# Notes

## Nuclear Magnetic Resonance Spectra of Cyclic Amines. Shielding of $\alpha$ Protons Trans to a Lone Pair and Cis to an *N*-Methyl Group in Pyrrolidines

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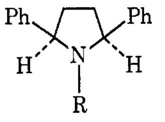
The shielding of axial $\alpha$ protons in saturated six-membered nitrogen heterocycles is well documented.[1-4] This shielding is presumably caused by the anisotropy of the trans axial lone pair and that of the C–N bond of the equatorial alkyl substituent on the nitrogen, the former being the dominant factor.[4]

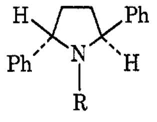
In N-substituted pyrrolidines no such observation, concerning differentiation between $\alpha$ protons cis and trans to the lone pair, has been reported by nmr measurements at room temperature. It was, however, found recently that upon cooling the $\alpha$ protons of *N*-methylpyrrolidine separate into two peaks with $\Delta\delta$ of 1.08 ppm that coalesce at about $-100$°.[5]

In this communication we assess the contributions of a trans lone electron pair and of a cis-*N*-methyl group to the shielding of $\alpha$ protons in pyrrolidines. Our observations also provide a method to assign the stereochemistry of *N*-alkyl-$\alpha,\alpha'$-disubstituted pyrrolidines.

In the course of our studies concerning the Leuckart reaction of cyclopropyl ketones that produce derivatives of pyrrolidine,[6,7] we have prepared *cis*- and *trans*-2,5-diphenylpyrrolidine[8] (**2a** and **3a**) and their *N*-methyl derivatives[9] (**2b** and **3b**).



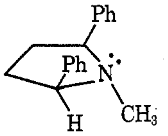
**2**



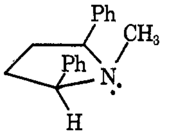
**3**

**a**, R = H; **b**, R = Me

Considering the possibility of nitrogen inversion in these pyrrolidines,[10] it is evident that in the cases of **3a** and **3b** the two pairs of invertomers are identical, and that the two possible invertomers of **2a** should not differ much in energies. In contrast, **2b** should exist predominantly or even perhaps exclusively in the transoid conformation **2b**-I, due to increased nonbonded interactions in conformation **2b**-II. In conformation **2b**-I both $\alpha$ protons are trans to the lone pair and cis to the *N*-methyl group.



**2b**-I



**2b**-II

Examination of the nmr data (CDCl$_3$) listed in Table I reveals that the benzylic methine protons of the cis compounds (**2a** and **2b**) appear at higher field than those of the trans isomers (**3a** and **3b**), respectively. It can also be seen that N-methylation causes a considerably larger shift in the cis series (0.91 ppm) than it does for pyrrolidine and *trans*-2,5-diphenylpyrrolidine (0.33 ppm).

TABLE I
CHEMICAL SHIFTS OF $\alpha$ PROTONS OF PYRROLIDINE AND SOME OF ITS DERIVATIVES[a]

| | $\delta$, ppm | |
|---|---|---|
| | CDCl$_3$ | CDCl$_3$ + TFA |
| Pyrrolidine (**1a**) | 2.78 | 3.40 |
| *cis*-2,5-Diphenylpyrrolidine (**2a**) | 4.25 | 5.00 |
| *trans*-2,5-Diphenylpyrrolidine (**3a**) | 4.43 | 5.00 |
| *N*-Methylpyrrolidine (**1b**) | 2.45 | 3.76, 3.00 |
| *cis*-1-Methyl-2,5-diphenylpyrrolidine (**2b**) | 3.34 | 4.45 |
| *trans*-1-Methyl-2,5-diphenylpyrrolidine (**3b**) | 4.10 | 5.20, 4.37 |

[a] Measured by a Jeol C-60H instrument with TMS as internal standard.

Assuming that **2a**, **3a**, and **3b** exist as 1:1 mixtures of their invertomers and that **2b** exist entirely as the transoid ivertomer **2b**-I it follows that (1) the $\alpha$ protons of **2a**, **3a**, and **3b** are shielded to the extent of 50% by the trans lone pair, (2) the $\alpha$ protons of **3b** are shielded to the extent of 50% also by the *cis*-*N*-methyl group, and (3) the $\alpha$ protons of **2b** are 100% shielded both by the *cis*-*N*-methyl group and by the trans lone pair.

Consequently, the difference of 0.33 ppm between the chemical shifts of **3a** and **3b** represents 50% of the shielding by the *cis*-*N*-methyl group (compare **1a** and **1b**). The difference of 0.91 ppm between the chemical shifts of **2a** and **2b** should be due to 100% shielding of the $\alpha$ protons by a *cis*-*N*-methyl group (0.66 ppm), plus 50% shielding by the trans lone pair: 0.25 ppm ($= 0.91 - 0.66$). The chemical shift difference of 0.18 ppm between **2a** and **3a** may be due to deshielding of the $\alpha$ protons of **3a** by the *cis*-phenyl groups.[11] On

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(1) H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964).

(2) H. Booth and J. H. Little, *Tetrahedron*, **23**, 291 (1967).

(3) R. O. Hutchins, L. D. Kopp, and E. L. Eliel, *J. Amer. Chem. Soc.*, **90**, 7174 (1968).

(4) J. B. Lambert and R. G. Keske, *Tetrahedron Lett.*, 2023 (1969).

(5) J. B. Lambert and W. L. Oliver, *J. Amer. Chem. Soc.*, **91**, 7774 (1969).

(6) E. Breuer and Y. Stein, *Israel J. Chem.*, **6**, 901 (1968).

(7) E. Breuer and D. Melumad, *Tetrahedron Lett.*, 3595 (1969).

(9) C. G. Overberger, M. Valentine, and J. P. Anselme, *J. Amer. Chem. Soc.*, **91**, 687 (1969).

(9) E. Breuer and D. Melumad, *J. Org. Chem.*, **37**, 3949 (1972).

(10) The other conceivable process for pyrrolidines is pseudorotation, which is of such low energy that it has not been observed by nmr;[5] therefore the pyrrolidines are assumed to be planar for the purpose of this discussion.

(11) This difference may also indicate that the two possible conformations of **2a** are not equally populated and that the invertomer with the N–H trans to the phenyl groups predominates. This seems to be supported by the identity of the $\delta$ values of **2a** and **3a** in acidic medium. If this view is accepted the value for 50% shielding by a trans lone pair should be corrected from 0.25 to 0.43 ppm.

the basis of these data we can estimate the chemical shift difference between the α protons of *N*-methylpyrrolidine in the absence of nitrogen inversion. In this case two of the α protons should be fully shielded both by the trans lone pair (0.50 ppm) and by the *cis*-*N*-methyl group (0.66 ppm); therefore the shift should amount to 1.16 ppm, which is in good agreement with the observed value of 1.08 ppm.[5]

The present conclusions are borne out by the results from the protonation experiments (Table I, column 2). In the presence of excess trifluoroacetic acid (TFA) the α protons of **2b** appear as one signal indicating a single protonated species. The α protons of **1b** and **3b** are split into two signals of equal areas with a chemical shift difference of 0.76–0.83 ppm, which presumably results from full-scale shielding of half of the α protons in **1b** and **3b** by a *cis-N*-methyl group. It is worthy of note that the high field signal of **3b** corresponds well with the chemical shift of the α protons of **2b**, both of which are fully shielded by a *cis-N*-methyl group.

From the data presented the following conclusions can be drawn. (1) The α protons of a pyrrolidine are shielded when situated trans to an electron pair and cis to an *N*-methyl group. (2) The chemical shift difference of 1.08 ppm observed at −100° between the α protons of *N*-methylpyrrolidine[5] is caused predominantly (0.66–0.83 ppm) by the *cis-N*-methyl group and to a lesser degree by the trans lone pair. (3) The stereochemistry of a symmetrically *N*,α,α′-trisubstituted pyrrolidine (and presumably any symmetrical nitrogen heterocycle) can be established by examination of the nmr spectrum of the protonated form. In the cis isomer the α protons should appear together, while in the trans isomer they should appear separately. (4) The treatment presented can easily be applied to assess the contribution of a trans lone pair and that of a *cis-N*-alkyl group to the shielding of α protons in any saturated symmetrical nitrogen heterocycle.

The shielding of α protons in azacycloalkanes by a trans lone pair[12] and by a *cis-N*-alkyl group seems to be a general phenomenon. A consequence of this is that in pairs of cis,trans isomers of *N*-alkyl-α,α′ symmetrically disubstituted azacycloalkanes the α protons of the cis isomer should always appear in the nmr at higher field than those of the trans isomer. No exception to this was found in an extensive literature survey of nmr data of appropriate three-, five-, and six-membered azacycloalkanes.[13]

Further study of this problem in other ring systems is in progress.

**Registry No.**—**1a**, 123-75-1; **1b**, 120-94-5; **2a**, 22147-83-7; **2b**, 35657-63-7; **3a**, 22147-84-8; **3b**, 35657-66-0.

**Acknowledgment.**—We wish to thank Professor S. Sarel for his comments concerning this work.

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[12] Although this phenomenon is usually viewed as shielding of α protons trans to a lone pair,[1-4] it may also be viewed as deshielding by a skew or cis related lone pair: C. C. Price, *Tetrahedron Lett.*, 4527 (1971). We thank Dr. C. C. Price for directing our attention to his results.

[13] No data were found for appropriate azetidines and hexahydroazepines.

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# The Reactivity of Diazo Ketones. IV.[1] Reaction of α-Diazo Ketones with Molecular Oxygen

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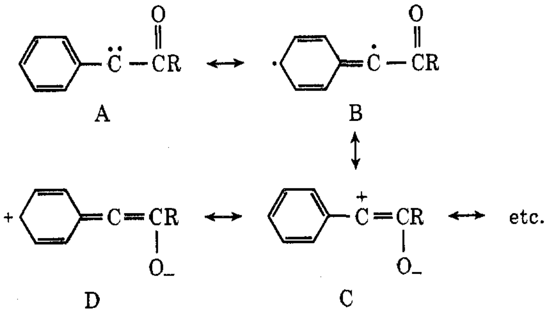
It was reported[1a] that $\mathrm{Ph\ddot{C}COR}$ (R = Ph, Me) type ketocarbenes react with sulfur dioxide to give the ketosulfenes in competition with the Wolff rearrangement, while $\mathrm{R\ddot{C}COPh}$ (R = Me, H) type ketocarbenes do not react, but yield the products resulting from 1,2-hydrogen shift and a 1,3-dipolar addition reaction. In this case, it was suggested[1a] that the resonance form A or B of the $\mathrm{Ph\ddot{C}COR}$ type ketocarbene as shown in Scheme I reacts with sulfur dioxide, for sulfur dioxide is known to react electrophilically and radically, but no nucleophilically.

Scheme I



In order to obtain further information on the reactivity of the ketocarbene, thermal or photochemical reactions of several α-diazo ketones with molecular oxygen were investigated.

A number of reports[2] on the photochemical reactions of diaryldiazomethane and the thermal reactions of tetraarylethylenes with molecular oxygen have been published. These reactions are explained by the addition of diarylcarbenes to molecular oxygen[2-4] (Scheme II).

A "carbonyl oxide" (E) has been suggested[4] as the primary product[4b] in the formation of cyclic peroxide[4a] from the photooxidation of diphenyldiazomethane. Also, the formation of benzophenone from the "carbonyl oxide" (E) on irradiation of diphenyldiazomethane in solid air matrix at 20°K has been reported.[4c]

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[1] (a) M. Tanaka, T. Nagai, and N. Tokura, *J. Org. Chem.*, **37**, 4106 (1972); (b) T. Nagai, M. Tanaka, and N. Tokura, *Tetrahedron Lett.*, 6293 (1968); (c) M. Tanaka, T. Nagai, and N. Tokura, *ibid.*, 4979 (1972).

[2] (a) H. Staudinger, E. Anthes, and F. Pfenninger, *Ber. Deut. Chem. Ges.*, **49**, 1928 (1916); (b) W. Kirmse, L. Horner, and H. Hoffman, *Justus Liebigs Ann. Chem.*, **619**, 19 (1958); (c) P. D. Bartlett and T. G. Traylor, *J. Amer. Chem. Soc.*, **84**, 3408 (1962); (d) R. W. Murray and A. M. Trozzolo, *J. Org. Chem.*, **26**, 3109 (1961).

[3] V. Franzen and H. I. Joschek, *Justus Liebigs Ann. Chem.*, **633**, 7 (1960).

[4] (a) P. D. Bartlett and T. G. Traylor, *J. Amer. Chem. Soc.*, **84**, 3408 (1962). (b) Peroxidic zwitterion F is suggested to be formed from the radical structure E as shown in Scheme II: R. W. Murray and A. Suzui, *ibid.*, **93**, 4963 (1971). (c) Benzophenone is suggested to be obtained from the related carbonyl oxide, but the mechanism of the deoxygenation from the carbonyl oxide is not determined.[2c]