Restricted Rotation and Ring-Chain Conformation in Hindered 7-Cis Isomers of Retinal and Related Compounds. A Nuclear Magnetic Resonance Study

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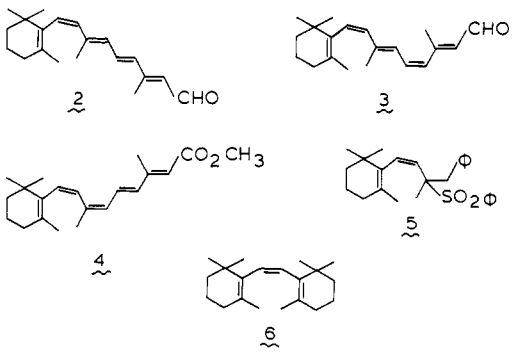
The ring-chain conformations of three 7-cis isomers of vitamin A and several related hindered trienes have been examined by ^1H NMR methods (long-range coupling constant, NOE, and DNMR). The dihedral angles are shown to be significantly higher than those of the related 7-trans isomers. The barriers of rotation of the 6,7 single bond, as measured by $\Delta G^{\ddagger}_{c}$, fall in the range of 11–14 kcal/mol. For a much more hindered 7-cis diene, the corresponding barrier was found to be 19.7 ± 0.3 kcal/mol.

The configurational isomers of retinal and their conformational properties are of considerable importance to the current understanding of the visual process.[1] For example, working with six geometric isomers of retinal, Wald et al. first identified the correct geometry of the chromophore in the visual pigment and then examined the stereospecificity of the binding site of the visual protein, opsin.[2] Conformationally induced chirality is believed to be a possible contributing cause for the circular dichroism of the visual pigment.[3] And, the 12-*S*-cis,12-*S*-trans equilibrium is believed to play an important role in the absorption and the decay properties of the pigment.[4]

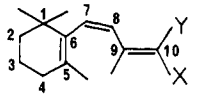
In recent years nuclear magnetic resonance spectroscopy has been used extensively in studies of the conformational properties of the isomers of retinal and related compounds. Among these are the early ^1H work by Patel,[5] later more detailed studies by Sykes and co-workers,[6] the lanthanide shift reagent work by Lienard and Thomson,[7] and the ^{13}C work by several research groups.[8] All these studies involved the all-trans and/or the earlier known five cis isomers of retinal (9-cis, 11-cis, 13-cis, 9,13-dicis, 11,13-dicis). But since 1975, a series of new geometric isomers (7-cis, 7,9-dicis, 7,13-dicis, 7,9,13-tricis,[9] 7,11-dicis,[10] 9,11-dicis,[11] 7,9,11-tricis,[12] 9,11,13-tricis[13]) became available, most of them containing the previously unavailable 7-cis geometry.[14] The severe steric crowding in such isomers is expected to lead to uniquely different conformation of the chromophore. Yet, all of them are capable of forming pigment analogues when incubated with bovine opsin.[10,11,15] A detailed analysis of the conformational properties of such molecules is therefore of interest. Earlier the NMR properties of several cis dienes in the vitamin A series were described.[16] Now we report results of a study on several trienes and longer polyenes.

Chart I



Results

The compounds used in the current study included several key intermediates (**1a–d,h,i**) in the synthesis of the



1a, X = CHO; Y = H
b, X = H; Y = CHO
c, X = CHO; Y = F
d, X = F; Y = CHO
e, X = $CONC_6H_4CH_3$; Y = H
f, X = H; Y = $CONC_6H_4CH_3$
g, X = CN; Y = CN
h, X = *t*-CH=CHCOCH$_3$; Y = H
i, X = H; Y = *t*-CH=CHCOCH$_3$

7-cis isomers of retinal[9,17] and fluorinated retinals.[18] The

(1) For recent review see: (a) Uhl, R.; Abrahamson, E. W. *Chem. Rev.* **1981**, *81*, 291–312. (b) Birge, R. *Annu. Rev. Biophys. Bioeng.* **1981**, *10*, 315–354.
(2) (a) Summarized in: Wald, G. *Science (Washington, D. C)* **1968**, *162*, 230–239. (b) Wald, G.; Brown, P. K.; Hubbard, R.; Oroshnik, W. *Natl. Acad. Sci. U.S.A.* **1955**, *41*, 438–450; **1956**, *42*, 578–580.
(3) Kropf, A.; Wittenberger, B. P.; Goff, S. P.; Waggoner, A. S. *Exp. Eye Res.* **1973**, *17*, 591–606.
(4) (a) Honig, B.; Karplus, M. *Nature (London)* **1971**, *229*, 558–560. (b) Warshel, A.; Karplus, M.; *J. Am. Chem. Soc.* **1974**, *96*, 5677–5689.
(5) Patel, D. *Nature (London)* **1969**, *221*, 825–828.
(6) (a) Honig, B.; Hudson, B.; Sykes, B. D.; Karplus, M. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1289–1293. (b) Rowan, R., III; Sykes, B. D. *J. Am. Chem. Soc.* **1975**, *97*, 1023–1027. (c) Rowan, R., III; Warshel A.; Sykes, B. D.; Karplus, M. *Biochemistry* **1974**, *13*, 970–981.
(7) Lienard, B. H. S.; Thomson, A. J. *J. Chem. Soc., Perkin Trans.* **1977**, 1400–1410.
(8) (a) Rowan, R., III; Sykes, B. D. *J. Am. Chem. Soc.* **1974**, *96*, 7000–7008. (b) Becker, R. S.; Berger, S.; Dalling, D. K.; Grant, D. M.; Pugmire, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 7008–7014. (c) Inoue, Y.; Takahashi, A.; Tokito, Y.; Chujo, R.; Miyoshi, Y.; *J. Org. Magn Reson.* **1974**, *6*, 487–491. (d) Englert, G. *Helv. Chim. Acta* **1975**, *58*, 2367–2390. (e) Shriver, J. W.; Abrahamson, E. W.; Mateescu, G. D. *J. Am. Chem. Soc.* **1976**, *98*, 2407–2409.
(9) (a) Ramamurthy, V.; Liu, R. S. H. *Tetrahedron* **1975**, *31*, 201–206. (b) Asato, A. E.; Liu, R. S. H. *J. Am. Chem. Soc.* **1975**, *97*, 4128–4130. (c) Liu, R. S. H.; Asato, A. E. *Methods Enzymol.* **1982**, *88*, 506–516.
(10) Kini, A.; Matsumoto, H.; Liu, R. S. H. *J. Am. Chem. Soc.* **1979**, *101*, 5078–5079.
(11) Kini, A.; Matsumoto, H.; Liu, R. S. H. *Bioorg. Chem.* **1980**, *9*, 406–410.
(12) Asato, A. E.; Kini, A.; Denny, M.; Liu, R. S. H. *J. Am. Chem. Soc.* **1983**, *105*, 2923–2924.
(13) Knudsen, C. G.; Carey, S. C.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6355–6356.
(14) For a review on synthesis and photochemistry of stereoisomers of vitamin A, see: Liu, R. S. H.; Asato, A. E. *Tetrahedron*, in press.
(15) DeGrip, W. J.; Liu, R. S. H.; Ramamurthy, V.; Asato, A. E. *Nature (London)* **1976**, *262*, 416–418
(16) (a) Ramamurthy, V.; Bopp, T. T.; Liu, R. S. H. *Tetrahedron Lett.* **1972**, 3915–3916. (b) Ramamurthy, V.; Liu, R. S. H. *Proc.—Indian Acad. Sci., Sect. A* **1979**, *88A*, 239–247.
(17) Ramamurthy, V.; Tustin, G.; Yau, C. C.; Liu, R. S. H. *Tetrahedron* **1975**, *31*, 193–199.
(18) Asato, A. E., Matsumoto, H.; Denny, M.; Liu, R. S. H. *J. Am. Chem. Soc.* **1978**, *100*, 5957–5960.

0022-3263/83/1948-4817$01.50/0

Table I. Chemical Shift Difference ($\Delta\delta$) of 1,1-Dimethyl Groups, the Coalescence Temperature (T_c), and Free Energy of Activation ($\Delta G^{\ddagger}_c$) in Compounds in the Vitamin A Series Containing the 7-Cis Geometry

compd	solvent[a]	T_c, K	$\Delta\delta$, Hz[b]	$\Delta G^{\ddagger}_c$, kcal/mol
1a	C	255	8.64	13.3
1b	C	220	10.0	11.4
1c	A	260	9.6	13.5
1d	A	228	9.6	11.8
1e	C	264	15.5	13.5
1f	C	260	11.5	13.5
1h	C	262	8.5	13.7
1i	C	242	9.1	12.6
2	C	269	9.95	14.0
3	A	260	9.1	13.6
4	C	235	12.7	11.8
5[c]	D	423	85.0	20.3
		401	38.0	19.9
		413	59.0	19.5
		363	4.1	19.5

[a] C = chloroform-d; A = acetone-d_6; D = Me_2SO-d_6. [b] Difference in the chemical shifts of the 1,1-dimethyl groups in the slow exchange region. [c] The spectra exhibit five different pairs of temperature-dependent signals all with different $\Delta\delta$'s, hence different T_c's. The data are listed in the order of CH_3-1,1, CH_3-1',1', CH_3-5, benzylic H's, and H_8. The last two have identical $\Delta\delta$'s of 4.1 Hz.

7-cis isomers of the triene derivatives,[17,19] including the "minicarotene" **6**,[20] were obtained by selective triplet sensitized isomerization of the corresponding all-trans isomer. The two C_{18} ketones (**1h,i**), via acetone condensation with **1a** or **1b**, and the vitamin A derivatives (**2–4**, Chart I), via C_2 chain extension of the C_{18} ketones,[9,10] were obtained in synthetic studies described previously. Compound **5**, a colorless solid, was described earlier.[21]

Dynamic NMR Studies. The spectra of all compounds with the 7-cis geometry exhibited similar temperature-dependent behavior. While most signals were essentially temperture independent, those of the 1,1-dimethyl groups changed from a sharp singlet at room temperature to two singlets upon cooling to ≤–60°. Within this temperature range the spectra corresponded to those of a two-site exchange. The coalescence temperature (T_c) and the difference in chemical shifts of the two singlets at low temperatures ($\Delta\delta$) varied depending on the substituents and the polyene geometry. These values are tabulated in Table I.

In most cases experimental difficulties (e.g., relatively small $\Delta\delta$ values) precluded accurate determination of the exchange rate constants over a sufficiently large temperature range to allow a reliable determination of the enthalpy and entropy of activation for the exchange processes. Instead, the $\Delta G^{\ddagger}_c$ values, the free energies of activation at coalescence temperatures (T_c) were calculated by using the standard equation[22] (eq 1). The calculated values are listed in Table I.

$$\Delta G^{\ddagger}_c = RT_c[\ln (k/h) + \ln (2^{1/2}T_c/\pi\Delta\delta)]$$
$$= 4.575T_c[9.972 + \log (T_c/\Delta\delta)] \quad (1)$$

Compound **5**, even though a diene, is included because it represents the most sterically congested molecule in the series so far prepared. At room temperature its ^1H NMR spectrum was rather complex, containing several singlets at an unusually high field. A careful analysis led to the conclusion that the spectrum corresponds to a mixture of diastereomeric rotamers in a ratio of 55% to 45%. Examination of space-filling molecular models indicated that either (or both) the benzyl or the phenylsulfonyl group lies directly above the CH_3-5 and one of the 1,1-dimethyl groups, accounting for the high-field signals.[23] The extent of ring current effect on the different methyl groups suggests that the most likely structures for the diastereomers are those shown in Figure 1. Assignments of all of the signals are also shown.

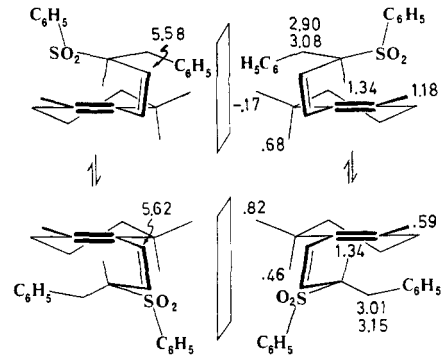


Figure 1. Structures and assignments of ^1H NMR signals (at room temperature in Me_2SO-d_6) for the diastereomeric rotamers of the sulfone **5**, with the phenylsulfonyl group assuming an averaged conformation away from the cyclohexenyl ring.

At temperatures above 90 °C, the 100-MHz spectra exhibited dynamic behavior, interestingly with five pairs of signals (CH_3-16,17,18, benzylic CH_2, and H_8) coalescing at different temperatures (due to different $\Delta\delta$'s). The fast-exchange limit, however, was never reached. At 190 °C the compound underwent irreversible degradation. The highest temperature at which the compound was sufficiently stable for studies was 160 °C, where the methyl region was rather complex, corresponding to signals of fast (for small $\Delta\delta$'s) and moderately fast (for large $\Delta\delta$'s) exchanges. The approximate $\Delta G^{\ddagger}_c$'s were calculated from the five groups of signals, giving an averaged value of 19.7 ± 0.3 kcal/mol.

The ^{13}C NMR spectra of several of these compounds have been recorded. Peak assignments were aided by a gated decoupling technique,[24] as well as by comparison with model 7-trans compounds[8] (see Experimental Section). Again only 1,1-$(CH_3)_2$ signals showed temperature dependence. For example, for compound **1f** the sharp singlet at 28.7 ppm in the room-temperature noise-decoupled spectrum began to broaden at 0 °C and eventually separated into two singlets at ≤-20 °C ($\Delta\delta$ = 9.4 Hz).

On the other hand, neither the ^1H nor ^{13}C NMR spectra (in toluene-d_8) of the highly crowded hydrocarbon **6** showed temperature dependence. Accidental equivalence of chemical shifts of the nonequivalent 1,1-dimethyl groups was probably the cause which was also attributed to similar results in the related 3,3-dimethylcyclohexene.[25]

Long-Range Coupling Constants. By use of the empirical eq 2 and 3 (where A is an empirical constant = 5–8

$$J_{5,7} \simeq A/2 \sin^2 \phi \quad (2)$$

$$J_{4,7} \simeq 0.3 + 3A/4 \sin^2 \phi \quad (3)$$

(19) Ramamurthy, V.; Butt, Y.; Yang, C.; Yang, P.; Liu, R. S. H. *J. Org. Chem.* **1973**, *38*, 1247–1249.
(20) Gapski, G.; Kini, A.; Liu, R. S. H. *Chem. Lett.* **1978**, *803*–804.
(21) Miller, D.; Trammell, M.; Kini, A.; Liu, R. S. H. *Tetrahedron Lett.* **1981**, *22*, 409–412.
(22) See, e.g.: Jackman, L. M.; Cotton, F. A. "Dynamic Nuclear Magnetic Resonance"; Academic Press: New York, 1975; p 76.
(23) Yang, C. S. C.; Liu, R. S. H. *Tetrahedron Lett.* **1973**, *4811*–4814.
(24) LeCocq, C.; Lallemand, J.-Y. *J. Chem. Soc., Chem. Commun.* **1981**, *150*.
(25) Bernard, M.; St. Jacques, M. *Tetrahedron* **1973**, *29*, 2539–2544.

Table II. Vicinal and Long-Range Coupling Constants in 7-Cis Compounds in the Vitamin A Series

compd	coupling constants, Hz						dihedral angle,[c] deg
	$J_{7,8}$	$J_{7,10}$	$J_{8,10}$	$J_{CH_2\text{-}4,7}$	$J_{CH_3\text{-}5,7}$	$J_{CH_3\text{-}9,10}$	
1g[a]	12.28			2.40	1.14		32-48
1c[b]	11.80	0.62	2.53	2.32	1.34	3.37	35-47
1d[b]	12.47	1.53	0.34	2.29	1.31	4.25	34-46

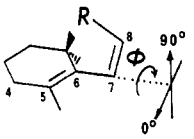
[a] Experimental values from selective decoupling ±0.05. [b] Experimental values confirmed by computer simulation ±0.02. [c] Calculated values based on eq 1 and 2 in the text.

Table III. Nuclear Overhauser Effect in 9-*cis*- and 7-*cis*,9-*cis*-10-Fluoro C_{15} Aldehyde in $CDCl_3$ at 20 °C[a]

signal irradiated	isomer	signal enhancement,[b] %		
		H_7	H_8	H_{11}
1,1-CH_3	9-cis	12.5 ± 2.6	8.2 ± 0.9	
	7-cis,9-cis	20.4 ± 0.6	0.2 ± 0.9	
5-CH_3	9-cis	2.4 ± 2.6	6.3 ± 0.9	0.3 ± 0.4
	7-cis,9-cis	−6.6 ± 0.6	1.3 ± 0.9	
9-CH_3	9-cis	11.2 ± 2.6	4.8 ± 0.9	
	7-cis,9-cis	4.8 ± 0.6	0.4 ± 0.9	
11-H	9-cis	4.8 ± 0.3	27.2 ± 0.3	
	7-cis,9-cis	1.1 ± 1.2	14.5 ± 1.4	

[a] All samples were sealed after three freeze–pump–thaw cycles. [b] Error limits reflect accuracies of data obtained by averaging off resonance-controlled runs before and after NOE experiments.

Hz), Karplus and co-workers were able to evaluate the ring–chain dihedral angle (ϕ) of β-ionone and related



compounds from the five-bond coupling constants between H-7 and 4-CH_2 or 5-CH_3.[6] The larger dihedral angles suspected for the sterically crowded 7-cis compounds would suggest larger five-bond coupling constants. Experimentally this expectation has been verified. Selective decoupling permitted accurate measurement of the long-range coupling constants. For compounds containing a hydrogen at C-10, the additional five-bond coupling constant between H_7 and H_{10} at a magnitude just sufficient to obscure fine structures for direct measurements of coupling constants introduced some difficulties. However, in **1c** and **1d** because of the larger five-bond H_7–F_{10} coupling constants, the fine structures again became observable. In Table II are listed the long-range coupling constant data and the calculated dihedral angles.

Nuclear Overhauser Effect (NOE). Enhancement of the signal intensity of the vinyl hydrogens upon irradiation of the ring methyls in β-ionone was shown to be a useful method for determining the proximity of the nonbonded hydrogens on the ring and in the chain, hence providing information on the conformation of the polyene chain.[6a] We have now conducted a similar study on 7-*cis*,9-*cis*-10-fluoro C_{15} aldehyde **1d**. For comparison, the corresponding 9-cis isomer was also examined. The data are listed in Table III.

Discussion

Both the 7-cis and the 11-cis isomers of carotenoids are historically referred to as being sterically hindered.[26] But the extent of steric crowding in the two cases is actually quite different. The steric crowding as a result of 1,7 hydrogen–hydrogen interaction between H_{10} and 20-CH_3

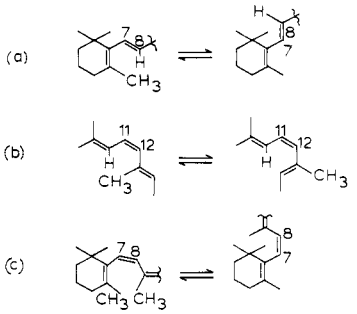


Figure 2. Nonbonded interactions in isomers of vitamin A: (a) 1,7 hydrogen–hydrogen interaction in all 7-trans isomers. (b) 1,7 hydrogen–hydrogen interaction in 11-cis isomers. (c) 1,9 hydrogen–hydrogen interaction in 7-cis isomers.

in the 11-cis isomer is relatively small, not as severe as that around the 7-cis geometry. It is identical with the ring–chain interaction in all of the 7-trans compounds (Figure 2a,b), which somewhat inconsistently have not been considered sterically hindered. Not surprisingly, the extents of distortion away from coplanarity around these two centers are quite similar. For example, for 11-*cis*-retinal, the 5,6,7,8 angle = 41.4°, and the 11,12,13,14 angle = 38.7° as determined by X-ray crystallography.[27]

The 1,9 hydrogen–hydrogen interaction in either the 6-*S*-cis or the 6-*S*-trans conformation of the 7-cis isomers (Figure 2c) increases substantially the extent of steric crowding around the ring. Therefore, it might be reasonable for such compounds to assume a highly twisted ring–chain orientation where the nonbonded interactions are minimized. The range of ring–chain dihedral angles as determined from analyses of long-range coupling constants (Table II) is at first surprisingly small. They are, however, on the average 10° greater than those of the analogous 7-trans compounds. A similar trend was seen in the X-ray crystal structure of vitamin A. For example, the corresponding ring–chain dihedral angle in methyl 7-*cis*,9-*cis*-retinoate was observed to be 53°,[28] less than 15° greater than the corresponding value in 11-*cis*-retinal. Upon inspection of molecular models, it became apparent that a simultaneous twisting of the 8,9 bond and a smaller twisting of the 6,7 bond could achieve the same degree of steric relief relative to only the amount the 6,7 bond is twisted. The crystal structure of methyl 7-*cis*,9-*cis*-retinoate in fact showed the 7,8,9,10 dihedral angle to be 26° vs. 9.2° in 11-*cis*-retinal.[27]

The NOE results of 7-*cis*,9-*cis*-10-fluoro C_{15} aldehyde **1d** and the corresponding 9-cis isomer (Table III) are also in agreement with the above conclusion. The large enhancement of the H-7 signal upon irradiation of the 1,1-dimethyl group and the lack of enhancement of the same proton upon irradiation of 5-CH_3 indicate that the twisted 6-*S*-cis conformer is more stable than the 6-*S*-trans form.

(26) See, e.g.: Zechmeister, L. "Cis-trans Isomeric Carotenoids, Vitamin A and Arylpolyenes"; Academic Press: New York 1962.

(27) Gilardi, R. D.; Karle, I. L.; Karle, J. *Acta Crystallogr., Sect. B* **1972**, *B28*, 2605–2612.

(28) Matsumoto, H.; Liu, R. S. H.; Simmons, C.; Seff, K. *J. Am. Chem. Soc.* **1980**, *102*, 4259–4262.

These results suggest a different shape of the torsional potential curve about the 6,7-single bond as in the case of 7-trans isomers. For the latter the 6-*S*-trans conformer was thought to be near the more stable 6-*S*-cis conformer with both separated by a low barrier.[6c] It is also interesting to note a smaller enhancement of H-8 upon irradiation of H-11 in the 7-cis,9-cis than in the 9-cis isomer. The result is in agreement with a nonplanar conformation around the 8,9-single bond in **1d**. Therefore, relief of steric crowding is achieved through twisting both the 6,7 and 8,9 single bonds.

A twisted 6-*S*-cis conformation is also consistent with the unusually high-field signal of the 5-methyl group.[17] In such a conformation the C_5-methyl group is oriented directly toward C-9 and is in the shielding cone of the 9,10-double bond.

The most characteristic features for the hindered 7-cis isomers are the dynamic NMR behavior of the 1,1-methyl groups (proton and carbon). The measured barrier for the dynamic process (12–14 kcal/mol) is substantially higher than that attributed to interconversion of half chairs of 3,3-dimethylcyclohexene ($\Delta G^{\ddagger}_c$ = 6.3 kcal/mol).[25] On consideration of the steric crowding and the temperature independence of the signals for the remaining portion of the compounds, it seems reasonable to associate the temperature-dependent, two-site exchange process with hindered rotation of the chain around the ring (e.g., see Figure 1). The barrier of rotation[29] averages 13.6 ± 0.3 kcal/mol for the 7-cis isomer and 12.2 ± 0.6 kcal/mol for the 7-cis,9-cis isomers. Since the 9,10 geometry is too remote to have a significant effect on the relative heights of the transition states, the lower values for the dicis isomer are most likely due to the lower stability of the conformation adopted by such isomers. It is noteworthy that none of the corresponding 7-trans isomers demonstrated similar temperature-dependent behavior within the same (or even lower)[30] temperature range. If one assumes similar $\Delta\delta$ values for the two methyl groups in the 7-trans isomer, an upper limit of ~7 kcal/mol can be assigned to the $\Delta G^{\ddagger}_c$ for the corresponding process of the 7-trans isomers. The difference of the $\Delta G^{\ddagger}_c$ values (~5–7 kcal/mol) for the two types of compounds is a reflection of the different extent of steric crowding between 7-cis and 7-trans isomers of compounds in the vitamine A series.

The rotational isomers are enantiomeric. While the barriers of rotation are too low for resolution of such optical isomers, it is interesting to speculate whether with additional assistance, e.g., by the medium, formation of one rotamer can be enhanced. One might speculate that the chirality exhibited by the 7-cis analogues of rhodopsin[32] could be due to interaction of visual protein opsin selectively with one enantiomer of the retinal.

There are two interesting points related to compound **5**. First, the asymmetric center at C-9 when coupled with the temperature-dependent molecular asymmetry caused by ring–chain orientations makes the molecule exhibit temperature-dependent diastereomerism. Second, the bulky substituents on the quaternary center cause the barrier of rotation to be much higher than those in 7-cis trienes, longer polyenes, and other 7-cis dienes reported earlier.[16] Under the proper conditions separation of diastereomers might be possible.[33]

Experimental Section

General Methods. All NMR studies were carried out primarily on an IBM NR-80 and to a limited extent on a Varian XL-100 spectrometer. Me_4Si or $CFCl_3$ was used as an internal standard. A modified LAOCOON-2 program was used for simulation and analyses of the DNMR spectra. The IBM Inst. PANIC (*P*arameter *A*djustment in *N*MR by *I*teration *C*alculation) program was used for simulation and analyses of the decoupled spectra. For NOE studies, degassed and sealed samples were used. The block-averaged alternating on/off pulse sequence for the decoupling frequency was followed.

Material. Several compounds containing the 7-cis geometry were accumulated in recent years at Hawaii through a general program of synthesis of new isomers of vitamin A: **1a** and **1b**,[9c,17] **1h** and **1i**,[9a] **2** and **4**,[9c] and **3**.[10] The compounds were repurified by flash chromatography or high-pressure liquid chromatograph (HPLC) before use. Other 7-cis compounds were prepared by selective photosensitized isomerization of the 7-trans compound.

Preparation of 7-Trans Isomers. The 7-trans isomers of β-ionylidenemalononitrile (**7**),[17] β-ionylidenefluoroacetaldehyde (**8**),[34] and β-ionyl phenyl sulfone (**9**)[25] were prepared according to literature procedures. *N*-Methyl-*N*-phenyl-β-ionylideneacetamide was prepared by the Emmons reaction of β-ionone (19.2 g, 0.10 mol) with *N*-methyl-*N*-phenyl(diethylphosphono)acetamide (28.5 g, 0.10 mol) in benzene (0.4 L) and NaH (2.40 g, 0.10 mol) at room temperature for 11 h. The crude product, a colorless solid (18.5 g, 57% yield), was recrystallized from aqueous EtOH; mp 72–74 °C. The ^1H NMR (CD_3COCD_3) is consistent with the all-trans geometry: δ 0.95, 1.57, 2.24 (CH_3-1,5,9), 3.23, 3.28 (NCH_3, 3:2 mixture of C–N rotational isomers), 5.61 (H_{10}), 5.81 (d, H_8), 6.40 (d, H_7) ($J_{7,8}$ = 15.9 Hz); MS, *m/e* (M^+) 323.227 ± 0.032 (calcd for $C_{22}H_{29}NO$ 323.225); UV (hexane) 294 nm.

***trans*-1,2-Bis(2,6,6-trimethylcyclohex-1-enyl)ethylene (10).** To a slurry of 7.72 (0.05 mol) of $TiCl_3$ in 150 mL of dry THF under N_2 was added 0.95 g (0.025 mol) of powdered $LiAlH_4$ followed by 3.6 g of β-cyclocitral (0.024 mol) in 50 mL of THF. After 6 h at room temperature, the mixture was refluxed for 12 h. At 0 °C, 200 mL of 15% HCl was added dropwise, and the mixture extracted with ether. After the usual workup 3.01 g of a white solid was obtained. After purification on a silica gel column, the solid (mp 103–105 °C) showed expected spectroscopic properties for the triene: ^1H NMR (C_6D_6) δ 1.13, 1.49 (CH_3-1 and -5), 5.98 (vinyl H's); IR 960 cm^{-1} (for trans disubstituted double bond); MS, *m/e* 272 (M^+).

Preparation of 7-Cis Isomers. The method of selective photosensitization has been described in detail.[17,35] The following general procedure is useful for conversion of small amounts of the trans isomer(s) to the hindered 7-cis isomer(s) of the trienes. A 50–100-mg sample of the 7-trans isomer(s) was placed in a 5-mm NMR sample tube together with catalytic amounts (2–5 mg) of Rose Bengal and ~0.5 mL of deuterated acetone. The sample tube was deoxygenated by freeze–pump–thaw cycles, sealed under vacuum, and then irradiated with filtered light (≥420 nm, Corning 3-74 plate; 450-W medium-pressure Hg lamp). The progress of reaction was monitored by ^1H NMR. After having reached a photostationary state (1–2 days), the solution was filtered through a short column of silica gel to remove the sensitizer. The solution,

(29) The use of $\Delta G^{\ddagger}_c$ as a basis for comparing the barriers of rotation for related molecules assumes that the $\Delta S^{\ddagger}$'s are very similar. In fact, for the intramolecular rotations they are probably very small. See, e.g.: Allen, E. A.; Hobson, R. F.; Reeves, L. W.; Shaw, K. N. *J. Am. Chem. Soc.* **1972**, *94*, 6604–6611. In one case (**1d**), the rate constants obtained from simulated spectra were fitted linearly to the equation: $\ln(k/T) = \ln(k_b/h + \Delta S^{\ddagger}/R) - (\Delta H^{\ddagger}/R)(1/T)$, giving the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values of 12.5 kcal/mol and 5 eu, respectively. The calculated $\Delta G^{\ddagger}$ is 11.3 kcal/mol.

(30) In a preliminary low-temperature NMR experiment in search of the 6-*S*-trans and 6-*S*-cis conformers identified in a crystal of 13-*cis*-retinal,[28,31] we found that at temperatures below −90 °C, the 1,1-CH_3 of 13-*cis*-retinal began to broaden before other peaks. The peak was not resolved at −117 °C. Solvent viscosity (toluene-d_8 + $CFCl_3$; CD_2Cl_2 + $CFCl_3$) prevented studies at even lower temperatures. The temperature range of this DNMR behavior is, however, close to that of half-chair inversion of dimethylcyclohexene.[25]

(31) Simmons, C.; Liu, R. S. H.; Denny, M.; Seff, K. *Acta Crystallogr., Sect. B* **1981**, *B37*, 2197–2205.

(32) Liu, R. S. H.; Matsumoto, H.; Kini, A.; Asato, A. E.; Denny, M.; Kropf, A.; deGrip, W. J. *Tetrahedron*, in press.

(33) For resolution of related hindered styrenes see: Adams, R.; Mecorney, J. W. *J. Am. Chem. Soc.* **1945**, *67*, 798–802 and ref 23.

(34) Machleidt, H.; Wessendorf, R. *Justus Liebigs Ann. Chem.* **1964**, *679*, 20–25.

(35) Ramamurthy, V.; Liu, R. S. H. *Org. Photochem. Synth.* **1976**, *2*, 70–71.

after concentration, was subjected to preparative HPLC separation (25 in. × 10 mm Lichrosorb Si-60, 5- or 10-μm column with 2–10% ether in hexane as the solvent). Chloroform-*d* was used as the solvent for irradiation when benzanthrone was used as a sensitizer.

7-*cis*- and 7-*cis*,9-*cis*-β-Ionylidenefluoroacetaldehyde (1c,d). Rose Bengal sensitized irradiation gave a mixture of all four isomers in the following relative amounts (by ^{19}F nmr): 11%, 9%, 19%, and 61% all-trans, 9-cis, 7-cis, 7-cis, and 9-cis. They were separated by preparative HPLC (solvent 10% ether in hexane).

1c: ^1H NMR ($CDCl_3$) δ 1.04, 1.49, 2.11 (CH_3-1,5,9), 6.34 (H_7), 6.56 (H_8), 9.79 (H_{11}) ($J_{7,8}$ = 11.8 Hz, $J_{10,11}$ = 16.9 Hz, $J_{CHO,10}$ = 3.4 Hz); ^{19}F NMR ($CDCl_3$, $CFCl_3$) −129.4 ppm (F_{10}, $J_{H,F}$ = 16.9 Hz).

1d: ^1H NMR ($CDCl_3$) δ 1.04, 1.48, 1.94 (CH_3-1,5,9), 6.35 (H_7), 6.72 (H_8), 9.82 (H_{11}) ($J_{7,8}$ = 12.5 Hz, $J_{10,11}$ = 17.3 Hz, $J_{CH_3\text{-}9,10}$ = 4.3 Hz); ^{19}F NMR −131.0 ppm (F_{10}, $J_{H,F}$ = 17.3 Hz).

7-*cis*- and 7-*cis*,9-*cis*-*N*-Methyl-*N*-phenyl-β-ionylideneacetamide (1e,f). Rose Bengal sensitization resulted in a mixture containing a 2.5:1 ratio of the 7-cis,9-cis and 7-cis isomers with trace amounts of the two 7-trans isomers (in the order of HPLC elution time). They were separated by preparative HPLC (solvent 15% ether in hexane). Both cis isomers were viscous oils.

1e: ^1H NMR ($CDCl_3$) δ 0.89, 1.36, 2.13, 3.29 (CH_3-1,5,9 and NCH_3), 5.86–5.80 (H_7 and H_8), 5.65 (H_{10}).

1f: ^1H NMR ($CDCl_3$) δ 1.02, 1.46, 1.67, 3.30 (CH_3-1,5,9, N-CH_3), 5.42 (H_{10}), 6.10 (d, H_7), 7.09 (d, H_8) ($J_{7,8}$ = 12.6 Hz); ^{13}C NMR ($CDCl_3$) 28.7, 21.7, 21.5, 36.8 (CH_3-1,5,9, NCH_3), 39.1, 19.0 32.2 (CH_3-2,3,4) 34.2 (C-1), 130.1, 136.6, 129.8, 129.2, 148.3, 126.9, and 166.7 ppm (C-5,6,7,8,9,10,11, respectively).

7-*cis*-β-Ionylidenemalononitrile (1g). Rose Bengal sensitization of **7** only resulted in partial conversion (15%) to the 7-cis isomer. It was isolated by preparative HPLC (solvent 5% ether in hexane): ^1H nmr (CD_3COCD_3) δ 1.09, 1.55, 2.36, (CH_3-1,5,9), 6.71 (d, H_8), 6.86 (d, H_7) ($J_{7,8}$ = 12.2 Hz); UV (hexane) 267 nm.

7-*cis*-1,2-Bis(2,6,6-trimethylcyclohex-1-enyl)ethylene (6). Benzanthrone sensitization of **10** (in C_6D_6) resulted in quantitative conversion to the cis isomer. Passage through a short silica gel column gave the cis triene as a viscous oil: ^1H NMR (C_6D_6) δ 1.13, 1.84 (CH_3-1 and -5), 5.97 (vinyl H's).

***cis*-β-Ionyl Phenyl Sulfone (10). Preparative Irradiation.** A benzene (30 mL) solution of 1.15 g of **9** and catalytic amounts of β-acetonaphthone was distributed into four 13-mm test tubes. After being purged with N_2, the solution was irradiated with a 200-W Hanovia medium-pressure Hg lamp for 72 h. After evaporation of solvent, the mixture was chromatographed on a silica gel column with solvents starting with chloroform and going to 20% of ethyl acetate in chloroform. A total of 320 mg of a viscous oil was obtained. Its ^1H NMR spectrum ($J_{7,8}$ = 12 Hz) was consistent with the cis isomer. No residual trans isomer could be detected by NMR.

***cis*-9-Benzyl-β-ionyl Phenyl Sulfone (5).** To a mixture of 300 mg of **10** in 4 mL of DMA at −5 to −8 °C was added 400 mg of finely ground NaOH. The mixture was stirred for 10 min, and then a solution of 0.12 mL of benzyl chloride in 1 mL of DMA was added. The mixture was then allowed to warm to room temperature and stirred overnight. It was then extracted with petroleum ether. Attempts to crystallize the solid resulted in recovery of the purified white solid (165 mg, 40% yield: mp 150 °C dec). For the ^1H NMR see the text.

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Registry No. **1a**, 56013-12-8; **1b**, 56013-13-9; **1c**, 87782-35-2; **1d**, 87782-36-3; **1e**, 87782-37-4; **1f**, 87801-34-1; **1h**, 53402-96-3; **1i**, 53402-97-4; **2**, 24315-14-8; **3**, 67737-35-3; **4**, 74464-49-6; **5**, 87782-38-5; **6**, 67895-24-3; **7**, 56013-18-4; **8**, 3917-36-0; **9**, 87782-39-6; **10**, 61201-36-3.

Supplementary Material Available: Figures 3–6 showing representative experimental and calculated spectra of several 7-cis isomers (**1i**, **1d** and **5**) (5 pages). Ordering information is given on any current masthead page.

Macrocyclic Receptor Molecules for Guanidinium Cations. Preparation, X-ray Structures, and Kinetic Stabilities of 1:1 Complexes of Guanidinium Perchlorate with Benzo-27-crown-9, Dibenzo-27-crown-9, and Dibenzo-30-crown-10

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The complexation of guanidinium perchlorate with crown ethers of different ring size (18–33 ring atoms) and with different subunits, e.g., catechol and 1,3-xylyl moieties, has been studied by using two-phase extraction experiments. The results demonstrate that the 18-crown ethers are able to form *perching* complexes, whereas crown ethers with ≥27 ring atoms have a suitable ring size to form *encapsulated* complexes with guanidinium perchlorate. Aromatic, catechol, and especially 1,3-xylyl moieties have a destabilizing effect on the complex formation. The crystal and the molecular structures of the 1:1 complexes of guanidinium perchlorate with benzo-27-crown-9 (**7**), dibenzo-27-crown-9 (**8**), and dibenzo-30-crown-10 (**11**) have been determined by X-ray crystallography. In these encapsulated complexes all hydrogen atoms of the guanidinium cation are used in hydrogen bonds to the macrocyclic host. The 27-crown ethers show an optimal fit between cation and the macrocyclic host with a complementary binding scheme. Dynamic 500-MHz ^1H NMR spectroscopy gave the kinetic stabilities of these complexes with $\Delta G_d^{\ddagger}$ values of 11.5, 11.2, and 12.0 kcal mol^{-1} for the complexes with benzo-27-crown-9, dibenzo-27-crown-9, and dibenzo-30-crown-10, respectively.

Introduction

With the ultimate objective of our work to find the optimal synthetic receptor molecule for urea we are currently interested in the complexation of crown ethers with both charged and neutral organic molecules. Previously we have shown[1] that 18-crown-6 does form an adduct with

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(1) Harkema, S.; van Hummel, G. J.; Daasvatn, K.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1981**, 368.

0022-3263/83/1948-4821$01.50/0