science Foundation. The Sherman Fairchild Distinguished Scholars Program at California Institute of Technology provided computer funds and partial support for one of us (D. M. G.) during 1973–1974. SB is a Deutsche Forschungsgemeinschaft Postdoctoral Fellow, 1973–1974. We also wish to thank Hoffmann-La Roche Chemical Co. for the generous gift of 11-*cis*-retinal and Mr. James C. Smith for assistance in acquiring data.

Cope Elimination and Meisenheimer Rearrangement with *N*,*N*-Dimethyl-3-aminohomoadamantane *N*-Oxide. Evidence for 3-Homoadamantene[1]

Benjamin L. Adams[2,3] and Peter Kovacic*

Contribution from the Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201. *Received May 16, 1974*

Abstract: Decomposition of *N*,*N*-dimethyl-3-aminohomoadamantane *N*-oxide yielded dimers of bridgehead homoadamantene (9%), 4-homoadamantene (5%), *N*,*N*-dimethyl-*O*-(3-homoadamantyl)hydroxylamine (25%), homoadamantane (29%), 3-hydroxyhomoadamantane (2%), and *N*,*N*-dimethyl-3-aminohomoadamantane (12%). Elimination appears to take place with predominant formation of 3-homoadamantene. Trapping of the strained alkene was successfully carried out by Diels–Alder cycloaddition with 1,3-diphenylisobenzofuran. The Meisenheimer product was formed by the unusual migration of a tertiary group, 3-homoadamantyl, during reaction. Thermolysis of the amine oxide in the presence of furan gave a mixture containing 2-(3-homoadamantyl)furan.

The topic of the limits of Bredt's rule is of considerable current interest.[4–8] A variety of methods has been applied to generate these bridgehead alkenes, such as Hofmann elimination,[4] Corey–Winter[5] synthesis, bisdehalogenation of vicinal diiodides,[6] and type II photoelimination.[7] Although Cope elimination[9] of tertiary amine oxides is a well-known route to alkenes, this procedure has not been previously used for preparation of highly strained bridgehead double bonds. The present work reports the generation, as well as subsequent trapping, of 3-homoadamantene from pyrolysis of *N*,*N*-dimethyl-3-aminohomoadamantane *N*-oxide (**1**).

In addition to elimination, the unusual migration of a tertiary group, 3-homoadamantyl, by Meisenheimer rearrangement was observed. Meisenheimer rearrangement[9] generally occurs with a migrating entity capable of stabilizing a negative charge or radical. Very little has been reported[10] for purely alkyl systems.

Results and Discussion

Decomposition of *N*,*N*-dimethyl-3-aminohomoadamantane *N*-oxide[11] (**1**) at 140–175° (1 mm) provided a hydrocarbon mixture (**2**; 9%) composed of dimers of 3-homoadamantene, 4-homoadamantene[12] (**3**; 5%), *N*,-

(1) Paper X, Adamantanes and Related Compounds; preliminary communication, B. L. Adams and P. Kovacic, *J. Amer. Chem. Soc.*, **95**, 8206 (1973).

(2) Graduate School Fellow, 1973–1974.

(3) Taken in part from the Ph.D. thesis of B. L. Adams, 1974.

(4) (a) J. R. Wiseman and W. A. Pletcher, *J. Amer. Chem. Soc.*, **92**, 956 (1970); (b) J. R. Wiseman, H. F. Chan, and C. J. Ahola, *J. Amer. Chem. Soc.*, **91**, 2812 (1969); (c) J. R. Wiseman and J. A. Chong, *J. Amer. Chem. Soc.*, **91**, 7775 (1969).

(5) J. A. Chong and J. R. Wiseman, *J. Amer. Chem. Soc.*, **94**, 8627 (1972).

(6) (a) R. Keese and E-P. Krebs, *Angew. Chem., Int. Ed. Engl.*, **10**, 262 (1971); (b) *ibid*,, **11**, 518 (1972); (c) D. Grant, M. A. McKervey, J. J. Rooney, N. G. Samman and G. Step, *J. Chem. Soc., Chem. Commun.*, 1186 (1972); (d) D. Lenoir, *Tetrahedron Lett.*, 4049 (1972).

(7) J. E. Gano and L. Eizenberg, *J. Amer. Chem. Soc.*, **95**, 972 (1973).

(8) J. A. Marshall and H. Faubl, *J. Amer. Chem. Soc.*, **92**, 948 (1970); (b) A. H. Alberts, J. Strating, and H. Wynberg, *Tetrahedron Lett.*, 3047 (1973); (c) H. H. Grootveld, C. Blomberg, and F. Bickelhaupt, *J. Chem. Soc., Chem. Commun.*, 542 (1973); (d) G. L. Buchanan and G. Jamieson, *Tetrahedron*, **28**, 1123, 1129 (1972); (e) S. F. Campbell, R. Stephens, and J. C. Tatlow, *Tetrahedron*, **21**, 2997 (1965); (f) A. D. Wolf and M. Jones, Jr., *J. Amer. Chem. Soc.*, **95**, 8209 (1973).

(9) A. C. Cope and E. R. Trumbull, *Org. React.*, **11**, 317 (1960).

(10) (a) J. I. Brauman and W. A. Sanderson, *Tetrahedron*, **23**, 37 (1967); (b) Y. Hattori, *J. Pharm. Soc. Jap.*, **60**, 24 (1940); *Chem. Abstr.*, **34**, 3387 (1940).

(11) E. I. duPont de Nemours & Co., Netherland Patent 6404755 (1964); *Chem. Abstr.*, **63**, 6887 (1965).

(12) R. M. Black and G. B. Gill, *J. Chem. Soc. C*, 671 (1970); Z. Majerski, S. H. Liggero, and P. v. R. Schleyer, *Chem. Commun.*, 949 (1970). We thank Dr. G. B. Gill and Dr. Z. Majerski for samples of 4-homoadamantene.