Restricted rotation involving the tetrahedral carbon. V. Direct observation of the hindered rotation of a methyl group by high resolution nuclear magnetic resonance spectroscopy

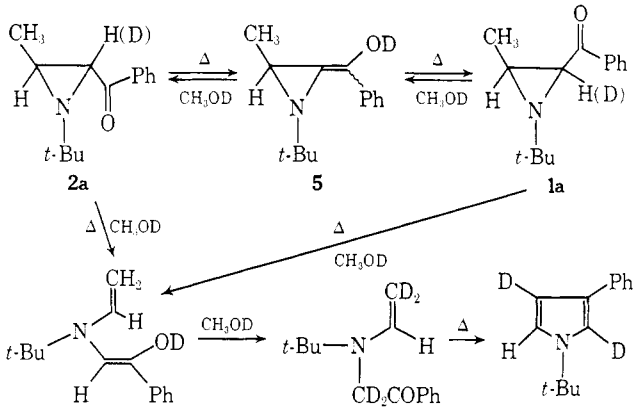
ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · OCTOBER 1973

Impact Factor: 12.11 · DOI: 10.1021/ja00802a052

3 AUTHORS, INCLUDING:

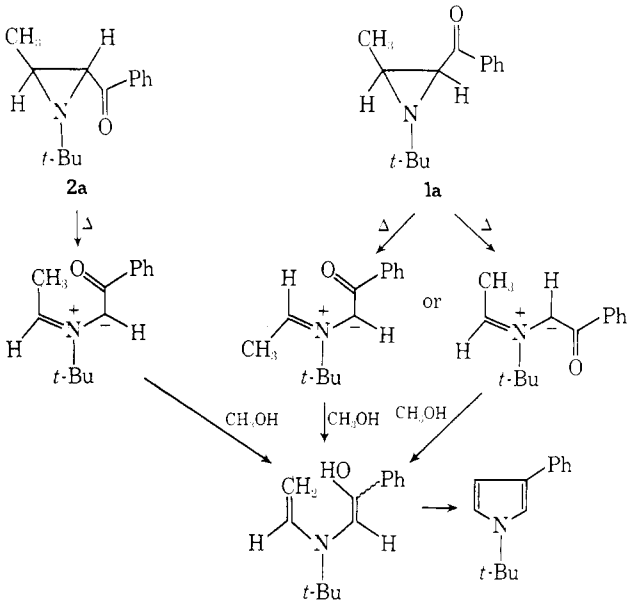
Mikio Nakamura
Toho University
177 PUBLICATIONS **2,659** CITATIONS

ylides in the trans → cis isomerization.[19] Similar results were obtained with *trans*-aziridine **2a**, except that in this case the recovered aziridine was mostly the epimerized cis *3-d_1* isomer. The most direct interpretation of the above data involves enol **5** as the reactive intermediate responsible for the epimerization.



It is interesting to note that the pyrrole isolated from the thermolysis of the *cis*-aziridine in CH_3OD contained deuterium atoms in both the 2 and 4 positions of the pyrrole ring.[21] A further experiment utilizing *cis-N-tert*-butyl-2-methyl-3-benzoylaziridine-*2-methyl-d_3*[22] (**6**) and methanol confirmed this intermolecular hydrogen exchange. No detectable deuterium was found in the final product **4a** when deuterated *cis*-aziridine **6** was heated at 120° in methanol for 2.5 hr. These observations may be explained in terms of a rapid intermolecular exchange of the vinyl hydrogens of enamine **3** with the solvent prior to cyclization. It should also be pointed out that recovered *cis*-aziridine **1a** did not incorporate deuterium into the methyl group when **1a** was heated in deuteriomethanol.[23] The lack of deuterium incorporation on the methyl group also argues against the "enolene" mechanism[5-7] for rearrangement of these aziridines. Also noteworthy is the absence of a primary deuterium isotope effect on the rate of rearrangement of *cis*-aziridine **6**.

The simplest mechanism consistent with the observed rearrangement patterns of the substituted aziridines examined is the one outlined below. It is based on the knowledge that aziridines readily undergo thermal cleavage to azomethine ylides by conrotation of the substituent groups.[20] The higher energy requirement for rearrangement of the cis isomer can be attributed to the stereochemical consequences of orbital-symmetry control. Conrotatory rotation in either direction for the cis isomer causes one of the rotating groups to encounter a large steric interaction with the adjacent *tert*-butyl group. With the trans isomer, however, conrotation will result in a smaller steric interaction since neither the methyl nor benzoyl group needs to rotate toward the large *tert*-butyl group. Since no adduct was formed when the thermolyses were carried out in the presence of a potent dipolarophile, it would appear that the initially formed azomethine ylides have very short lifetimes and undergo rapid exchange with the protic solvent.



The difference in the thermal behavior observed with these aziridines and those studied previously[20,24] can be attributed to the availability of a proton β to the nitrogen atom which can be lost to form an enamine. Further work on the thermal and photochemical behavior of these systems is in progress and will be reported at a later date.

Acknowledgment. We gratefully acknowledge support of this work by the National Science Foundation (Grant GP-37550). The National Science Foundation also provided financial assistance in the purchase of the nmr spectrometer used in this research.

(19) Since azomethine ylides can be readily trapped in the presence of dipolarophiles,[20] one would anticipate a marked diminution in the yield of pyrrole if an azomethine ylide were involved in the trans → cis isomerization.

(20) R. Huisgen and H. Mader, *J. Amer. Chem. Soc.*, **93**, 1777 (1971).

(21) A control experiment indicated that pyrrole **4a** only incorporates deuterium into the 2 position of the ring under these conditions.

(22) Crotonophenone-d_3 was obtained by exchanging the methyl protons with sodium hydroxide, D_2O, and dioxane at 80°. The deuterated ketone was subsequently converted to aziridine **6**.

(23) Similar results were obtained upon heating *cis*-aziridine **6** in methanol. The recovered ketone did not exchange hydrogen for deuterium.

(24) A. Padwa and W. Eisenhardt, *J. Org. Chem.*, **35**, 2472 (1970).

(25) Alfred P. Sloan Foundation Fellow, 1968–1972; NATO Senior Postdoctoral Fellow, 1973.

Albert Padwa,*[25] David Dean, Arthur Mazzu, Eligio Vega
Department of Chemistry
State University of New York at Buffalo
Buffalo, New York 14214

Received July 21, 1973

Restricted Rotation Involving the Tetrahedral Carbon. V. Direct Observation of the Hindered Rotation of a Methyl Group by High Resolution Nuclear Magnetic Resonance Spectroscopy[1]

Sir:

We wish to report an observation of splitting of a methyl signal in high resolution proton nmr spectroscopy. Since the barrier to rotation of the methyl group is rather low,[2] the rotation of methyl groups has gen-

(1) H. Nakanishi, O. Yamamoto, M. Nakamura, and M. Ōki, *Tetrahedron Lett.*, 727 (1973).

(2) The barrier to rotation of the methyl group in 2,2-dimethylpropane, which is one of a typical example of high barrier, is reported to be 4.3 kcal/mol from far-infrared studies (J. R. During, *et al.*, *J. Chem. Phys.*, **52**, 2046 (1970)), whereas Allinger, *et al.*, calculated the barrier to be 4.64 kcal/mol (*J. Amer. Chem. Soc.*, **90**, 1199 (1968)).

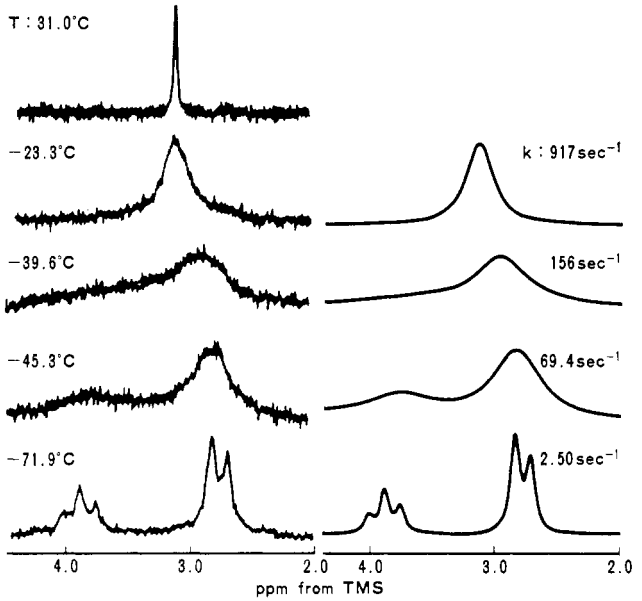
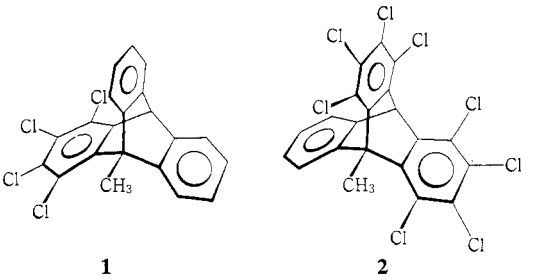


Figure 1. The observed and computed spectra of **2** at various temperatures.

erally been studied by measuring T_1 by broad-line nmr in the field of nuclear magnetic resonance; the barriers to rotation of 2,2-dimethylpropane,[3] methylammonium chlorides,[4] and some polymethyl aromatic compounds[5] have thus been obtained. The only exception has been a report by Bartle, *et al.*,[6] who observed the line broadening of the methyl signal of 9-methyl-9,9′-bifluorenyl in solution at −60°.

We have recently been able to show the slow rotation of methyl groups in 1-*tert*-butyl-1,4-dihydronaphthalene 1,4-epoxide derivatives[1] and are interested in seeking a clear example of restricted rotation of the methyl group. Since it is known that the barrier to rotation of the *tert*-butyl and related groups in triptycene-type structures is extremely high[7-9] and Sergeyev, *et al.*,[10] claimed the rotational barrier in 9-chloromethyltriptycene to be *ca.* 16 kcal/mol, 9-methyltriptycene derivatives are candidates for exhibiting such a phenomenon.

9-Methylanthracene was treated with tetrachlorobenzyne generated *in situ*[11] to give 1,2,3,4-tetrachloro-9-methyltriptycene (**1**), mp 276°. *Anal.* Calcd for $C_{21}H_{12}Cl_4$: C, 62.10; H, 2.98; Cl, 34.92. Found: C, 62.16; H, 2.79; Cl, 34.99. Nmr ($CDCl_3$, δ from TMS): 2.73 (3 H, s), 6.03 (1 H, s), 7.0–7.6 (8 H, m). Similarly treatment of 9-methyl-1,2,3,4-tetrachloroanthracene with tetrachlorobenzyne afforded 1,2,3,4,5,6,7,8-octachloro-9-methyltriprycene (**2**), mp >300°. *Anal.* Calcd for $C_{21}H_8Cl_8$: C, 46.37; H, 1.48; Cl, 52.14. Found: C, 46.56; H, 1.22; Cl, 52.06. Nmr ($CDCl_3$, δ from TMS): 3.17 (3 H, s), 6.75 (1 H, s), 7.0–7.6 (4 H, m). The high resolution nmr spectra were recorded on a Varian HA 100D spectrometer operating at 100 MHz.

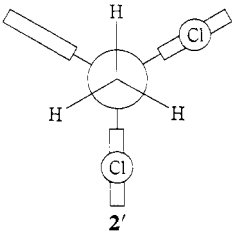


1 **2**

The pmr spectrum of **1** in $CDCl_3$–CH_2CHCl–CH_2Cl_2 (3:1:2) at room temperature showed a single sharp peak for the methyl group at 2.85 ppm from the internal TMS. The methyl signal, however, broadened considerably when cooled and the line shape became unsymmetrical at −67.3°. At −83.9°, the signal was split into two signals, although broad, and the ratio of the integrated intensities of the two was 1:2 (1 H at 2.3 and 2 H at 3.0 ppm from TMS). The signal did not show further splitting even at −95.5°.

We then switched to compound **2** in a hope that the greater steric repulsion at the transition state of rotation may increase the barrier. The pmr spectrum of **2** in $CDCl_3$–CS_2 (8:1) at room temperature showed a rather broad signal for the methyl group at 3.14 ppm. On lowering the temperature, **2** showed a dramatic change in the line shape, as shown in Figure 1. At −45.3°, a very broad signal was observed to split into two with relative areas of 1:2. At −71.9°, the signal at the lower magnetic field was split into three, whereas that at the higher field into two.

This phenomenon may be understood when one looks at the Newman type projection (**2′**) of **2** through



2′

the C_9–C_{CH_3} bond. Since two hydrogens of the methyl group are located in one environment and the third in a different environment, the methyl protons should give an AB_2 or ABB′ pattern when the rotation is frozen. The real case seen in the figure seems to be close to the AX_2 type because of the large difference in the chemical shifts of these protons.

Since it is not possible to obtain accurate experimental values of chemical shifts and coupling constants at present, the spectral curves were simulated, using the LAOCOON MBYH program for the ABC system.[12] The best-fit curve for that observed at −71.9°, as shown in Figure 1, was obtained by taking the chemical shifts of H_1, H_2, and H_3 as 277.8, 277.8, and 389.4 Hz, respectively, and the coupling constant (assumed as $J_{12} = J_{23} = J_{13}$) as −12.58 Hz.

The computer simulation was performed to obtain

(3) (a) E. O. Stejskal, D. E. Woessner, T. C. Farrar, and H. S. Gutowsky, *J. Chem. Phys.*, **31**, 55 (1959); (b) G. W. Smith, *ibid.*, **42**, 4229 (1965).

(4) E. R. Andrew and P. C. Canepa, *J. Magn. Resonance*, **7**, 429 (1972).

(5) P. S. Allen and A. Cowking, *J. Chem. Phys.*, **47**, 4286 (1967); **49**, 789 (1968); A. Saika, A. Kawamori, and R. Takagi, *J. Magn. Resonance*, **7**, 324 (1972).

(6) K. D. Bartle, P. M. G. Bavin, D. W. Jones, and R. L'Amie, *Tetrahedron*, **26**, 911 (1970).

(7) J. P. N. Brewer, H. Heaney, and B. A. Marples, *Chem. Commun.*, 27 (1967).

(8) M. Ōki and M. Suda, *Bull. Chem. Soc. Jap.*, **44**, 1876 (1971).

(9) M. Ōki and G. Yamamoto, *Chemistry Lett.*, 45 (1972).

(10) N. M. Sergeyev, K. F. Abdulla, and V. R. Skvarchenko, *J. Chem. Soc., Chem. Commun.*, 368 (1972).

(11) H. Heaney and J. M. Jablonski, *J. Chem. Soc. C*, 1895 (1968).

(12) These programs were written by Dr. O. Yamamoto, National Chemical Laboratory for Industry, Tokyo.

the rate constants of the exchange at various temperatures, using the INVERS EXII program[12] and the parameters as above. The Arrhenius plot yielded the activation energy of 14.1 ± 0.6 kcal/mol. Then the enthalpy, entropy, and free energy of activation at 25° were obtained as 13.5 ± 0.6 kcal/mol, 9.8 ± 3.0 eu, and 10.6 ± 1.0 kcal/mol, respectively.[13]

To the best of our knowledge, this is the first example of observing the nonequivalence of the methyl protons in high resolution nmr spectroscopy.[14]

(13) The large entropy of activation was critically commented by a referee. The careful redetermination of the spectra and simulation using the INVERS EXII program, which takes not only the rotating motion of the methyl group in one direction but also the to-and-fro motion into consideration, gave a little smaller $\Delta S^{\ddagger}$ but the value is still large. This value may include some intractable systematic errors.

(14) Another referee gave a comment that we should be very careful in interpreting the results because even the line broadening in a differential way had been observed by the prevention of isotropic tumbling of the large molecule due to the increase in solvent viscosity. We believe, however, that the cause is the slow rotation of the methyl group for the following two reasons. (1) The computed spectra by assuming the AB_2 pattern are in good agreement with the observed ones and (2) the signal of the bridgehead proton has the line width of less than 1.5 Hz at −71.9°, where the splitting of the methyl signal is seen as shown in Figure 1.

Mikio Nakamura, Michinori Ōki*

Department of Chemistry, Faculty of Science
The University of Tokyo, Tokyo 113, Japan

Hiroshi Nakanishi

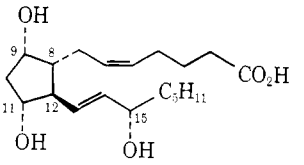
National Chemical Laboratory for Industry
Shibuya, Tokyo 151, Japan

Received February 8, 1973

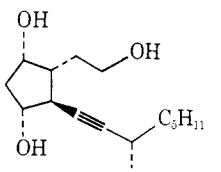
Asymmetric Synthesis of Prostaglandin Intermediates

Sir:

The salient structural features of the primary prostaglandin $F_{2\alpha}$ (**1**) include the five chiral centers, 8*R*, 9*S*, 11*R*, 12*R*, and 15*S*, four of which are situated on the cyclopentane ring.[1] In this communication we report the asymmetric formation of the intermediates **11**[2] and **13**[3,4] which possess the four nuclear chiral centers needed to prepare this natural prostaglandin. The addition of (3*S*)-*tert*-butoxy-1-octynyldimethylalane to epoxydiol **13** is an efficient process[5] and leads to triol **2**, which contains all five asymmetric centers



1 ($PGF_{2\alpha}$)

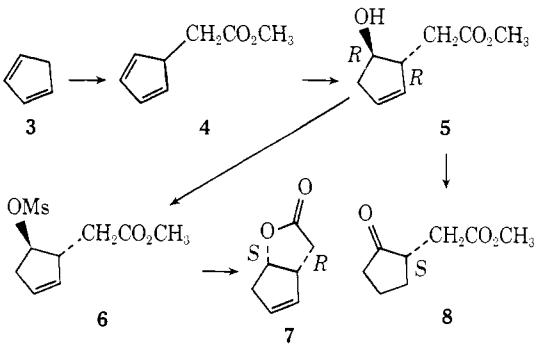


2

needed for prostaglandin $F_{2\alpha}$. Previously, Fried and coworkers had converted racemic triol **2** to *dl*-prostaglandin $F_{2\alpha}$.[3]

The sodium salt of cyclopentadiene (**3**) was stirred with methyl bromoacetate in tetrahydrofuran solution at −78° to generate *in situ* diene **4**. This substance was immediately treated with (+)-di-3-pinanylborane followed by alkaline hydrogen peroxide oxidation[6] to yield hydroxy ester **5**,[7] $[\alpha]_D$ −136°, in 45% yield (Scheme I). Similar treatment of diene **4** with (−)-di-3-pinanylborane yielded the antipode of **5**, $[\alpha]_D$ +136°. To determine the optical purity of **5** and its antipode, the corresponding (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetates were prepared.[6] The 100-MHz nmr spectra of these substances showed chemical-shift differences in the methyl ester region and indicated that the alcohols were at least 92% optically pure.[6] However, comparison of the above optical rotations with those of the optically pure hydroxy esters ($[\alpha]_D$ −141 and +141°, obtained by resolution) indicated that the asymmetric hydroboration products were at least 96% optically pure.

Scheme I[a]



[a] While the structures depicted above correspond to the absolute configuration of the natural prostaglandins, all reactions were carried out with both optical antipodes as well as the racemates.

The hydroxy ester **5** was quantitatively converted into mesylate **6**, $[\alpha]_D$ −85°, which afforded the crystalline optically pure lactone **7**, mp 46–47°, $[\alpha]_D$ −106°, in 92% yield on treatment with aqueous sodium hydroxide in tetrahydrofuran at 0°. The crystalline lactone **7** could also be prepared by saponification of hydroxy ester **5** to the corresponding crystalline hydroxy acid, mp 56–57°, $[\alpha]_D$ −148°, which was exposed to methanesulfonyl chloride in pyridine. Thus, lactone **7** or its antipode could be readily prepared in optically pure form in over 40% yield from cyclopentadiene (**3**) without resorting to chemical resolution.

The absolute stereochemistry of the hydroxy ester

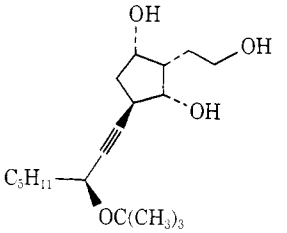
(1) For recent reviews on prostaglandin synthesis, see: G. L. Bundy, *Ann. Rep. Med. Chem.*, 7, 157 (1972); U. Axen, J. E. Pike, and W. P. Schneider in "The Total Synthesis of Natural Products," Vol. 1, J. ApSimon, Ed., Wiley-Interscience, New York, N. Y., 1973, pp 81–142; P. H. Bentley, *Chem. Soc. Rev.* (*London*), 2, 29 (1973); N. M. Weinshenker and N. H. Andersen in "The Prostaglandins," Vol. 1, P. W. Ramwell, Ed., Plenum Press, New York, N. Y., 1973, pp 5–82.

(2) E. J. Corey and R. Noyori, *Tetrahedron Lett.*, 311 (1970).

(3) J. Fried, J. C. Sih, C. H. Lin, and P. Dalven, *J. Amer. Chem. Soc.*, **94**, 4343 (1972).

(4) J. Fried and C. H. Lin, *J. Med. Chem.*, **16**, 429 (1973).

(5) We obtained triol **2**, $[\alpha]_D$ −40.9° (*c* 1.07, $CHCl_3$), in 55–60% yield along with *ca.* 20% of the isomeric triol **i**, $[\alpha]_D$ −1.4° (*c* 1.01, $CHCl_3$), when epoxydiol **13** was treated with 5–10 equiv of (3*S*)-*tert*-butoxy-1-octynyldimethylalane in toluene at 60°. The optimum conditions for forming triol **2** are discussed in a forthcoming publication by J. Fried and J. C. Sih (personal communication).



(6) *Cf.* J. J. Partridge, N. K. Chadha, and M. R. Uskoković, *J. Amer. Chem. Soc.*, **95**, 532 (1973), and references therein.

(7) Optical rotations were taken in 1% methanol solutions at 25° unless otherwise indicated. All substances were completely characterized spectrally and gave acceptable combustion analyses.