Tetrahedron Letters, Vol. 33, No. 45, pp. 6771-6774, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Conformations and Relative Energies of Tetrahydropyridines

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Abstract: The ground state conformations of three tetrahydropyridine isomers (2,3,4,5-tetrahydropyridine 1, 1,2,3,4-tetrahydropyridine 2, and 1,2,3,6-tetrahydropyridine 3), optimized at MP2/6-31G*, are half chairs. The only conformation found for 2 has the nitrogen lone pair in the axial position in order to conjugate with the π-bond. The relative energies of 1–3 are 0.0, 6.39, and 11.9 kcal/mol. The equatorial conformer of 3 lies 0.32 kcal/mol above the axial form.

The conformational analysis of cyclohexene is well studied and the lowest energy conformer is the half chair form.[1] Similar studies of tetrahydropyridines are unknown, though a number of examples of all three isomers (2,3,4,5-tetrahydropyridine **1**, 1,2,3,4-tetrahydropyridine **2**, and 1,2,3,6-tetrahydropyridine **3**) have been isolated.[2-7] Recent interest in the Diels-Alder reactions of aza-1,3,-butadienes has led to the preparation and characterization of substituted examples of these heterocycles.[8] We report here *ab initio* calculations of the ground state conformations of these isomers to explore their structure and relative energies.

The structures of **1–3** were completely optimized at both the HF/6-31G* and MP2/6-31G* levels using the standard techniques in GAUSSIAN-90.[9] The geometries of these molecules at these two levels are quite similar and only the MP2 structures are shown in Figure 1. The HF and MP2 total and relative energies are listed in Table 1. Analytical frequency analysis at HF/6-31G* confirmed that these geometries are local minima and the calculated zero-point energies (scaled by 0.9) are added to give our best estimate of the relative energies in the last column of Table 1.

As anticipated, the ground state conformation of these compounds is the half chair. Both **2** and **3** can, in principal, exist in two half chair forms, having the hydrogen attached to nitrogen in the axial or equatorial positions. We could locate minima corresponding to both forms for **3**, labeled as **3a** for the axial isomer and **3e** for the equatorial isomer. Only the equatorial form of **2** could be located. Attempts to optimize an axial conformer led to ring flip and the equatorial isomer only.

Table 1. Energy (au) and Relative Energy of **1-3**.

compound	HF/6-31G*	E_{rel}	MP2/6-31G*	E_{rel}	E_{rel} + ZPE
1	-249.014816	0.00	-249.846503	0.00	0.00
2	-249.005496	5.85	-249.836762	6.11	6.39
3a	-248.998424	10.29	-249.828049	11.58	11.90
3e	-248.998228	10.41	-249.827504	11.92	12.22

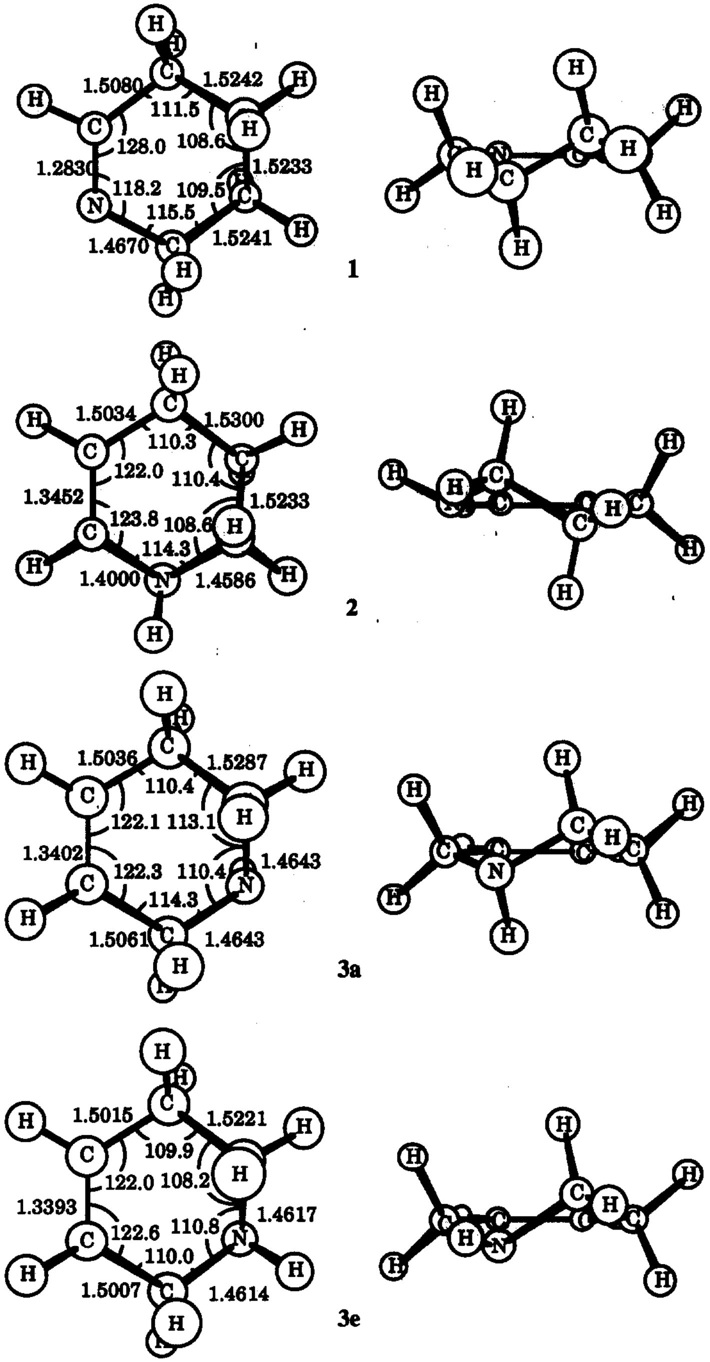


Figure 1. MP2 optimized geometries of 1-3. All distances in Å and all angles in deg.

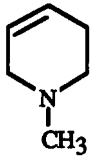
A limited number of x-ray crystal structures of tetrahydropyridines are available. All experimental structures exist in the half chair conformation. The crystal structure of only one monocyclic analogue of **1** has been reported.[2] This heavily substituted tetrahydropyridine has r(C=N) = 1.262Å and r(C-N) = 1.496Å with the ring angles about N and C6 of 121.0° and 128.5°, respectively. Boger has reported the crystal structures of a series of *N*-sulfonyl-1,2,3,4-tetrahydropyridines.[3-5] The C=C distance ranges from 1.304 to 1.315Å. The C2-N distance varies from 1.405 to 1.440Å, while the C6-N distance is significantly longer, ranging from 1.477 to 1.522Å. The sulfonyl group occupies the psuedo-equatorial position in all of these structures. The interior angle about N ranges from 114.9° to 118.4°. The sum of the angles about nitrogen is at least 351°, indicating a nearly planar nitrogen atom. Finally, in the two crystal structures[6,7] of substituted analogues of **3** that lack conjugating groups on nitrogen, the C=C distance is 1.322 and 1.323Å, while the C-N distances range from 1.458 to 1.468Å. The interior angle about nitrogen is 109.5° and 110.3° and the nitrogen is pyramidal in both structures. The nitrogen substituent occupies the equatorial position in both structures.

The comparison with our calculated structures shown in Figure 1 is remarkably good. All important features are reproduced. The rings exist has half chairs. The C=N distance and relative sizes of the angles about the double bond in **1** are close to the experimental structure. The very short N-C6 distance found in the crystal structures of the analogues of **2** is reproduced in our calculation, along with the strong preference for equatorial substitution on nitrogen. The C=C and C-N distances in **3a** and **3e** are very similar to each other and to the crystal structures.

The relative energies of the tetrahydropyridines are only slightly affected by the inclusion of electron correlation through MP2. Nevertheless, we will refer specifically to the MP2 relative energies with ZPE corrections. **1** is the lowest energy isomer with **2** lying 6.39 kcal/mol higher and **3a** 5.51 kcal/mol higher still. **3a** is 0.32 kcal/mol more stable than **3e**. That **1** is the lowest energy isomer is expected; the C=N double bond is stronger than the C=C double bond and the N-H bond is stronger than the C-H bond. In terms of simple additivity of bond energies, **2** and **3** should have similar energies. Their calculated energy difference of about 5.5 kcal/mol is attributable to the conjugation of the nitrogen lone pair with the π-bond in **2**. This conjugation is maximized when the lone pair is in the axial position, which accounts for the lack of a stable axial conformer of **2**. The short C2-N distance (about 0.06Å shorter than the other C-N distances in this series) strongly supports the conjugation across this bond.

Contrary to the crystal structures of substituted analogues of **3** which have the nitrogen substituents in the expected equatorial position, we find that **3a** is slightly more stable than **3e**. In this parent compound, the nitrogen lone pair is more sterically demanding than hydrogen and consequently prefers the sterically less congested equatorial position.

The relative energies of **2** and **3** is in agreement with the few studies addressing the relative stabilities of allyl vs. vinyl amines. The vinyl amines **5** and **7** are measured to be 4.0[10] and 10.5[11] kcal/mol more stable than their allyl amine isomers **4** and **6**, respectively. Calculations at HF/3-21G estimate that **9** lies 1.5 kcal/mol below **8**.[12] The energy difference in this last case is reduced due to the conjugation of the C=C double bond with the aldehyde in the allyl amine.



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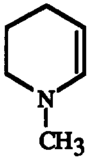

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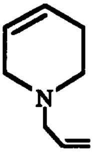

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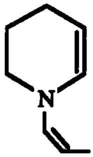

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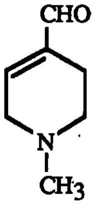

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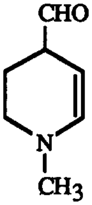

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In summary, tetrahydropyridines favor the half chair conformation. Vinyl amines, typified by **2**, are stabilized by significant conjugation between the nitrogen lone pair and the π-bond, resulting in a short C-N bond and only equatorial substitution at nitrogen. .

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(Received in USA 25 June 1992; accepted 11 August 1992)