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Probing Molecular Shape. 1. Conformational Studies of 5-Hydroxyhexahydropyrimidine and Related Compounds

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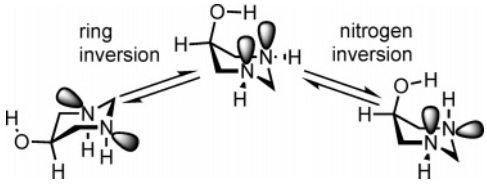

Understanding the factors that determine molecular shape enables scientists to begin to understand and tailor molecular properties and reactivity. Many biomolecules and bioactive compounds contain aliphatic heterocyclic rings whose conformations play a major role in their biological activity. The interplay of a number of factors, both steric and electronic, is examined for 5-hydroxyhexahydropyrimidine (**1**) and related compounds with use of spectroscopy and molecular modeling.

Introduction

The physical properties and reactivity of molecules are well-known to be strongly influenced by their preferred molecular shapes.[1] The dominant conformation of even a low molecular weight aliphatic heterocycle may be influenced by a number of steric and electronic factors. Since many biomolecules and bioactive compounds contain aliphatic heterocyclic rings, the study of the influence and interplay of these effects in simpler systems provides valuable insight into their structure and hence their properties and reactivity.

Such studies were zealously undertaken by Crab, Eliel, Katritzky, and others[2] in the 1960s and 1970s with the development of appropriate spectroscopic techniques; modern concepts of conformational analysis, including stereoelectronic effects (such as the anomeric[3] and gauche[4]), began to evolve. These investigations and consequent discoveries were, however, restricted by the fact that any understanding of most of these effects was in its infancy, and by the more limited spectroscopic and computational tools available at that time.

The conformations of 5-hydroxyhexahydropyrimidine (**1)** would be expected to be determined by the interplay of nonbonded (steric) interactions, anomeric and gauche effects, and hydrogen bonding, resulting from the interaction of the hydroxyl group and the endocyclic nitrogen atoms. 5-Hydroxyhexahydropyrimidine (**1)** is therefore a simple model compound to investigate and quantify the contributions and interplay of these effects in a single system by comparison with the parent compound, hexahydropyrimidine (**2)**, and the oxygen analogues, 1,3-dioxane (**3)** and 1,3-dioxan-5-ol (**4**).

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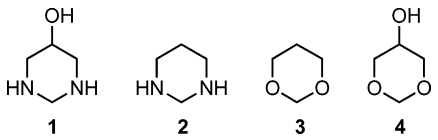
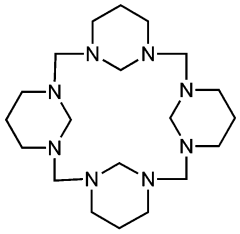


1 **2** **3** **4**

Results and Discussion

Synthesis. 5-Hydroxyhexahydropyrimidine (**1**) was synthesized from 1,3-diamino-2-propanol and formalin. ^{1}H NMR spectra of the crude products showed that this method usually produced **1** in greater than 95% purity. The crude 5-hydroxyhexahydropyrimidine was then purified by vacuum sublimation. In contrast, a reported synthesis[5] was found to give a product highly contaminated with unreacted 1,3-diamino-2-propanol.

Synthesis of hexahydropyrimidine (**2**) was accomplished by using a published method.[6] It proved difficult to isolate **2** from 1,3-diaminopropane and the macrocycle **5**, which has been



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identified as a product of this reaction in other studies.[7,8] Compound **2** was purified by combining a freshly distilled mixture of **2** and 1,3-diaminopropane (9:1) with *o*-hydroxybenzaldehyde in the presence of K_2CO_3. The 1,3-diaminopropane formed the mono- and/or bisimine and the more volatile **2** was removed by vacuum distillation.

1,3-Dioxan-5-ol (**4**) was synthesized via the benzoate ester, using the combined methods of Hibbert[9] and Barker.[10] The identity and purity of compounds **1**−**4** was confirmed with ^{1}H and ^{13}C NMR spectroscopy. Spectral assignments were made by using a combination of techniques including D_2O exchange, selective 1D ^{1}H NMR decoupling, DEPT, gCOSY, gHSQC, and gHMBC experiments. ^{1}H NMR coupling constants were measured from the 1D spectra acquired in the relevant solvents. A tabulated summary of coupling constant values for compounds **1** and **4** can be found in the Supporting Information (Table S1).

Orientation of the Hydroxyl Group. Separate signals were observed for the axial and equatorial protons in the ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of 5-hydroxyhexahydropyrimidine (**1**) at 298 K. These well-resolved signals most likely arise from the dominating presence of a single highly favored conformer. The magnitudes of the coupling constants between H4a[11] and H4e with H5, 2.9 and 3.1 Hz, respectively, indicated that the hydroxyl group was axial. The broadening of the doublets at 3.75 and 2.87 ppm allowed assignment of these signals to H2e and H4e, respectively. Broadening of the signals was due to an unresolved W coupling ($^4J_{2e4e} < 1$ Hz), which was confirmed by narrowing of the signals after decoupling.[12] The small H4a to H5e coupling in **1** and the occurrence of the signal for the H4e upfield from the signal of H4a provided further evidence for the axial orientation of the hydroxyl group in the dominant conformation. This phenomenon has been observed in other systems with electronegative substituents.[13] For example, studies in steroids have shown that an exocyclic substituent such as OH or SH in an axial position caused the vicinal equatorial proton to shift upfield by 0.1 to 0.3 ppm and moved the signal from the vicinal axial proton downfield by approximately 0.3 ppm. The magnitudes of vicinal coupling constants are also influenced by the orientation of an electronegative substituent. In steroid systems with an axial substituent the most significant effect is observed for the $^3J_{a,e}$ value, which is significantly diminished while the expected value of $^3J_{e,e}$ increases. In **1**, the effect of the axial hydroxyl group on the vicinal protons was also seen in the size of the coupling constants, as $^3J_{4a,5e}$ was significantly diminished compared to $^3J_{4e,5e}$.

There are two obvious influences in this system that may stabilize the hydroxyl group in the axial position. The OH proton may form an intramolecular hydrogen bond to either or both endocyclic nitrogen atoms. There is also a possible gauche effect involved in the stabilization of an axial hydroxyl group, although this effect would probably be weaker than the potential intramolecular hydrogen bond(s) in $CDCl_3$. As expected, the spectrum of **1** in D_2O was consistent with an equatorial OD group, ($^3J_{4a,5a} = 7.8$ Hz and $^3J_{4e,5a} = 3.8$ Hz), presumably because the intramolecular hydrogen bond that stabilizes the axial hydroxyl group was disrupted in preference to intermolecular hydrogen bonding with the solvent. The ^{1}H NMR spectrum ($CDCl_3$) of **4** also showed strong evidence of an axial OH group. A coupling of approximately 0.5 Hz between the doublet at 4.93 ppm and the doublet of doublets at 3.87 ppm was observed and was again attributed to a $^4J_{2e,4e}$W coupling, which was confirmed by decoupling. As in **1**, H4a resonated downfield from H4e and the magnitudes of $^3J_{4e,5e}$ (3.2 Hz) and $^3J_{4a,5e}$ (2.2 Hz) were consistent with the hydroxyl group being axial. There was no large diaxial coupling between H5 and H4a, implying H5 was equatorial.

Intramolecular hydrogen bonding in **4** and related dioxanols has been well documented,[14] mostly through IR studies carried out with dilute samples in aprotic solvents. This was confirmed by the ^{1}H NMR spectrum of **4** ($CDCl_3$), which showed strong evidence of hydrogen bonding. The hydroxyl proton resonated as a doublet at 2.96 ppm. Assignment of this signal and coupling was confirmed by D_2O exchange in $CDCl_3$, with the concomitant loss of a large coupling in the H5 multiplet at 3.62 ppm. Decoupling of the H5 and hydroxyl proton signals also confirmed this assignment. The vicinal coupling constant across

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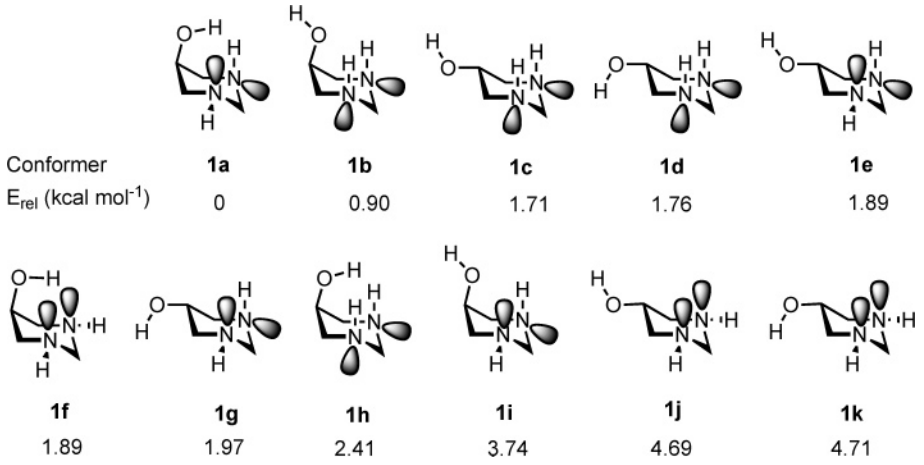

FIGURE 1. The relative energies (E_{rel}) calculated for conformers **1a**−**1k** at the DFT level (B3LYP, 6-311+G**).

the H5−C−O−H path was 9.9 Hz. Scalar coupling across the HCOH path displays a Karplus-like relationship and a typical value for free rotation about the C−O axis is in the range of 6.5 ± 1 Hz; a coupling constant of 9.9 Hz corresponds to a dihedral angle of 150°.[15] It is likely that rotation about the C−O axis is retarded by the presence of an intramolecular hydrogen bond. The magnitude of the $^3J_{5e,OH}$ coupling constant suggests that the hydroxyl group was intramolecularly hydrogen bonded to an endocyclic oxygen atom or is possibly fluctuating between the two annular oxygen atoms as this rotamer population averages to the observed angle.

Attempts to measure the ^3J coupling across the H5−C−O−H segment of 5-hydroxyhexahydropyrimidine (**1**) in $CDCl_3$ were unsuccessful. It is likely that the amine protons and the hydroxyl proton were exchanging. It is also likely that the facile nature of amine inversion resulted in the hydrogen bond being highly transient and that the observed signal was due to a mixture of rotamers being present.

The preferred conformation of 1,3-dioxan-5-ol (**4**) changed in DMSO. Coupling constants and chemical shifts showed that the inverted ring with the hydroxyl group in an equatorial position was the dominant conformer in the more polar solvent. The long-range (H2e to H4e) W coupling was still observed in this solvent and facilitated assignment of axial and equatorial signals. In the more polar solvent intermolecular hydrogen bonding to the solvent presumably replaced intramolecular hydrogen bonding. The signal from the hydroxyl proton in the ^{1}H NMR spectrum (298 K) was a doublet at 5.07 ppm and the $^3J_{5e,OH}$ coupling constant was reduced to 4.7 Hz (relative to $^3J_{5e,OH}$ in $CDCl_3$), which possibly reflects the presence of a more averaged rotamer population.

The possibility of an intramolecular hydrogen bond influencing the preferred conformation of **1** was investigated further by using molecular modeling. Selected chair conformers of **1**, **2**, and **4** were built and optimized at two different levels of theory (ab initio, using the 6-31G* basis set; DFT, B3LYP, G-3111+G**). The results agree remarkably well between the two levels of theory. The DFT results are presented and discussed here. The ab initio results are available as a table in the Supporting Information. The orientation of the OH hydrogen in **1** and **4** was also investigated (see the Experimental Section). The relative energy (E_{rel}) for each conformer in the gas phase was calculated from the difference in total energy of the most stable conformer and the less stable conformers.

The most stable conformer of 5-hydroxyhexahydropyrimidine, **1a**, was calculated to have an axial hydroxyl group and the configuration of the N−H bonds was axial−equatorial. The hydroxyl proton was directed toward the amine nitrogen in which the N−H bond was in the equatorial position, forming a single transannular hydrogen bond. The distance from the hydroxyl proton to the nitrogen atom was calculated to be 2.32 Å.

Comparison of the E_{rel} calculated for each conformer can give approximate energy contributions to conformer stability by the different interactions (Figure 1). From comparison of **1a** and conformer **1i**, in which the hydroxyl proton is synclinal to H5, it is apparent that the major contribution to the stability of **1a** is an intramolecular hydrogen bond. The single hydrogen bond provides an extra 3.74 kcal mol^{-1} in stability, although this number needs to be attenuated to account for any unfavorable interactions of the hydroxyl proton with H5 in **1i**. This hydrogen bond is therefore weak due to the less-than-optimal angle between the three atoms involved (113°). Conformer **1f** exhibits a symmetrical bifurcated intramolecular hydrogen bond with the hydroxyl proton calculated to be 2.53 Å from each endocyclic nitrogen atom, but no anomeric interactions (see below). This bifurcated hydrogen bond is also expected to be quite weak due to the distances and less than optimal angles (104°) involved. The stability of the all-axial conformer **1b** is unexpected. It may be due in part to a double anomeric interaction, which is also possible in **1c** and **1d**. Further stabilization of the axial OH group in **1b** could occur via a gauche effect and/or a bifurcated hydrogen bond between the two NH groups and the oxygen. This hydrogen bond would be expected to be weaker than the bifurcated hydrogen bond in **1f**, because the distances and angles involved are even less favorable (distances 2.74, 2.79 Å; angles 93°, 94°), and the N−H bonds are less polar than the O−H bond. The comparison of conformers **1e** and **1i** indicates that there is no gauche effect in operation in the gas phase; the equatorial OH group is calculated to be more stable by 1.85 kcal mol^{-1} (neglecting again any

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unfavorable interactions of the hydroxyl proton with H5 in **1i** and also neglecting any reverse hydrogen bond in **1i**).

We also investigated the simpler model compound 1,3-dioxan-5-ol (**4**), where no reverse hydrogen bonding (as in **1b** and **1i**) and no anomeric interactions are possible. Our calculations indicate that the conformer in which the hydroxyl group participates in a symmetrical bifurcated intramolecular hydrogen bond (**4a**) is more stable than the conformer with the hydroxyl group synclinal to H5 by 3.57 kcal mol^{-1}, confirming a fairly weak, bifurcated hydrogen bond; the calculated distances from the hydroxyl proton to the endocyclic oxygens were 2.62 Å in each case (the angles were both 101°). The conformer in which the hydroxyl group was in an equatorial position was again calculated to be more stable (by 1.94 kcal mol^{-1}) than the conformer with the hydroxyl group axial and not participating in a hydrogen bond. This likewise suggests that there is no gauche effect in the dioxanol in the gas phase. Indeed, the preference of the OH group for the equatorial position is more pronounced in the heterocyclic compounds; we calculated a difference of only 0.77 kcal mol^{-1} between and axial and an equatorial OH group in cyclohexanol. This can be attributed to the shorter C−N and C−O bonds, leading to more crowded rings. We calculated bond lengths of 1.53, 1.45, and 1.43 Å for equivalent C−C, C−N, and C−O bonds.

Orientation of the N−H Bonds. The situation is further complicated by the fact that nitrogen inversion can occur independently of ring inversion.[2a] Clearly, the orientation of the N−H bonds is important in determining the preferred conformer of **1**. The least favored conformers **1j** and **1k** exhibit neither a stabilizing hydrogen bond nor a significant anomeric interaction. The anomeric effect in hexahydropyrimidines has been investigated[12,16,17,18] and the configuration of the N−H bonds has been previously reported to be influenced by an anomeric effect.[19] The optimum geometry for a significant anomeric interaction occurs when the lone pair (n_N) is antiperiplanar to a C2−N bond and can interact with the antibonding C2−N orbital (σ^*_{C-N}). In the most stable conformer **1a** only one $n_N \rightarrow \sigma^*_{C-N}$ interaction is possible, whereas two such interactions are possible in **1b**.

^{15}N NMR spectroscopy has been used for investigating the stereochemistry of alicyclic amines; however, the conclusions that could be drawn from these results have not been clear-cut. While the ^{15}N chemical shifts of cyclic tertiary amines appeared to depend on the configuration at nitrogen, those on secondary cyclic amines did not.[20] Indeed, "N−H (hence lone-pair) conformation does not influence ^{15}N resonance positions in piperidines and conversely that ^{15}N chemical shift determinations are of little value in probing lone-pair orientations in these compounds."[21] In addition, the rapid disproportionation of hexahydropyrimidine **2** via a series of complicated equilibria[7,8] and the extremely low solubility of 5-hydroxyhexahydropyrimidine **1** in the less polar solvents required for the investigation of intramolecular hydrogen bonding made variable-temperature ^{15}N NMR spectroscopy studies impractical.

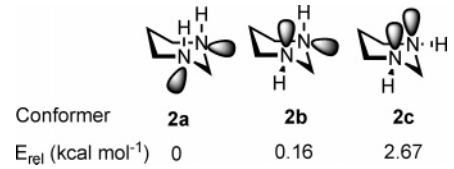

FIGURE 2. The relative energies (E_{rel}) calculated for conformers of **2** at the DFT level (B3LYP, 6-311+G**).

Although by no means a common technique, some early conformational studies used near-IR spectroscopy to determine the stereochemistry of alicyclic secondary amines.[22] When this methodology was applied to a dilute solution if **1** in $CHCl_3$, two weak, overlapping bands were observed in the N−H first overtone region (~6500 cm^{-1}). The more intense was the lower frequency band at 6488 cm^{-1}; the second band appeared as a shoulder on the first at 6540 cm^{-1}. The higher frequency band in nitrogen heterocycles has been assigned to the equatorial N−H configuration.[23] Therefore the higher frequency, less intense band in the near-IR spectrum of **1** may be assigned to the equatorial N−H bond. This suggests that a higher percentage of the conformer population of **1** (in dilute $CHCl_3$ solution) has N−H bonds occupying axial positions, as is also suggested by the stability of the conformers **1a**, **1b**, **1c**, and **1d** in vacuo.

The parent hexahydropyrimidine ring (**2**) was investigated by using molecular modeling to look more closely at the stability of different combinations of N−H bond orientations. In the most stable conformer **2a** the lone pairs of both nitrogen atoms are equatorial and form a planar W arrangement across the N1−C2−N2 bonds. In this conformation each nitrogen lone pair is in the optimum position for $n_N \rightarrow \sigma^*_{C-N}$ hyperconjugative interactions to take place, resulting in the possibility of a double anomeric interaction. The least stable conformer **2c** allows for no $n_N \rightarrow \sigma^*_{C-N}$ anomeric interactions. The anomeric effect is stabilizing and there is a significant difference (2.67 kcal mol^{-1}) between the energy of **2a** and **2c**. We calculated the preference for an NH bond in piperidine to be equatorial to amount to 0.66 kcal mol^{-1}. Assuming then that **2a** is destabilized by two axial NH bonds, and **2b** by one axial NH bond, this would lead to an estimate of 3.2 kcal mol^{-1} stabilizing effect of one anomeric interaction in **2b** or 4.0 kcal mol^{-1} in **2a** for two anomeric interactions.

Other theoretical studies of hexahydropyrimidine[16−19] also show little difference between the energies of the two most stable conformers in a1l the reported results, and the diequatorial **2c** was always much less stable (Figure 2). Natural Bond Orbital analysis[19] of hexahydropyrimidine showed that the dipole repulsions between the lone electron pairs are much smaller than repulsion between the N−H bonds. It was suggested that the similar energies of conformers **2a** and **2b** arise because these conformers are a compromise between "maximizing hyperconjugative stabilization and avoiding repulsions".[19]

If we assume that the stabilization by an anomeric interaction and destabilization by repulsion of two axial NH bonds is of the same magnitude in the 5-hydroxy compound (**1**) as in the parent (**2**), we can estimate the contributions of the two bifurcated hydrogen bonds to the stability of conformers **1b** and **1f**. Comparing **1h** and **1b**, we can estimate that the bifurcated inverse hydrogen bond contributes 1.5 kcal mol^{-1}. In terms of anomeric interactions alone, and using the calculated values for

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(23) Baldock, R. W.; Katritzky, A. R. *J. Chem. Soc.* (*B*) **1968**, 1470

2, **1b** should be more stable than **1f** by 2.67 kcal mol^{-1}. However, the difference is 0.99 kcal mol^{-1} only. This can be explained by the difference in stability of the two hydrogen bonds. The bifurcated hydrogen bond involving the OH proton is therefore estimated to contribute 3.2 kcal mol^{-1} to the stability of **1f**. By comparison, the bifurcated hydrogen bond in the dioxanol (**4**) was found to have a stabilizing effect of 3.6 kcal mol^{-1}, and the single hydrogen bond in **1a** had an effect of 3.7 kcal mol^{-1}.

Ring Inversion. The occurrence of either an intra- or intermolecular hydrogen bond, or stereoelectronic effects can significantly favor one conformation of a heterocycle and consequently, the ring would be expected to exist as largely one conformer. In our case, hydrogen bonding stabilizes an axial hydroxyl group in the alcohols **1** and **4** in nonpolar solvents. To calculate the free energy of the axial stabilization, it is necessary to take account of the inherent equatorial preference of the hydroxyl group. This can be accomplished by using the appropriate *A* value (steric conformational energy). The equation then becomes

$$\Delta G_{\mathrm{AX-OH}} = \Delta G_{\mathrm{HET-OH}} + A_{\mathrm{OH}}$$

where $\Delta G_{\mathrm{HET-OH}}$ is the free energy of activation for ring inversion in the hydroxylated heterocycle and A_{OH} is the *A* value of the hydroxyl group. The *A* value or conformational energy for the hydroxyl group is solvent dependent but is generally less than 1 kcal mol^{-1}.[24] A_{OH} values show that an equatorial position is favored for this substituent in aprotic solvents. The method used in this case does not include a correction for the difference in steric requirements of the hydroxyl group in the heterocycle and cyclohexane, which results from the shorter C−N bonds (relative to C−C bonds). Our calculations showed that for relative conformational energies, the preference for an equatorial OH group in cyclohexanol is indeed below 1 kcal mol^{-1} in vacuo but this value is substantially higher for the heterocycles **1** and **4** (see the Supporting Information).

In theory, it is also possible to determine the axial stabilization energy by comparing the free energy of activation for ring inversion of the hydroxylated ring ($\Delta G^{\ddagger}_{\mathrm{HET-OH}}$) with the free energy of activation for ring inversion of the unsubstituted parent heterocycle ($\Delta G^{\ddagger}_{\mathrm{HET}}$). The difference in energies required for ring inversion should be equivalent to the energy gained through stabilizing interactions of the hydroxyl substituent, including a correction for the conformational energy of the substituent. Accordingly, attempts were made to determine the free energy of ring inversion of the parent rings **2** and **3** by VT NMR spectroscopy and to compare the values to those of the alcohols **1** and **4**. The coupling constant values measured from the rt 1D ^{1}H NMR spectra were used to construct simulated spectra for the analysis of the variable-temperature experiments. The simulated spectra were identical to those obtained by experiment.

The 300 MHz ^{1}H NMR spectrum of hexahydropyrimidine **2** in $CDCl_3$ at room temperature showed only inversion-averaged signals for the axial and equatorial protons. Coalescence for **2** occurred at 236 ± 5 K. This corresponds to a free energy of activation for ring inversion, $\Delta G^{\ddagger}_{298}$, of 12.2 kcal mol^{-1}. Complete line shape analysis of the signals arising from the C2 protons of **2** permitted further evaluation of thermodynamic parameters. The $\Delta H^{\ddagger}_{298}$ was found to be 12.4 kcal mol^{-1} and the $\Delta S^{\ddagger}_{298}$ was 6.2 cal K^{-1} mol^{-1}. The $\Delta H^{\ddagger}_{298}$ value compares favorably to published values for hexahydropyrimidines (∼11 kcal mol^{-1}).[2a,25]

Coalescence for 1,3-dioxane **3** occurred at 213 ± 5 K at 400 MHz. This corresponds to a $\Delta G^{\ddagger}_{213}$ of 10.0 kcal mol^{-1}. This value compares favorably to the published value (∼9.0−9.9 kcal mol^{-1}).[26] Complete line shape analysis of the signals arising from the C2 protons yielded values for $\Delta H^{\ddagger}_{213}$ of 11.3 kcal mol^{-1} and for $\Delta S^{\ddagger}_{213}$ of 7.0 cal K^{-1} mol^{-1}. Investigation of the ^{1}H NMR spectra of 5-hydroxyhexahydropyrimidine **1** in nonpolar solvents was not possible due to the insolubility of **1** in these solvents at temperatures below 298 K. While it was recognized that coalescence and complete line shape analysis was probably achievable in polar solvents, this was not explored because it would not give information pertinent to quantifying the strength of intramolecular hydrogen bonding in this system. It was possible to acquire low-temperature ^{1}H NMR spectra (400 MHz) of the alcohol **4** in CD_2Cl_2. At 233 K the well-resolved signals for the ring protons had flattened into a series of broad unresolved peaks and at 183 K two sets of signals which resemble a mixture of a minor and major conformer become apparent; however, both sets of signals were unresolved and unable to be characterized in any detail.

At room temperature, the ^{1}H NMR spectra of 1,3-dioxan-5-ol and 5-hydroxyhexahydropyrimidine in $CDCl_3$ show only one conformer. In an attempt to observe possible changes in the spectra at higher temperatures, the solvent was changed to the higher boiling $CDBr_3$ because it best matched the polarity and solvating properties of $CDCl_3$. The sample signals in the room temperature ^{1}H NMR spectra in $CDBr_3$ of both alcohols were identical with those in $CDCl_3$.

High-temperature ^{1}H NMR spectra (300 MHz) of 1,3-dioxan-5-ol were obtained to 368 K, with spectra measured at 10 deg intervals. Increasing the temperature of the 1,3-dioxan-5-ol sample had no effect until, at 258 K, the coupling constant for the hydroxyl proton doublet broadened slightly and the $^3J_{\mathrm{HCOH}}$ coupling constant decreased to 9.3 Hz. At 368 K, the H−C−O−H coupling constant decreased to 8.8 Hz and concomitant changes were apparent in the signal of the methine proton, which had the appearance of a broadened singlet. The changes observed in the signal shape of the methine and hydroxyl protons and the diminished $^3J_{\mathrm{HCOH}}$ coupling constant were most likely due to a change in the rotamer population of the hydroxyl group. The rotamer population would vary as the intramolecular hydrogen bond was disrupted with increasing temperature. There was no change observed in the other dioxane ring protons.

High-temperature ^{1}H NMR spectra (300 MHz) of 5-hydroxyhexahydropyrimidine were obtained to 371 K. Increasing the temperature of the sample produced major changes to the signals from the C2 protons but little change was observed in the rest of the signals. As the temperature was raised, the doublets of the AB quartet from the C2 protons began to move toward each other. At 343 K, the inner, more intense peaks began to overlap until at 355 K the inner peaks were almost coincident. When the sample temperature reached 363 K the inner peaks displayed a singlet-like appearance, while the outer peaks had all but disappeared. The peaks did not broaden in any way and coupling

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(25) Riddell, F. G. *The Conformational Analysis of Heterocyclic Compounds*; Academic Press:, London, 1982; Chapter 5.

(26) Binsch, G.; Eliel, E. L.; Mager, S. *J. Org. Chem.* **1973**, *38*, 4079 and references cited therein.

was still observed. The signals for the axial and the equatorial proton were moving toward each other until the inner signals overlapped at 363 K. The increased intensity of the inner peaks and the highly diminished intensity of the outer peaks may be explained by this movement of the doublets toward each other.

Conclusions

We have demonstrated by ^{1}H NMR and IR spectroscopy that the hydroxyl group in 5-hydroxyhexahydropyrimidine (**1**) is stabilized in an axial orientation by hydrogen bonding and that the N−H bonds are also stabilized in an axial orientation, presumably by anomeric interactions. For 1,3-dioxan-5-ol (**4**) the stabilization of the axial OH group by hydrogen bonding is even more pronounced. We also attempted to determine the extent to which intramolecular hydrogen bonding stabilizes the dominant conformer and inhibits ring inversion; however, that was not possible in these systems due to solubility problems in suitable solvents.

To gain further insights into the steric and electronic effects governing the stability of conformers of 5-hydroxyhexahydropyrimidine (**1**), we have undertaken molecular modeling calculations on **1** and on simpler model systems (**4**, **2**, cyclohexanol, and piperidine). The results from these calculations which were performed in vacuo at two different levels of theory (ab initio and DFT methods) agreed very well with the experimental findings in solution ($CDCl_3$ for NMR spectroscopy and $CHCl_3$ for IR spectroscopy).

No gauche effect can be observed in either **1** or **4** in $CDCl_3$ or in our modeling in vacuo; rather the opposite effect is seen. Due to steric crowding of the heterocycles, an equatorial position of the hydroxyl group is preferred even more strongly than in cyclohexanol (1.9 kcal mol^{-1} for **4**, 1.9 kcal mol^{-1} for **1**, and 0.8 kcal mol^{-1} for cyclohexanol). This tendency is more than counterbalanced by intramolecular hydrogen bonding, which is only possible when the OH group is axial. This situation is dependent upon the solvent. It has recently been demonstrated, for example, that intramolecular hydrogen bonding in ethylene glycol[27] is unlikely to be important in determining conformational preferences, except possibly in fairly nonpolar solvents, and that the gauche effect is very important for ethylene glycol, particularly in polar solvents such as water.

In **4**, a bifurcated hydrogen bond has been calculated to contribute 3.6 kcal mol^{-1} to the stability of the lowest energy conformer. For **1** three different hydrogen bonds are possible, depending on the orientation of the N−H bonds. A single OH to N hydrogen bond leads to a stabilization of 3.7 kcal mol^{-1}, a bifurcated reverse hydrogen bond involving the oxygen and two axial N−H atoms contributes 1.5 kcal mol^{-1}, and a bifurcated hydrogen bond involving the OH hydrogen adds 3.2 kcal mol^{-1}.

The orientation of the N−H bonds appears to be governed by anomeric interactions which are maximal for axial N−H bonds. Two axial N−H bonds are, however, destabilized by dipole repulsions. We have been able to estimate that stabilization by one anomeric effect amounts to 3.2 kcal mol^{-1} and that the further stabilizing effect by a second anomeric interaction is slightly more (about 0.2 kcal mol^{-1}) than the dipole repulsion between two axial N−H atoms.

(27) Petterson, K. A.; Stein, R. S.; Drake, M. D.; Roberts, J. D. *Magn. Reson. Chem.* **2005**, *43*, 225.

Experimental Section

Synthesis: 5-Hydroxyhexahydropyrimidine (1). Formalin (39%, 0.88 mL, 11.1 mmol) was added dropwise to a stirred solution of 1,3-diamino-2-propanol (1.0 g, 11.1 mmol) in water (2 mL). The reaction mixture was stirred for 24 h at room temperature and then lyophilized. The crude residue was purified by vacuum sublimation, which yielded a highly hygroscopic white solid at 70 °C/55 Torr (0.6 g, 53%); mp 101−103 °C (lit.[5] mp 99−102 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.78 (br s, 3H, OH and NH), 2.87 (dd, $J_{4e,5}$ = 3.1 Hz, $J_{4e,2e}$ < 1 Hz, 2H, H4e and H6e), 3.07 (dd, $J_{4a,4e}$ = 12.8 Hz, $J_{4a,5}$ = 2.9 Hz, 2H, H4a and H6a), 3.57 (m, 1H, H5), 3.70 (d, $J_{2a,2e}$ = 12.5 Hz, 1H, H 2a), 3.75 (d, 1H, H2e). ^{1}H NMR (D_2O, 300 MHz) δ 1.94 (dd, $J_{4a,5}$ = 7.8 Hz, 2H, H4a and H6a), 2.41 (dd, $J_{4a,4e}$ = 12.9 Hz, $J_{4e,5}$ = 3.8 Hz, 2H, H4e and H6e), 2.76 (d, $J_{2a,2e}$ = 12.5 Hz, 1H, H2a), 2.90 (m, 1H, H5), 3.00 (d, 1H, H2e). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 3.31 (dd, $J_{4a,4e}$ = 12.9 Hz, $J_{4a,5}$ = 7.9 Hz, 2H, H4a and H6a), 2.93 (dd, $J_{4e,5}$ = 3.1 Hz, 2H, H4e and H6e), 3.19 (m, 1H, H5), 3.25 (d, $J_{2a,2e}$ = 12.6 Hz, 1H, H2a), 3.50 (d, 1H, H2e), 5.07 (very broad flat singlet, 3H, NH and OH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 48.9 (C4, C6), 58.8 (C2), 63.2 (C5). Low-resolution EI MS 102 ([M]$^+$), 101 ([M − H]$^+$). The quoted ^{1}H and ^{13}C NMR shifts are in agreement with published values.[5]

Hexahydropyrimidine (2).[6] Formalin (39%, 45.8 mL, 0.3 mol) was added dropwise to an ice-cooled, stirred solution of 1,3-diaminopropane (40 g, 0.27 mol) in water (40 mL) and the mixture was then stirred for 2 h at room temperature. The mixture was cooled in an ice bath and NaOH pellets were added. The layers that formed were separated and the upper layer of crude hexahydropyrimidine was dried over NaOH pellets and vacuum distilled. The fraction with bp 37−53 °C/55 Torr (lit.[6] bp 58−60 °C/20 mmHg) contained approximately 90% hexahydropyrimidine and 10% 1,3-diaminopropane (14 g in total). An ice-cooled aliquot of this fraction (6 g total, containing 5.6 mmol of 1,3-diaminopropane) was stirred over K_2CO_3 and then *o*-hydroxybenzaldehyde (1.51 g, 12.4 mmol) was added dropwise to the suspension. The resulting bright yellow mixture was stirred on ice for 30 min with the addition of extra K_2CO_3 desiccant as the reaction progressed. The crude reaction mixture was decanted from the K_2CO_3 and placed under vacuum (55 Torr) and a liquid nitrogen cooled trap was attached to collect the product, which was a colorless fuming liquid (2.4 g, 51% based on the mass of hexahydropyrimidine in 6 g of mixture). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52 (m, 2H, H5), 1.72 (br s, 2H, NH), 2.98 (t, $J_{5,4}$ = 5.5 Hz, 4H, H4 and H6), 3.80 (s, 2H, H2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.9 (C5), 45.8 (C4, C6), 63.0 (C2).

1,3-Dioxane (3). This compound was obtained commercially and dried over NaOH pellets before use. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.77 (m, 2H, H5), 3.91 (t, $J_{5,4}$ = 5.4 Hz, 4H, H4 and H6), 4.86 (s, 2H, H2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.6 (C5), 66.9 (C4, C6), 94.2 (C2).

1,3-Dioxan-5-ol (4). 1,3-Dioxan-5-ol benzoate (**6**) was isolated as colorless, needlelike crystals (26.7 g, 10%), mp 75.5−76.5 °C (lit.[9] mp 72 °C), using the method of Hibbert.[9] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.06 (dd, $J_{4e,5}$ = 3.9 Hz, 2H, H4e and H6e), 4.12 (dd, $J_{4a,4e}$ = 12.0 Hz, $J_{4a,5}$ = 3.0 Hz, 2H, H4a and H6a), 4.87 (d, $J_{2a,2e}$ = 6.3 Hz, 1H, H2a), 4.98 (d, 1H, H2e), 4.97 (m, 1H, H5), 7.46−7.50 (m, 2H, H4′ and H6′), 7.54−7.62 (m, 1H, H5′), 8.08−8.14 (m, 2H, H3′ and H7′). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 66.1 (C5), 68.6 (C4, C6), 93.7 (C2), 128.4(C4′ and C6′), 129.6 (C2′), 129.8 (C3′ and C7′), 133.3 (C5′), 166.2 (C1′). Low-resolution EI MS 207 ([M − H]$^+$).

1,3-Dioxan-5-ol was isolated as a colorless liquid (0.48 g, 48%), bp 50 °C/55 Torr (lit.[10] bp 80−85 °C/11 mmHg), using the method of Barker.[10] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.96 (d, $J_{OH,H5}$ = 9.9 Hz, 1H, OH), 3.62 (m, 1H, H5), 3.87 (ddd, $J_{4e,5}$ = 3.2 Hz, $J_{2e,4e}$ = 0.5 Hz, 2H, H4e and H6e), 3.92 (dd, $J_{4a,4e}$ = 11.1 Hz, $J_{4a,5}$ = 2.2 Hz, 2H, H4a and H6a), 4.76 (d, $J_{2a,2e}$ = 6.2 Hz, 1H, H2a), 4.93 (dd, 1H, H2e). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 3.31 (dd,

$J_{4a,4e}$ = 11.3 Hz, $J_{4a,5}$ = 7.6 Hz, 2H, H4a and H6a), 3.50 (m, 1H, H5), 3.92 (dd, $J_{4e,5}$ = 4.3 Hz, 2H, H4e and H6e), 4.50 (d, $J_{2a,2e}$ = 5.9 Hz, 1H, H2a), 4.78 (d, 1H, H2e), 5.07 (d, $J_{OH,5}$ = 4.7 Hz, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 64.1 (C5), 71.7 (C4, C6), 94.0 (C2).

Molecular Modeling of Conformers. Molecular modeling was executed on a Silicon Graphics Fuel workstation with use of the SPARTAN '02 software[28] by Wavefunction, Inc. All possible chair conformations were built for each compound and their geometries optimized in vacuo at ab initio level with use of HF theory and the 6-31G* basis set. The orientation of the hydroxyl proton was investigated by rotation around the C−OH bond, usually by 180°, after minimization. The rotated structures were re-minimized. If the hydroxyl protons involved a hydrogen bond they reverted to the initial structure. If the hydroxyl group was equatorial different minima were observed (**1e** vs **1g**; **1c** vs **1d**; **1j** vs **1k**). The resulting structures from the ab initio (HF/6-31G*) level calculations were re-optimized at the DFT level with the hybrid B3LYP functional and the 6-311+G** basis set.

Near-IR Spectra. The near-IR spectrum (2000−7000 cm^{-1}) of **1** (2.3 mg mL^{-1}) was measured in dry $CHCl_3$ with CaF_2 cells.

Variable-Temperature ^{1}H NMR Spectra Acquisition: High-Temperature VT ^{1}H NMR Spectroscopy. High-temperature ^{1}H NMR spectra of compounds **1** and **4** were recorded on a 300 MHz spectrometer at 10 deg intervals between 298 and 388 K in $CDBr_3$, using a sample concentration of approximately 0.5 mg mL^{-1}. The $CDBr_3$ (copper stabilized) was passed through a small plug of basic alumina before being used in sample preparation.

(28) *SPARTAN '02*; Wavefunction Inc.: 18401 Von Karman Ave., Suite 370, Irvine, CA 92715, copyright 1991−2001.

(29) *gNMR* V3.6 for the Macintosh; IvorySoft Scientific Software, distributed by Cherwell Scientific Publishing: Oxford, UK, copyright 1995.

Low-Temperature ^{1}H NMR Spectroscopy. Low-temperature ^{1}H NMR spectra of compounds **2** and **3** were recorded on a 400 MHz spectrometer. Spectra were acquired at approximately 10 deg intervals between 298 and 218 K ($CDCl_3$) for compound **2** and between 298 and 183 K (CD_2Cl_2) for compound **3**. The temperature dependence of the rate constants for compounds **2** and **3** was evaluated by using line shape analysis of the signals arising from the protons on C2. Computer simulation was conducted with the gNMR[29] program.

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Supporting Information Available: General synthesis/experimental conditions, details of the synthesis of **4**, a tabulated summary of coupling constants for compounds **1** and **4** in various solvents, ^{1}H, ^{13}C, selected 2D (gCOSY, gHSQC, and gHMBC), and DEPT spectra of **1**, **2**, **3**, **4**, and 1,3-dioxan-5-ol benzoate, details of the acquisition and analysis of VT ^{1}H NMR spectra for compounds **1**−**4**, the computed total energies (ab initio and DFT methods) and calculated E_{rel} for the conformers of **1**, **2**, **4**, cyclohexanol, and piperidine and the *xyz* coordinates for modeled conformers (ab initio and DFT). This material is available free of charge via the Internet at http://pubs.acs.org.

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