

Conformationally Homogeneous Secondary Amines at Room Temperature

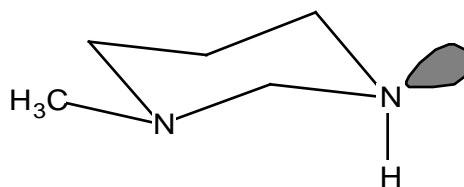
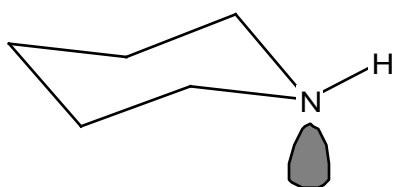
J. Thomas Ippoliti,^{†*} Susan Leta and Sergiu Gorun*

Corporate Research Laboratory

Exxon Research and Engineering Company

Annandale, New Jersey 08801

Conformational analysis of six-membered ring nitrogen-containing heterocycles has been a topic of interest for many years.¹ A considerable amount of research has been aimed at addressing the question of whether the lone pair of electrons on nitrogen prefers the equatorial or axial position in such systems. When the substituent on the nitrogen is hydrogen difficulties arise in assessing the position of the lone pair by NMR due to exchange processes with acid impurities and because inversion is rapid at room temperature. In the case of piperidine, it was determined that the conformation with the lone pair in the axial position is thermodynamically favored by 0.36 kcal/mol which gives a 35/65 equilibrium mixture at room temperature.² However, analysis of the ¹H NMR spectrum at -70 °C of N-methyl-1,3-diazacyclohexane showed that the preferred

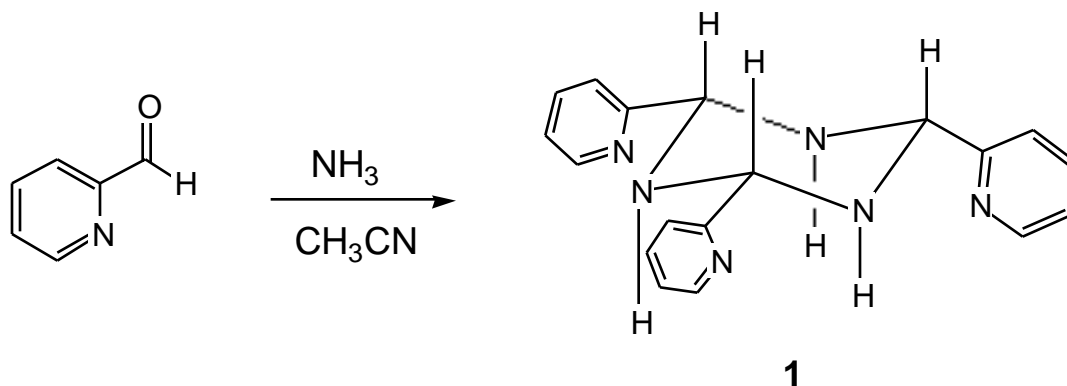


[†]Present address: Department of Chemistry, College of St. Thomas, 2115 Summit Avenue, St. Paul, MN 55105.

conformation is one in which the N-H bond is in the axial orientation; i.e. the lone pair prefers the equatorial position.³ Apparently, the second nitrogen produces an anomeric effect which stabilizes this conformation.⁴ Again, a mixture of conformational isomers is present at room temperature. We describe here the first observation of the predominance of a single isomer containing an axial N-H in a six-membered ring at *room temperature*.

Reaction of 2-pyridinecarboxaldehyde with anhydrous NH_3 in CH_3CN yielded 2,4,6-tri-(2-pyridyl)-1,3,5-hexahydrotriazine (**1**) as clear, colorless crystals upon standing overnight (Scheme I).^{5,6}

Scheme I



The structure of **1** is assigned to the chair conformation illustrated in Scheme I. Single crystal X-ray diffraction⁷ (vide infra) and solution NMR studies confirm the axial orientation of the N-H bonds both in solid state and solution. Especially convincing for the solution structure is

the ^1H NMR data (Figure 1).⁸ The **H-C-N-H** coupling constant of 11.4 Hz is consistent with a trans geometry.⁹

Figure 1.

A particularly noteworthy feature of the ^1H NMR spectrum is the sharpness of the N-**H** resonance.¹⁰ The ^{15}N -H coupling constant was measured from the ^{15}N satellites in the ^1H NMR to be 61.3 Hz, which is a typical value for $^1J(\text{N-H})$ in secondary amines.¹¹ Since ^{15}N -H and vicinal **CH-NH** coupling are clearly observed, the protons on the nitrogens are not exchanging to any significant extent. Non-exchanging protons attached to nitrogen are normally severely broadened due to coupling with the ^{14}N nucleus which possesses a quadrupole moment. Therefore, the N-H proton of compound **1** must be decoupled from the ^{14}N nucleus in order to show such a sharp resonance. This natural decoupling is almost certainly caused by very rapid relaxation of the ^{14}N nucleus.¹² For such a rapid relaxation to be occurring, an extremely efficient relaxation mechanism must be operating. At this time the cause of this efficient relaxation is uncertain. We speculate that there is a large electric field gradient at the nitrogen nucleus which is a result of the predominance of one isomer in which the lone pairs are all in the equatorial position.¹³ A large electric field gradient gives rise to a large quadrupolar coupling constant thus providing an efficient relaxation mechanism.¹⁴

The orientation of all the N-H protons in the axial position was rather striking and we

initially postulated that this preference was due to internal hydrogen bonding to the pyridine nitrogens which stabilized this conformation. This hypothesis appeared to be partially supported by the X-ray crystal structure. The structure determined by single crystal X-ray analysis¹⁵ is shown in Figure 2. No solvent or water molecules are present in the crystal lattice.¹⁶ The chair conformation of the triazane ring is clearly established, all the N-H and C-H hydrogens being trans to each other. The dihedral angles between planes defined by the pyridine rings (P2-P4, nitrogen labeled for identification) and the plane defined by the least squares plane drawn through the triazane ring (P1) are: P1/P2 (N4) = 90.40, P1/P3 (N6) = 108.30, P1/P4 (N5) = 81.60.¹⁷ As a consequence, the distances between the pyridine nitrogen atoms and amino hydrogens with which they could potentially form hydrogen bonds are non-equivalent: H1-N4 = 2.547 Å, H1-N6 = 2.800 Å, H3-N4 = 2.524 Å, H3-N5 = 2.401 Å, H5-N5 = 2.612 Å, H5-N6 = 2.441 Å. The fact that the nitrogen atoms of each pyridine ring point their lone pairs between the amino hydrogens of the triazane ring and even appear to orient themselves preferentially toward one hydrogen suggest that there might be some hydrogen bonding interaction.

Figure 2.

To test the hypothesis that hydrogen bonding is responsible for the conformational bias being observed for **1**, two other pyridine isomers, **2** and **3**, were synthesized by the same procedure used for producing **1**.¹⁸ A comparison of the chemical shifts and coupling constants of each isomer is shown in Figure 3.¹⁹ Note that the vicinal N-H, C-H coupling constants for

Figure 3.

isomers **2** and **3** are similar to **1**, albeit somewhat smaller.^{20,21} These coupling constants indicate that isomers **2** and **3** adopt the same conformation as **1**. Since it is not geometrically possible for the lone pair of the pyridine nitrogen in isomer **2** or **3** to be directed toward the N-H in the triazane ring, intramolecular hydrogen bonding is effectively ruled out as the sole factor responsible for compound **1** assuming a conformation with all the N-H's axial at room temperature. However, comparison of the N-H chemical shifts in isomers **1-3** (see Figure 3) show that there is a deshielding effect operating in **1** presumably due to a weak intramolecular hydrogen bonding interaction with the ortho nitrogen in the pyridine ring. This shift is not simply due to inductive effects since the C-H resonance is shifted less than 0.1 ppm going from compound **1** to **3** whereas the N-H is shifted more than 1 ppm.

Since hydrogen bonding is not the source of the strong conformational preference for the lone pair to be in the equatorial position in compounds **1-3** then another mechanism must be operating. If one conformational isomer predominates at room temperature by more than 99% (as is the case for **1**) then it must be at least 3 kcal/mol more stable than any other isomer. A stabilization energy of this magnitude can readily be attributed to the anomeric effect.²² The anomeric effect has been estimated to be worth about 1.4 kcal/mol.²³ There are *at least* 3 full fledged anomeric interactions in a triazane such as **1** since each lone pair can donate electron density into at least one C-N antibonding orbital. These interactions total to 4.2 kcal which can readily account for the >99% preference of one isomer.

Acknowledgement. M. Modrick is acknowledged for technical assistance and Professor A. Katritzky for helpful discussions.

Supplementary Material Available: Tables of bond distances and angles and atomic coordinates and equivalent isotropic displacement parameters for compound **1**. Ordering information is given on any current masthead page.

References

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2. Anet F. A.; Yavari, I. *J. Am. Chem. Soc.* **1977**, *99*, 2794.
3. Booth, H.; Lemieux, R. U. *Can. J. Chem.* **1971**, *49*, 777.
4. For other examples where the preferred orientation of an axial N-H in a six-membered ring has

been attributed to the anomeric effect see ref. 3 and Quast, H.; Berneth, C. P.; Peters, E. M.; Peters, K.; von Schnering, H. G. *Chem. Ber.* **1986**, *119*, 3842.

5. The synthesis of compound **1** was first reported by Lenart, G. H. *Liebigs Ann. Chem.* **1915**, *410*, 100, the only data given was a melting point and C, H, N analysis. Since no reference to this compound was found other than Lenart's original paper, further characterization was carried out and the data obtained follows: 360 MHz ^1H NMR (CDCl_3) δ 8.59 (3 H, dd, $J = 1.5, 5.0$ Hz), 7.67 (3 H, td, $J = 1.7, 7.5, 7.5$ Hz), 7.44 (3 H, bd, $J = 8$ Hz, decoupling experiments showed this signal to be composed of $J = 7.5, 1.5, 1.0$ Hz), 7.20 (3 H, ddd, $J = 1.1, 5.0, 7.5$ Hz), 5.34 (3 H, t, $J = 11.3$ Hz), 2.70 (3 H, t, $J = 11.4$ Hz, N-H, exch. D_2O). 90 MHz ^{13}C NMR (CDCl_3) δ 158.67 (tert. C), 149.46 (CH), 136.73 (CH), 123.08 (CH), 122.02 (CH), 73.09 (CH). IR (KBr) ν_{max} 3290 cm^{-1} (st., sharp, N-H), 1595, 1570 cm^{-1} (st., sharp), no Bohlman bands. IR (CDCl_3) 3290 cm^{-1} (m, N-H), 1595, 1570 cm^{-1} (st., sharp), no Bohlman bands.

6. For synthesis of other 2,4,6-trisubstituted-1,3,5-hexahydrotriazines using similar conditions see: (a) Nielsen, A. T.; Atkins, R. L.; DiPol, J.; Moore, D. W. *J. Org. Chem.* **1974**, *39*, 1349. (b) Nielsen, A. T.; Atkins, R. L.; Moore, D. W.; Scott, R.; Mallory, D.; LaBerge, J. M. *J. Org. Chem.* **1973**, *38*, 3288. (c) Young, J. A.; Schmidt, J. J.; Krimmel, J. A. *J. Org. Chem.* **1971**, *36*, 347.

7. A single crystal X-ray structure has been determined for one other hexahydro-1,3,5-triazine: the trihydrate of the acetaldehyde ammonia trimer, see (a) Lund, E. W. *Acta. Chem. Scand.* **1958**, *12*,

1768 (b) Lund, E. W. *ibid.* **1951**, 5, 678 (c) Moerman, N. F. *Z. Kristallogr.* **1938**, 98, 447. The amine hydrogens were determined to occupy the axial position and were hydrogen bonded to the water molecules.

8. The ^1H NMR spectrum was taken in CDCl_3 , d_5 -Pyridine, and CD_3OD . In CD_3OD the triazane ring C-**H** was a singlet and no N-**H** was observed due to rapid exchange. CDCl_3 solutions of made from samples of **1** which had not been thoroughly dried gave ^1H NMR spectra which showed the ring C-**H** as a singlet. The spectra in d_5 -Pyridine also showed a clean sharp triplet for the N-**H** proton. No change was observed in the ^1H NMR spectrum upon cooling the CDCl_3 solution to -40°C .

9. Axial-axial couplings in six-membered rings containing a nitrogen atom range from 9-13 Hz; see ref. 3 and (a) Maryanoff, B. E.; McComsey, D. F.; Inners, R. R.; Mutter, M. S.; Wooden, G. P.; Mayo, S. L.; Olofson, R. A. *J. Am. Chem. Soc.* **1989**, 111, 2487 (b) Fraser, R. R.; Renaud, R. N.; Saunders, J. K.; Wigfield, Y. Y. *Can. J. Chem.* **1973**, 51, 2433 and (c) Crowley, P. J.; Morris, G. A.; Robinson, M. J. T. *Tetrahedron Lett.* **1976**, 3375 for examples.

10. Although numerous other hexahydrotriazines have been reported (for examples see reference 6) no sharp N-**H** resonances have been reported, probably due to insufficient drying of samples.

11. Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*; Wiley-Interscience: New York, 1979; Chapter 4.

12. This phenomena is well known and is the reason why ^{14}N - ^{13}C couplings are normally not observed, see Wasylishen, R. E. In *Annual Reports on NMR Spectroscopy* Webb, G. A., Ed.; Academic: New York, 1977; Vol. 7, p 262. For a more thorough discussion see Lehn, J. M.; Kintzinger, J. P. in *Nitrogen NMR*, Webb, G. A.; Witanowski, M., Eds.; Plenum: New York, 1973, Chapter 3, p 134.

13. This arrangement of the lone pairs leads to an abnormal electron density at the nitrogen nucleus presumably due to some type of W coupling of the lone pairs. Further details concerning other examples of W coupling will be presented in a future publication.

14. The relaxation time of the ^{14}N nucleus is inversely proportional to the square of the quadrupole coupling constant which, in turn, is directly proportional to the electric field gradient at the nucleus. For the exact equation see Witanowski, M.; Stefaniak, L. and Webb, G. A. In *Annual Reports on NMR Spectroscopy* Webb, G. A., Editor; Academic: New York, 1977; Vol. 7, p 234.

15. X-ray analysis: the compound **1** crystallizes in the monoclinic system, space group $P2_1/c$, with $a = 15.562(4) \text{ \AA}$, $b = 6.017(1) \text{ \AA}$, $c = 17.502(5) \text{ \AA}$, $\beta = 90.89(2)^\circ$, $V = 1638.7 \text{ \AA}^3$, d (calcd) = $1.23 \text{ g}\cdot\text{cm}^{-3}$, $Z = 4$. With the use of 2236 unique reflections ($F_o > 3\sigma(F_o)$) collected at 23° C with $\text{MoK}\alpha$ ($\lambda = 0.7107 \text{ \AA}$) radiation out to $2\theta = 55^\circ$, the structure was solved by direct and difference Fourier methods and refined using 217 variables to a current value of the discrepancy index $R1$ of 0.044. All hydrogens were located in difference Fourier maps and their geometries were subsequently idealized. Atomic, positional, and thermal parameters are provided as supplementary material. Full details will be reported elsewhere.

16. Therefore hydrogen bonding of water molecules stabilizing the conformation with the N-H's axial is not an issue. The presence of water could be used to rationalize the occurrence of this conformation in the trihydrate of the acetaldehyde ammonia trimer.⁷

17. Since these dihedral angles are not equal, the point group symmetry of **1** in the solid state is lowered from a potential C_{3V} to C_1 .

18. A thorough literature search resulted in a reference in which compounds **2** and **3** were mentioned: Gu, C.; Gu, W. *New Front. Organomet. Inorg. Chem., Proc. China-Jpn.-U.S.A. 2nd Trilateral Semin.*, 1982, 3-15. Edited by: B-K, Teo. Sci. Press: Beijing, Peop. Rep. China 1984. This reference does not include any spectral data or preparation procedures. Therefore, the following spectral data is presented. Compound **2**: 360 MHz ^1H NMR (CDCl_3) δ 8.89 (3 H, d, $J = 1.9$ Hz), 8.60 (3 H, dd, $J = 1.4, 4.7$ Hz), 7.95 (3 H, dd, $J = 7.9, 1.7$ Hz), 7.33 (3 H, dd, $J = 4.9, 7.9$ Hz), 5.30 (3 H, t, $J = 8.9$ Hz), 1.67 (3 H, t, $J = 8.9$ Hz, N-H, D_2O). 90 MHz ^{13}C NMR (CDCl_3) δ 149.76 (CH), 148.32 (CH), 136.35 (tert. C), 133.89 (CH), 123.31 (CH), 71.51 (CH). IR (KBr) ν_{max} 3235 cm^{-1} (st., sharp, N-H), 1594, 1577 cm^{-1} (st., sharp), no Bohlman bands. Compound **3**: 360 MHz ^1H NMR (CDCl_3) δ 8.65 (6 H, d, $J = 5.8$ Hz), 7.58 (6 H, d, $J = 5.8$ Hz), 5.29 (3 H, t, $J = 9.8$ Hz), 1.62 (3 H, t, $J = 9.8$ Hz, N-H). 90 MHz ^{13}C NMR (CDCl_3) δ 150.19 (CH), 149.12 (tert. C), 121.18 (CH), 71.60 (CH).

19. The N-H resonances in the ^1H NMR spectra of compounds **2** and **3** recorded in CDCl_3 are also sharp.

20. Coupling constants of ~10 Hz are still consistent with a trans geometry; see reference 9 for examples. Another explanation for a smaller coupling constant is that the spectrum is a weighted average of rapidly equilibrating isomers which have the N-**H** equatorial and axial, the smaller the coupling constant the more of the equatorial N-**H** isomer present. However, the chemical shifts of the triazane ring C-**H** do not support this reasoning. If the conformation with the lone pair axial were present to any appreciable extent one would expect to see an upfield shift for the C-**H** antiperiplanar to the lone pair.¹ A significant upfield shift is not observed for the C-**H** protons from **1** to **2** and even moves downfield from **3** to **2** which is opposite the direction one would predict. Also, no Bohlman bands (2700-2800 cm⁻¹), which are indicative of a nitrogen lone pair being antiperiplanar to a C-**H** bond, are observed in the solution IR spectrum of these compounds.²¹ These facts suggest that nitrogen inversion may indeed be frozen out in triazanes **1-3** at room temperature!

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