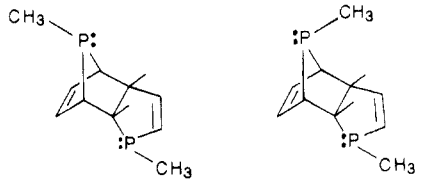
Nitrogen-15 NMR Spectra of Tertiary Amines with the 7-Azanorbornene Framework

Louis D. Quin,* Kenneth C. Caster,[1] Brian G. Marsi, and J. Allen Miller[1]

Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received April 17, 1986

During studies of ^{31}P NMR spectral effects among bridged tertiary phosphines, we noted some extremely strong influences operating on the phosphorus nucleus. Phosphine shifts are usually negative (upfield of H_3PO_4), but shifts as low as 100 to 150 ppm *downfield* were measured for these compounds.[2] These effects were mostly operative in structures where P occupied the 7-position of the norbornene framework, which presents a combination of severe angle strain at P and proximity to a π-center. Other nuclei at the 7-position also respond to these molecular features; for example, carbon-13,[3] oxygen-17,[4] and silicon-29[5] derivatives all exhibit pronounced deshielding of the heteroatom. This has been attributed to reduced electron density at the 7-position by a hyperconjugative interaction of the C–X σ electrons with a π^* orbital of the double bond.[5,6] Another effect, however, is known that is special to phosphorus; the syn–anti isomers that arise from the pyramidal stability of tertiary phosphines had a great difference in their ^{31}P shifts.[2] Thus, in compound **1** (syn) the bridging P had δ 96.5, while **2** (anti) had δ 30.2.



1 2

This difference disappeared when oxygen was added to the phosphorus. A theoretical explanation for this shift effect has not yet been developed.

A prominent element missing from such NMR structure studies is nitrogen, yet the similarity between tertiary phosphines and tertiary amines might suggest that the N nucleus would not only display the strong deshielding effect but the differential shift between syn and anti isomers as well. In almost all tertiary amines, the pyramidal stability of N is so low that procuring ^{15}N spectra to test these ideas is quite difficult. Fortunately, however, the norbornane framework, which is required for a comparative study of the effects on ^{15}N, gives nitrogen a relatively high pyramidal inversion barrier. Unsaturated derivatives with the 7-azanorbornane framework, which can be constructed from the action of pyrroles with Diels–Alder dienophiles, have been described as having inversion barriers so high

Scheme I

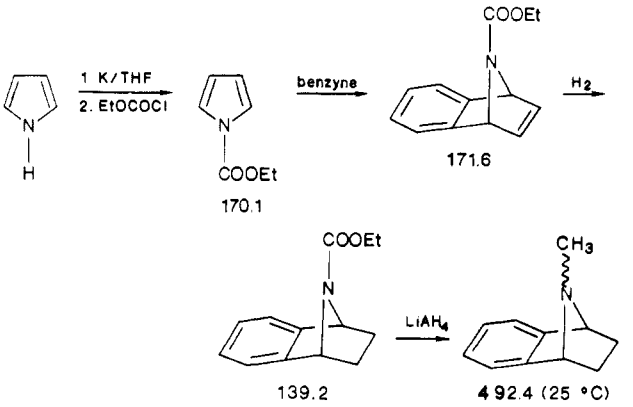
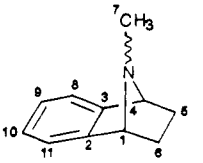


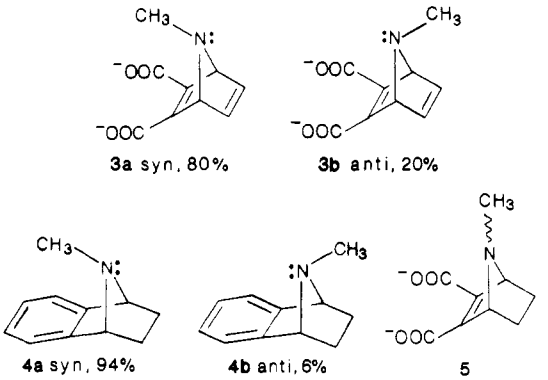
Table I. ^{13}C NMR Spectra of Compound 4 at Different Temperatures



temp, °C		C-1,4	C-5,6	C-7	C-2,3	C-8,11	C-9,10
+20		66.3	26.3	34.6	143.4	120.8	125.4
−30[a]	syn	66.1	26.2	34.4	142.9	120.9	125.3 (major)
	anti	64.5	21.2	34.8	145.5	118.0	124.7 (minor)

[a] Peak intensities of minor isomer were 5–8% of invertomer mixture.

that in some derivatives (e.g., the 7-azanorbornadiene derivative **3**) invertomers can be detected spectrally (^1H and ^{13}C NMR) at room temperature.[7]



We have now examined the benzo-7-azanorbornene derivative **4**, as well as the azanorbornene **3**, by natural abundance ^{15}N NMR at 90.4 MHz. Both compounds have been studied by other techniques,[7-9] and it is accepted that the invertomer with the N-substituent syn to the benzene ring or to the double bond is highly favored. Studies on the nature of the nonbonding interactions in these substances have also been published.[9,10] At probe temperature, the following results, relative to anhydrous ammonia as zero, were obtained: **4**, $\delta(^{15}N)$ 92.0; **5**, 88.4. These values are some 30–40 ppm downfield of any previously recorded

(1) Present address: L.D.Q.:* Department of Chemistry, University of Massachusetts, Amherst, MA 01003. K.C.C.: Union Carbide Corporation, South Charleston Technical Center, South Charleston, WV 25503. J.A.M.: Wellcome Research Laboratories, Beckenham, Kent BR3 3BS, England.

(2) (a) Quin, L. D.; Mesch, K. A. *J. Chem. Soc., Chem. Commun.* **1980**, 959. (b) Quin, L. D.; Caster, K. C.; Kisalus, J. C.; Mesch, K. A. *J. Am. Chem. Soc.* **1984**, *106*, 7021.

(3) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic Press: New York, 1972; Chapter 3.

(4) Nguyen, T. T.; Delseth, C.; Kintzinger, J.-P.; Carrupt, P.-A.; Vogel, P. *Tetrahedron* **1980**, *36*, 2793.

(5) Sakurai, H.; Nakadaira, Y.; Koyama, T.; Sakaba, H. *Chem. Lett.* **1983**, 213.

(6) Christl, M.; Herbert, R. *Org. Magn. Reson.* **1979**, *12*, 150.

(7) Yoshikawa, K.; Bekki, K.; Karatsu, M.; Toyoda, K.; Kamio, T.; Morishima, I. *J. Am. Chem. Soc.* **1976**, *98*, 3272.

(8) Marchand, A. P.; Allen, R. W. *Tetrahedron Lett.* **1977**, 619.

(9) Underwood, G. R.; Friedman, H. S. *J. Am. Chem. Soc.* **1977**, *99*, 27.

(10) Grutzner, J. B. *J. Am. Chem. Soc.* **1976**, *98*, 6386.

0022-3263/86/1951-3724$01.50/0

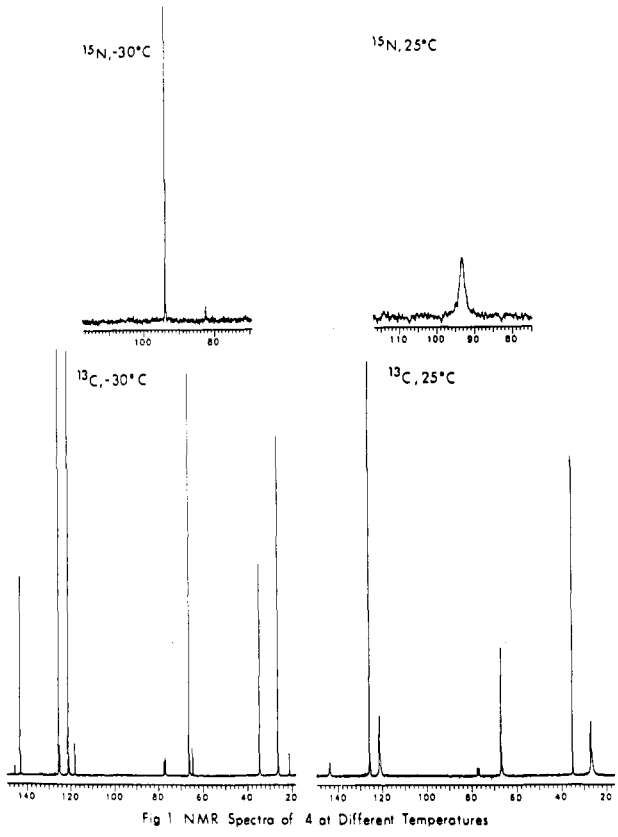


Figure 1. NMR spectra of **4** at different temperatures.

for a tertiary amine, and thus nitrogen is established to have the great sensitivity to the norbornene structure as found for other nuclei.[11] As would be expected from the value reported[8] for the barrier to inversion (13.0 kcal per mol) and peak coalescence temperature observed in the ^{1}H NMR spectrum (233 K at 100 MHz), only one signal was observed for each compound. The peak for the anti isomer, which should be observable below the coalescence temperature, should be quite small, and more favorable conditions for its detection were required. This was accomplished by synthesizing an isotopically enriched sample and by operation at higher magnetic field to obtain greater sensitivity. The synthesis of **4** was therefore repeated using pyrrole containing 23% ^{15}N as starting material. The ^{15}N NMR shifts for the intermediates of this process have not previously been published and are shown in Scheme I.

The ^{15}N NMR spectrum for **4** at 25 °C still consisted of a single broad line, and the ^{13}C NMR spectrum (Figure 1 and Table I) gave only one set of broadened signals. However, when the ^{15}N spectrum was obtained at −10 °C, a second signal appeared, and at −30 °C it was clearly present at δ 81.4, with the major signal at δ 91.9. Both signals were quite sharp and collapsed as the temperature was raised. The ratio of the signals at −30 °C was 96:4, close to the ratio reported[7,8] for the syn–anti isomers (94:6) when determined with ^{1}H NMR methods. The coalescence temperature is not readily measurable due to the large chemical shift and intensity difference of the two signals. The new resonance must be attributed to the anti isomer, and therefore we are observing the same chemical shift effect as found among the related phosphines; both isomers exhibit pronounced deshielding, but the syn isomer is the more strongly affected. The differential is 10.7 ppm, whereas it is as great as 70 ppm for ^{31}P. However, tertiary phosphines are much more sensitive to structural effects and recorded values span a range of about 370 ppm (−220 to +150). The range for tertiary amines is only about 120 ppm, hence a $\Delta\delta$ of 10.7 ppm in ^{15}N NMR is a relatively large effect. A $\Delta\delta$ of 18.2 ppm was noted[12] for the syn and anti isomers of an *N*-chlorobenzoazanorbornene but in the presence of Cr(acac)$_3$.

Compound **5** has not been further examined, but it is likely that subjecting it to similar treatment would provide valuable information about its invertomer population.

The ^{13}C NMR spectrum of *syn*-**4** in $CDCl_3$ has been published previously;[7] the anti isomer was not observed. By operating at −30 °C, well below the coalescence temperature, we have recorded the spectrum for both isomers. The anticipated changes in the anti spectrum should result from increased steric interactions (γ-shielding) between the *N*-methyl group and the $-CH_2CH_2-$ group and diminished interaction at the fusion carbons C-2,3. Indeed, the expected changes were observed; C-5,6 were shifted upfield by 5.0 ppm, while C-2,3 were shifted downfield by 2.6 ppm. All other ring carbons were also upfield-shifted in the anti isomer. The failure of previous investigators to observe a signal for the anti isomer is not due to a low concentration effect[7] but to performance of the NMR measurement above the coalescence temperature. It was reported,[7] however, that both isomers were observed when trifluoroacetic acid was used as the solvent. This solvent has been reported elsewhere[8] to cause N-protonation, and thus the signals observed are not for the free amine invertomers. It has also been stated[7] that in the ^{1}H NMR spectrum both isomers can be observed if Eu(fod)$_3$ is added, but it now appears that this medium is exerting an effect on the inversion phenomenon.

The ease of measurement of ^{15}N in a moderately enriched sample and the marked sensitivity of a bridging nitrogen to structural effects make dynamic ^{15}N NMR spectroscopy an important and direct method for the study of the inversion behavior of bicyclic amines. The difficulties in earlier ^{1}H and ^{13}C NMR studies, where the medium influences the equilibrium between invertomers, is avoided by this simple approach.

Experimental Section

Synthesis of 7-Methylbenzo-7-azanorbornene (4). The reactions are depicted in Scheme I and were performed as described.[13] The product **4** gave the expected ^{1}H and ^{13}C NMR spectra.

Synthesis of 7-Methyl-7-azanorbornene-2,3-dicarboxylic Acid (5). By a published procedure,[14] *N*-methylpyrrole and acetylenedicarboxylic acid were reacted in ether at reflux and, after several days, the precipitated adduct **3** was filtered off (19%). ^{1}H and ^{13}C NMR spectra matched those reported. A 6.0-g sample in 100 mL of 10% Na_2CO_3 was hydrogenated over 0.3 g of 10% Pd–C at atmospheric pressure until 1 equiv of hydrogen was consumed. The pH was adjusted to 2–3 with 6 N HCl and water removed on a rotary evaporator. The product **5** was extracted from the solid residue with hot methanol. Several recrystallizations from methanol gave an analytically pure sample: ^{1}H NMR ($(CD_3)_2SO$) δ 1.4–2.2 (m, 4 H, $-CH_2CH_2-$, 2.42 (s, NCH_3), 4.6 (m, 2 H, bridgehead CH); ^{13}C NMR (MeOH–D_2O, pH 11) δ 2.49 (C-5,6), 33.3 (NCH_3), 68.9 (C-1,4), 139.7 (C-2,3), 174.0 (CO_2^-).

Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.88; H, 5.58; N, 6.94.

(11) Our preliminary results, without data, were stated in a paper concerned with ^{31}P NMR spectral effects.[1b] A report from another laboratory[12] later showed that some benzoazanorbornenes and azanorbornadienes had very deshielded ^{15}N nuclei. No tertiary amines with the 7-azanorbornene framework were included, however.

(12) Davies, J. W.; Malpass, J. R. *Tetrahedron Lett.* **1985**, *26*, 4537.
(13) Anteunis, M. J.; Borremans, F. A. M.; Gelan, J.; Marchand, A. P.; Allen, R. W. *J. Am. Chem. Soc.* **1978**, *100*, 4050.
(14) Kitzing, R.; Fuchs, R.; Joyeux, M.; Prinzbach, H. *Helv. Chim. Acta* **1968**, *51*, 888.

NMR Measurements. All measurements were made in $CDCl_3$ on a JEOL FX-90Q spectrometer for ^{15}N (at 9.04 MHz) at natural abundance and a Varian XL-300 spectrometer with a 5-mm broadband probe for enriched samples. Operation frequencies for ^{13}C and ^{15}N on the Varian XL-300 were 75.429 and 30.406 MHz, respectively. The ^{13}C NMR spectra were based on Me_4Si as the internal standard; the ^{15}N spectra were referenced externally to CH_3NO_2, where δ CH_3NO_2 = 380.2 with liquid NH_3 as zero. All ^{15}N measurements were run using full proton decoupling. Samples were enriched to contain about 23% ^{15}N.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. 4, 55257-99-3; 5, 103836-46-0.

Synthesis of δ-Lactones via Radical C-C Bond Formation Using Chiral Radical Precursors

Dale B. Gerth and Bernd Giese*

Institut für Organische Chemie und Biochemie der Technischen Hochschule Darmstadt, D-6100 Darmstadt, West Germany

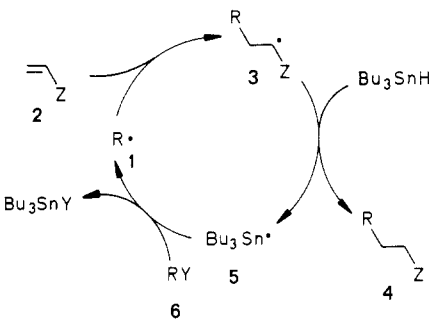
Received February 19, 1986

Carbon–carbon bond formation reactions employing addition of radical **1** to alkenes **2** have been successfully applied in organic synthesis.[1] Alkylmercury hydrides and tri-*n*-butyltin hydride act as efficient traps which convert adduct radicals **3** to products **4** before polymerization can occur (Scheme I).[2] In the case of the tin method, radicals **5** propagate the chain by reaction with suitable educts **6** to form radicals **1**. Halides, xanthanes, selenides, and tertiary nitro compounds can be used as radical precursors **6**.[2]

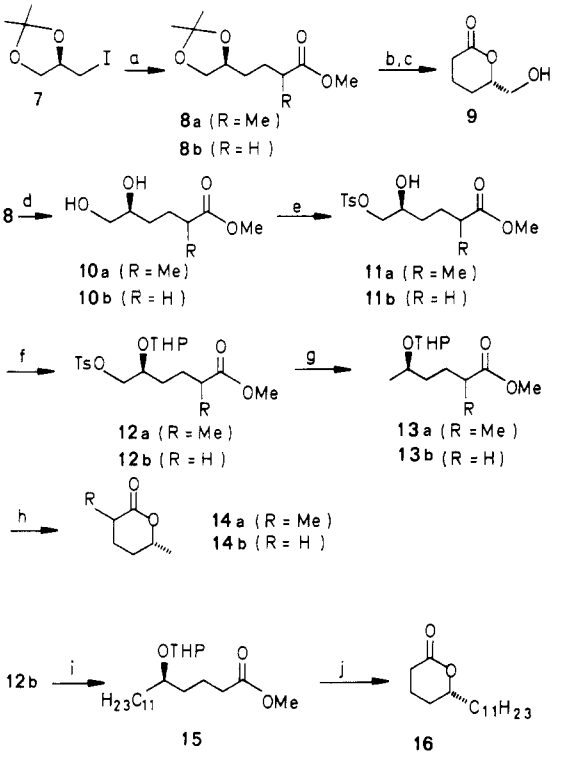
Since these radical reactions are very fast and occur under mild conditions, molecules containing sensitive chiral centers can be used. Therefore, we have applied this method to the synthesis of chiral δ-lactones starting from the readily available chiral precursors **7** and **17**. The δ-lactonic structure is found in several pheromones and could be a useful intermediate in the synthesis of other natural products.[3]

The synthesis that we have developed involves the generation of radicals with the radical center α to a chiral carbon atom and addition of these radicals to electron-poor alkenes. The radicals were generated from the chiral iodide **7**,[4] which was synthesized from (*R*)-(+)-2,3-*O*-isopropylideneglyceraldehyde.[5] The resulting adducts **8a** and **8b** were, after a series of transformations, converted to the lactonic pheromones of the carpenter bee **14a**[6] (cis and trans mixture) and the oriental hornet **16** (Scheme II).[7] Direct conversion of alcohol **9** to **14b** and **16** was not successful because of difficulties encountered in separating the product lactones from the reaction mixtures. However, **9** could be a useful "chiral building block" for other syntheses.

Scheme I



Scheme II[a]



[a] (a) $H_2C{=}CRCO_2Me$, Bu_3SnCl, $NaBH_4$, *hν*, EtOH, 20 °C, 45% (R = Me), 58% (R = H); (b) KOH, EtOH; (c) proton-exchange resin, MeCN, 25 °C, 67%; (d) TsOH, MeOH, 25 °C, 89% (R = Me), 81% (R = H); (e) TsCl, pyridine, 0 °C, 18 h, 70% (R = Me), 73% (R = H); (f) TsOH, DHP, CH_2Cl_2, 25 °C, 1 h, 93% (R = Me), 95% (R = H); (g) NaI, Bu_3SnH, AIBN, glyme, reflux, 3 h, 82% (R = Me), 78% (R = H); (h) proton-exchange resin, CH_3CN, 25 °C, 83% (R = Me), 94% (R = H); (i) $(C_{10}H_{21})_2CuLi$, ether, −30 °C, 4 h, 65%; (j) proton-exchange resin, CH_3CN, 25 °C, 88%.

In a similar scheme, L-(+)-2-(benzyloxy)propanol[8] was converted to the chiral iodide **17**,[9] which reacted in C–C bond formation reactions to give adducts **18**, **20a**, and **20b** (Scheme III). The yield of **20b** was unexpectedly lower than that for **20a** because of the formation of a new unidentified side product. Adducts **20a** and **20b** were deprotected and converted to lactones **21a** and **21b**.

The enantiometric purity of **14b** and **21b** was estimated to be in excess of 95% by using the chiral shift reagent

(1) Hart, D. J. *Science (Washington, D.C.)* **1984**, *223*, 883. See also "Selectivity and Synthetic Applications of Radical Reactions" *Tetrahedron Symp.* (Giese, B., Ed.): *Tetrahedron* **1985**, *41*, 3887.
(2) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 553.
(3) Ikan, R.; Gottlieb, R.; Bergmann, E. D.; Johay, J. *J. Insect Physiol.* **1969**, *15*, 1969. Wheeler, J. W.; Evans, S. L.; Blum, M. S.; Velthius, H. H. V.; de Camergo, J. M. F. *Tetrahedron Lett.* **1976**, 4029. Gais, H. J.; Lied, T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 145. Lichtenthaler, F. W.; Klingler, F. D.; Jarglis, P. *Carbohydr. Res.* **1984**, 132, C-1. Seebach, D.; Renaud, P. *Helv. Chim. Acta* **1985**, *68*, 2342.
(4) Takano, S.; Goto, E.; Hirama, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 951.
(5) Baer, E.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1939**, *61*, 761.
(6) (a) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169. (b) Mori, K.; senda, S. *Tetrahedron* **1985**, *41*, 541.
(7) (a) Fujisawa, T.; Itah, T.; Nakai, M.; Sato, T. *Tetrahedron Lett.* **1985**, *26*, 771. (b) Utaka, M.; Watabu, H.; Takeda, A. *Chem. Lett.* **1985**, 1475.
(8) Abbott, S. J.; Jones, S. R.; Weinman, S. A.; Bockhoff, F. M.; McLafferty, F. W.; Kowles, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 43.
(9) Steiner, K.; Graf, U.; Hardegger, E. *Helv. Chim. Acta* **1971**, *54*, 845.

0022-3263/86/1951-3726$01.50/0