Pergamon

Tetrahedron Letters, Vol. 35, No. 39, pp. 7177-7180, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 \$7.00+0.00

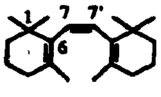
0040-4039(94)01568-6

Spiral Hexatrienes. The Hindered cis Isomer of Mini-carotene-3 and Hexakis-(2,2',4,4',6,6'-trifluoromethyl)stilbene.

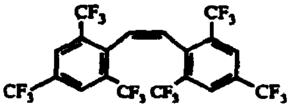
Rongliang Chen, Leticia U. Colmenares, J. R. Thiel & Robert S. H. Liu*
Department of Chemistry, University of Hawaii, Honolulu, HI 96822, U. S. A.

Abstract. Steric crowding in the cis isomer of "Mini-3", a chain shortened triene analog of β-carotene, and hexakis-(2,2',4,4',6,6'-trifluoromethyl)stilbene forces the polyene chromophores to adopt a spiral conformation. Some of the associated unusual spectroscopic properties (UV-VIS and NMR) of these compounds and a rare 1,7-H shift process are described.

Mini-3, **1**, is the lowest member of a series of chain shortened β-carotene homologs recently prepared for a spectroscopic study.[1] Its cis isomer, obtainable via triplet sensitized isomerization of the trans isomer,[2] has severe sterically crowding because of the "doubly" hindered 7-cis geometry. One would expect that such a compound should inherit, perhaps in a more amplified manner, many of the characteristic properties that are known for the 7-cis isomers of the retinoids.[3] In this paper we describe some of its unique properties along with those of the related compound **2**, hexakis-(2,2',4,4',6,6'-trifluoromethyl)stilbene.[4]

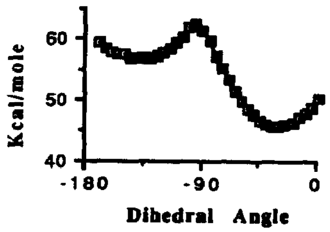


cis-1



cis-2

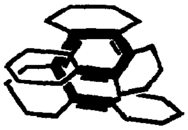
The preferred 6-S-cis ring-chain conformation of compounds in the retinoids and carotenoids[5] is likely the consequence of the steric bulk of the tetrasubstituted C-1 unit, in a manner similar to 2-t-butyl-1,3-butadiene or 2,5-di-t-butyl-1,3,5-hexatriene.[6] and the 5-Me/8-H interaction. For a 7-cis isomer, the additional 5-Me/9-Me interaction forces the chromophore into a more twisted 6-S-cis conformation with a dihedral angle estimated to be near 50°.[3] Hence, cis-Mini-3 should exist in a non-planar bis-S-cis conformation.



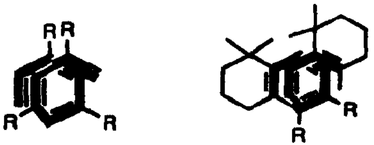
Results from molecular mechanics calculations (MM2, MM+ in HYPERCHEM) are in agreement; the energy minimized bis-S-cis conformer (lower minimum on the left) is ~11 kcal/mole more stable than the S-trans (upper minimum). The calculated results also show that bis-S-cis conformer should adopt a spiral conformation which, we believe, accounts for the unusual UV absorption and other properties.

The absorption maximum of cis-**1** (254.4 nm, ε = 6,800 in hexane) was found to be more red-shifted than that of trans-**1** (246.8 nm, ε = 7,800 in hexane). This red-shift, unexpected for a cis isomer, is likely due to secondary orbital interactions. The 1,6-p,p orbitals of the triene unit, as part of the spiral structure, are oriented in a direction suitable for overlap between the top lobe of one and the bottom lobe of the other (see Figure on the left). The resultant through space orbital interaction[7] is anti-bonding in the HOMO and bonding in the LUMO, leading to closing of the energy gap between these two frontier orbitals, hence the red-shift. Results from MNDO-AM1 (CI-singles) calculations of the vertical excitation energy (0-0 band) of the above energy minimized cis-Mini-3 show that it is lower than that of the minimized trans-Mini-3 by ~16 kcal/mole. (Detailed calculations of ground state and excitation energies for all conformers of the two isomers of Mini-3 are underway.) Similarly, for compound **2**, the cis isomer (λ_{max} = 253 nm, 95 % ethanol) was also found to be red shifted from the trans (λ_{max} = 249 nm).

A releted example in the literature is 2,5-di-t-butyl-1,3,5-cis-hexatriene which was reported to be more red-shifted than 2-t-butyl-1,3,5-cis-hexatriene (no comparison with the trans isomer was mentioned).[6] We suspect such trienes could be part of a series of poly-cis,poly-S-cis spiral polyenes. Analogous to helicenes,[8] these compounds can be classified as [3]-Spiralenes. Examples of other polyenes with n number of double bonds that are likely to retain the overall spiral structure ([n]-Spiralenes) are shown below.

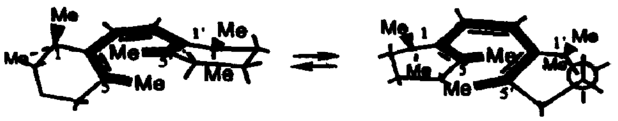


a [4]-spiralene

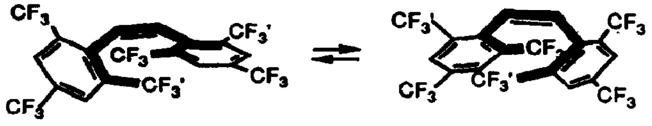


two [5]-spiralenes

The unusual conformation is also in agreement with the dNMR behavior exhibited by compounds **1** and **2**. For cis-Mini-3, the geminal 1,1-dimethyl singlet (0.98 ppm) in its room temperature H NMR spectrum (in toluene-d_8, 500 MHz spectra) splits into two singlets ($\Delta\delta$ = 68.8 Hz) upon cooling. The coalescence temperature (T_c = -69°C), and the calculated $\Delta G^\dagger$ (9.9 kcal/mole)[9] values, somewhat surprisingly, are lower than those of the 7-cis retinoids (coalescence temperatures usually near 0°C).[3] The dNMR behavior is likely due to equilibration of the two enantiomeric bis-S-cis conformers shown below (interchanging the pseudo axial and equitorial oriented 1,1-dimethyl groups). The process requires simultaneous rotation of two single bonds, a concerted process in agreement with the relatively small enthalpy of activation and large negative entropy of activation found for the compound ($\Delta H^\dagger$ = 4.6 kcal/mole and $\Delta S^\dagger$ = -24.4 eu).



The F NMR spectra (in THF-d_8, 283 MHz) of compound **2** also exhibits dNMR behavior. At room temperature, two singlets (δ -60.97 and -65.05 ppm) of 2: 1 relative intensities were observed corresponding to the *o*- and *p*-CF_3's. At lower temperatures, the major peak split into two singlets ($\Delta\delta$ = 136 Hz) with the coalescence temperature being -90°C, giving $\Delta G^\dagger$ = 9.3 kcal/mole. The higher field peak is most likely due to that of the inward CF_3 group, now frozen in a direction above the plane of second phenyl ring. The activation parameters ($\Delta H^\dagger$ = 4.4 kcal/mole, $\Delta S^\dagger$ -19.8 eu) are similar to those of cis-Mini-3, suggesting that a concerted motion is also involved in the equilibration process:[10]



The spiral conformation also led to the following 1,7-hydrogen migration, a process that is relatively

uncommon among compounds in the Vitamin A series. The reaction takes place at temperatures above 80°C, giving an equilibrium mixture of the above two compounds, slightly in favor of cis-Mini-3. Other retinoid derivatives reported to undergo similar 1,7-H shifts also contain the hindered 7-cis geometry: 7-cis retinylideneacetaldehyde[11] and 7,9-dicis-19,19,19-trifluororetinal.[12]

In conclusion, spectroscopic and chemical properties of the two hindered cis compounds are consistent with the expectation that their hexatriene chromophore exists in a spiral conformation. Whether this unique structural feature is retained in higher polyenes is the subject of our current investigation.

Acknowledgments. The work was supported in parts by a grant from the U. S. Public Health Services (DK-17806). We are grateful to Dr. F. T. Edelmann of Gottingen for a gift sample of trifluoromethylated mesitylene for preparation of the nonafluoromesitylaldehyde.

REFERENCES AND NOTES:

1. Andersson, P. O.; Gillbro, T.; Asato, A. E.; Liu, R. S. H., *J. Luminescence*, **1992**, *51*, 11-20.
2. Gapski, G.; Kini, A.; Liu, R. S. H., *Chem. Lett.*, **1978**, 803-804.
3. Liu, R. S. H.; Zingoni, J. P.; Kini, A.; Trammell, M.; Chu, D.; Asato, A. E.; Bopp, T. T., *J. Org. Chem.*, **1983**, *48*, 4817-4821.
4. Prepared from reductive dimerization of the corresponding nonafluoromesitylaldehyde followed by triplet sensitization.
5. Honig, B.; Hudson, B. Sykes, B. D.; Karplus, M., *Proc. Natl. Acad. Sci., USA*, **1971**, *68*, 1289-1293.
6. (a) Craig, D; Shipman, J. J.; Fowler, R. B., *J. Am. Chem. Soc.*, **1961**, *83*, 2885-2891; (b) Brouwer, A. M.; Cornelisse, J.; Jacobs, H. J. C., *J. Photochem. Photobiol.*, **1988**, *42*, 117-126.
7. Hoffmann, R., *Acc. Chem. Res.*, **1971**, *4*, 1-9.
8. Meurer, K. P.; Vogtle, F., *Topic Curr. Chem.*, **1985**, *127*, 1-76.
9. $\Delta G^{\dagger} = 4.57\ T_c\ [9.97 + \log T_c/(\Delta\delta + 6\ J)^{1/2}]$, J being zero for both **1** & **2**.
10. A closer examination reveals that the equilibration processes for 1 and 2 cannot be identical. For **2**, a concerted parallel rotation of two single bonds (i.e., in a synchronous conrotatory manner) results in equilibration of the inside and outside CF_3 groups. For **1**, the equilibration of the upper and the lower CH_3 groups can be achieved only after rotation of the same two single bonds in a net opposite direction (i.e., in a disrotatory manner, but probably not synchronous due to increased steric crowding between the two inward 5- and 5'-CH_3 groups during the rotation process).
11. Frater, G., *Helv. Chim. Acta*, **1974**, *57*, 2446-2454.
12. Unpublished results of Denny, M.; Asato, A. E.; Liu, R. S. H., cited in Mead, D. et al., *Tetrahedron Lett.*, **1987**, *28*, 259-263.

(*Received in USA* 20 *July* 1994; *accepted* 29 *July* 1994)