The Origin of the Anomeric Effect: Conformational Analysis of 2-Methoxy-1,3-dimethylhexahydropyrimidine

Charles L. Perrin,* Kathleen B. Armstrong, and Miles A. Fabian

Contribution from the Department of Chemistry, University of California—San Diego, La Jolla, California 92093-0506

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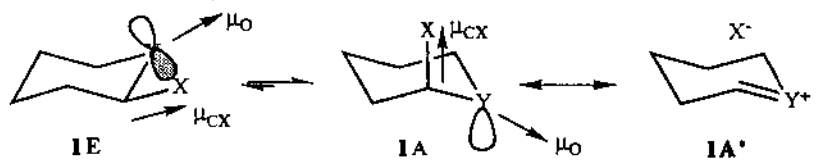
Abstract: The anomeric effect is thought to be the result of either molecular orbital interactions, which stabilize the axial conformer, or electrostatic interactions, which destabilize the equatorial. To test which of these is more important, it is proposed to determine the change in the anomeric effect on replacing the oxygen of an anomeric molecule by nitrogen. Nitrogen is less electronegative than oxygen, leading to weaker electrostatic interactions and stronger molecular orbital interactions, so the two interactions act in opposite directions. Accordingly, the conformational equilibrium of 2-methoxy-1,3-dimethylhexahydropyrimidine (**3**) was measured by ^1H and ^{13}C NMR. The proportion of axial conformer is almost the same as in 2-methoxy-1,3-dioxane. Corrections for steric effects, supported by AM1 and MMX calculations, indicate that the anomeric effect is weaker in the nitrogen analog, suggesting that electrostatic interactions predominate. We therefore conclude that in nonpolar solvents n–σ^* interactions are not primarily responsible for the anomeric effect. Moreover, it is shown that the bond length changes that have long been considered as strong evidence for n–σ^* interactions can be accounted for on the basis of dipole–dipole interactions.

Introduction

Anomeric Effect and Its Origin. The anomeric effect is the preference for axial conformer **1A** exhibited by six-membered heterocycles substituted at C2 with an electronegative group X. This preference must be corrected for the steric effects that favor the equatorial conformer **1E**. The quantitative relation is given in eq 1, where E_{An} is the preference (energy > 0) for the axial

$$E_{An} = \Delta G_{1A \rightarrow 1E} + A_X \qquad (1)$$

position due to the anomeric effect, $\Delta G_{1A \rightarrow 1E}$ is the observed free energy change, $-RT \ln([\mathbf{1E}]/[\mathbf{1A}])_{obs}$, and A_X is $RT \ln([\mathbf{E}]/[\mathbf{A}])_{model}$, the steric preference for equatorial X as measured in a model compound such as a cyclohexane. The effect is quite general and has been studied in a wide range of systems containing the Y–C–X fragment, including acyclic ones. Several extensive reviews on the anomeric effect and related phenomena have been published in recent years.[1] Values of E_{An} in O–C–O systems are 5-10 kJ mol^{-1}, which is small but significant. Two explanations have been proposed for the anomeric effect, electrostatic interactions and molecular orbital interactions.



The electrostatic theory[2] invokes the destabilizing interaction between the dipole moment of the C–X bond of **1** and the dipole moment that is the resultant of individual dipole moments from C–Y bonds and the lone pairs of Y. (This differs from the mutual repulsion due to overlap of lone pairs on X and Y, which is discredited[1a,3] as the origin of the anomeric effect.) Such a dipolar interaction is minimized when X is axial, and so conformer **1A** is preferred over conformer **1E**.

The molecular orbital explanation[4] for the anomeric effect considers the n–σ^* overlap between a filled nonbonding n electron pair on Y and the vacant σ^* orbital of the C–X bond. (For Y = O the high-energy lone pair is properly[1a] the 2p orbital, rather than a hybridized lone pair antiperiplanar to the C–X bond, although it is sometimes convenient to focus on the latter.) This is a stabilizing interaction that is more effective when X is axial, and so conformer **1A** is favored. In valence bond terms this corresponds to a hyperconjugative contribution of the double bond/no bond resonance form **1A′**. The stabilization is much weaker in conformer **1E**, where the high-energy p atomic orbital on Y is orthogonal to the C–X bond.

To distinguish the relative importance of each interaction has not been easy. It is likely that any Y–C–X system that exhibits the anomeric effect involves both kinds of interaction. There is no doubt that dipole–dipole repulsions and n–σ^* delocalization are operative, but our question is whether either is sufficient to account for the observations. We next consider the evidence for each of them.

Molecular Orbital Interactions. The best evidence is crystallographic data showing that species with Y–C–X fragments as in **1A** have shorter C1–Y bonds and longer C1–X bonds than do the corresponding **1E**.[4b,5] These are exactly the structural changes expected from n–σ^* delocalization or involvement of **1A′**. Moreover, it is claimed[1a,d,f] that they cannot be rationalized by the electrostatic explanation.

One intriguing result that supports the molecular orbital interpretation is the barrier to ring inversion in 2,2-dimethoxyoxane,[6] which is 7.6 kJ mol^{-1} lower than the average for cyclohexane, oxane, and 1,1-dimethoxycyclohexane. A similar reduction is seen in 2-methoxyoxane.[7] If the anomeric effect

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(1) (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983. (b) Sinnott, M. L. *Adv. Phys. Org. Chem.* **1988**, *24*, 113. (c) Szarek, W. A.; Horton, D., Eds. *The Anomeric Effect: Origin and Consequences*; ACS Symp. Ser. No. 87; American Chemical Society: Washington, DC, 1979. (d) Tvaroška, I.; Bleha, T. *Adv. Carbohydr. Chem.* **1989**, *47*, 45. (e) Box, V. G. S. *Heterocycles* **1990**, *31*, 1157. (f) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019.

(2) Edward, J. T. *Chem. Ind.* **1955**, 1102.

(3) Wolfe, S.; Rauk, A.; Tel, L. M.; Csizmadia, I. G. *J. Chem. Soc. B* **1971**, 136.

(4) (a) Lucken, E. A. C. *J. Chem. Soc.* **1959**, 2954. (b) Romers, C.; Altona, C.; Buys, H. R.; Havinga E. *Top. Stereochem.* **1969**, *4*, 39.

(5) (a) Luger, P.; Kothe, G.; Paulsen, H. *Chem. Ber.* **1976**, *109*, 1850. Kothe, G.; Luger, P.; Paulsen, H. *Acta Crystallogr.* **1979**, *B35*, 2079. (b) Jeffrey, G. A.; Pople, J. A.; Binkley, J. S.; Vishveshwara, S. *J. Am. Chem. Soc.* **1978**, *100*, 373. (c) Fuchs, B.; Schleifer, L.; Tartakovsky, E. *Nouv. J. Chem.* **1984**, *8*, 275. (d) Cossé-Barbi, A.; Dubois, J.-E. *J. Am. Chem. Soc.* **1987**, *109*, 1503. Cossé-Barbi, A.; Watson, D. G.; Dubois, J. E. *Tetrahedron Lett.* **1989**, *30*, 163. (e) Briggs, A. J.; Glenn, R.; Jones, P. G.; Kirby, A. J.; Ramaswamy, P. *J. Am. Chem. Soc.* **1984**, *106*, 6200.

(6) Perrin, C. L.; Nuñez, O. *J. Chem. Soc., Chem. Commun.* **1984**, 333.

(7) Ouedraogo, A.; Lessard, J. *Can. J. Chem.* **1991**, *69*, 474.

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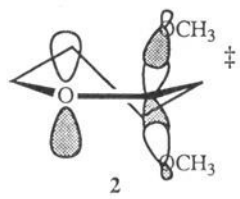
were due to dipole–dipole repulsions, it is readily shown[6] that they would be greater in the transition state **2** for ring inversion



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and the barrier would be higher. Since it is not, it was concluded that the anomeric effect is not due to electrostatic interactions. However, even if the anomeric effect is due to n–σ^* overlap in this transition state, where the 2p lone pair on the ring oxygen is aligned maximally with the π combination of C–OCH_3 σ^* orbitals, this need not be so for stable molecules, where the overlap is weaker. Similarly, the axial preference of glucopyranosylammonium ions[8] may be a special case of strong n–σ^* interactions, owing to the electronegativity of a cationic nitrogen.

Various calculations have provided support for the molecular orbital explanation. Electrostatic energies are found to be too small to account for conformational preferences in some systems.[4b] *Ab initio* and semiempirical calculations can reproduce the observed conformational energies of a number of systems and also the changes in bond lengths associated with the anomeric effect.[3,4b,9] According to Fourier analysis, which separates the potential energy for bond rotation into terms representing electrostatic (V_1), orbital-overlap (V_2), and intrinsic/steric (V_3) interactions, V_1 is less than V_2 in some cases but not all.[10]

Electrostatic Interactions. The importance of electrostatic interactions is demonstrated by the general observation that the conformer with the larger molecular dipole moment is the less stable one.[1f] Consequently the anomeric effect decreases as the solvent polarity increases.[11] If charge-separated resonance form **1A′** were responsible for the anomeric effect, it ought to become more important in more polar solvents. Although the solvent dependence is reproduced by molecular orbital calculations,[12] these necessarily include electrostatic interactions. Moreover, some electrostatic treatments have calculated conformational energies that do agree well with experimental values.[13] The preference of acids and esters for the syn (*Z*) conformation is certainly due to dipole–dipole interactions,[14] rather than to a "secondary stereoelectronic control",[15] or delocalization of the "buried" σ lone pair on the ester oxygen into $\sigma_{C=O}^*$. Moreover, electrostatic interactions are increasingly being recognized as responsible for influencing stability, regioselectivity, and stereoselectivity.[16]

There is some evidence that molecular orbital interactions cannot account for anomeric effects. Calculated and experimental electron densities in CH_3OCH_2F, $CH_2(OH)_2$, and *trans*-2,5-dichloro-1,4-dioxane are not simply attributable to n–σ^* overlap.[17] Nevertheless, the current practice is to invoke molecular orbital theory rather than electrostatics to account for anomeric effects.

Proposal. The anomeric effect is a key determinant of molecular structure, and it is important to understand its origin. To distinguish which of the two interactions is primarily responsible for the anomeric effect, a comparison system is needed in which one of them is definitely stronger and the other definitely weaker. For example, 2-substituted thianes ought to have stronger molecular orbital interactions than the analogous oxanes but weaker electrostatic interactions. However, poor S–C overlap and unique steric interactions complicate interpretation of thiane equilibria as a measure of the relative importance of these interactions.[18]

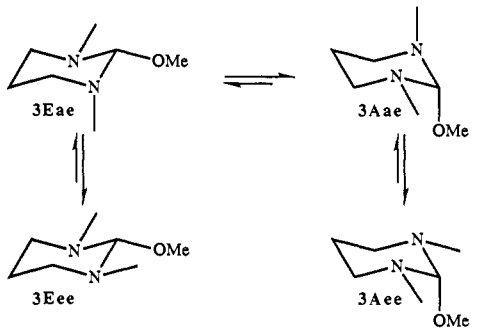
The relative importance of the two interactions may better be discerned through comparison of an N–C–O system with an analogous O–C–O system. Since the dipole moment of CH_3NH_2 is 1.28 D, smaller than the 1.69 D of CH_3OH,[19] dipole–dipole repulsions should decrease on substituting N for O. Since the ionization potential of CH_3NH_2 is 8.97 eV, substantially lower than the 10.85 eV of CH_3OH,[20] substitution of N for O should raise the energy of the filled n orbital and strengthen n–σ^* interactions. Alternatively, resonance form **1A′** contributes more for Y = N than for Y = O. Indeed, calculations on H_2NCH_2F and on $(CH_3)_2NCH_2OCH_3$ predict a 32.7 or 20.3 kJ mol^{-1} preference for the conformer with the nitrogen lone pair antiperiplanar to the C–F or C–O bond[21] (although the former has been attributed[22] to electrostatic repulsion between C–F and N–lone pair dipoles), and the experimentally determined barrier to combined rotation and inversion in $RCH_2N(CH_3)$–CH_2F (R = CH_3 or Ph) is 42 kJ mol^{-1}.[23] These are much higher than in oxygen analogs, suggesting strong n–σ^* interaction. Thus if electrostatic interactions are more important, substitution of N for O would reduce the anomeric effect, whereas if n–σ^* interaction is more important, substitution of N for O would strengthen the anomeric effect.

Experimental data on N–C–O systems are extremely sparse,[24] owing to their high reactivity. There is no question that an N–C–O anomeric effect exists, since molecular mechanics calculations based on 4-21G molecular orbital calculations show conformational preferences for the nitrogen lone pair to be antiperiplanar to the C–O bond.[25] However, there are only two experimental values that bear on the origin of the preference. The axial conformer of aqueous 5-amino-5-deoxy-D-glucopyranose (nojirimycin)[26] is stabilized by 2.9 kJ mol^{-1} relative to glucopyranose. The increased anomeric effect is consistent with n–σ^* interactions as origin, but some of the difference is due to the greater steric repulsions in a pyranose, which disfavor the axial conformer. Indeed, the conformer of 4,8,9,10-tetramethyl-1,5-dioxa-4,8-diazadecalin with both oxygens axial is favored over the one with

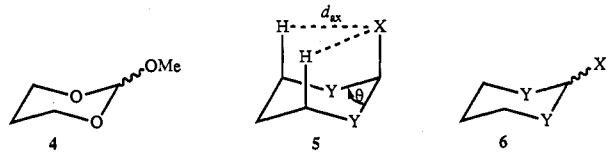
(8) Perrin, C. L.; Armstrong, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 6825.
(9) Jeffrey, G. A.; Pople, J. A.; Radom, L. *Carbohydr. Res.* **1972**, *25*, 117. David, S.; Eisenstein, O.; Hehre, W. J.; Salem, L.; Hoffmann, R. *J. Am. Chem. Soc.* **1973**, *95*, 3806. Zhdanov, Yu. A.; Minyaev, R. M.; Minkin, V. I. *J. Mol. Struct.* **1973**, *16*, 357. Wolfe, S.; Whangbo, M.-H.; Mitchell, D. J. *Carbohydr. Res.* **1979**, *69*, 1.
(10) Radom, L.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 2371. Zefirov, N. S. *Tetrahedron* **1977**, *33*, 3193. Jeffrey, G. A.; Yates, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 820. Ewig, C. S.; Van Wazer, J. R. *J. Am. Chem. Soc.* **1986**, *108*, 4774.
(11) Eliel, E. L.; Giza, C. A. *J. Org. Chem.* **1968**, *33*, 3754. Praly, J.-P.; Lemieux, R. U. *Can. J. Chem.* **1987**, *65*, 213.
(12) Tvaroška, I.; Bleha, T. *Collect. Czech. Chem. Commun.* **1980**, *45*, 1883. Montagnani, R.; Tomasi, J. *Int. J. Quantum Chem.* **1991**, *39*, 851. Kysel, O.; Mach, P. *J. Mol. Struct. (THEOCHEM 73)* **1991**, *227*, 285. Cramer, C. J. *J. Org. Chem.* **1992**, *57*, 7034. Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1993**, *115*, 5745.
(13) Anderson, C. B.; Sepp, D. T. *Tetrahedron* **1967**, *24*, 1707. Tvaroška, I.; Kožár, T. *J. Am. Chem. Soc.* **1980**, *102*, 6929.
(14) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935.
(15) Deslongchamps, P.; Beaulieu, N.; Chênevert, R.; Dickinson, R. A. *Can. J. Chem.* **1980**, *58*, 1051.
(16) Houk, K. N.; Eksterowicz, J. E.; Wu, Y.-D.; Fuglesang, C. D.; Mitchell, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 4170. Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638. Clennan, E. L.; Koola, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 3802. Ganguly, B.; Chandrasekhar, J.; Khan, F. A.; Mehta, G. *J. Org. Chem.* **1993**, *58*, 1734.
(17) Pichon-Pesme, V.; Hansen, N. K. *J. Mol. Struct. (THEOCHEM 52)* **1989**, *183*, 151. Koritsánszky, T.; Strumpel, M. K.; Buschmann, J.; Luger, P.; Hansen, N. K.; Pichon-Pesme, V. *J. Am. Chem. Soc.* **1991**, *113*, 9148.
(18) Zefirov, N. S.; Blagoveshchenskii, V. S.; Kazimirchik, I. V.; Yakovleva, O. P. *J. Org. Chem. USSR (Engl. Transl.)* **1971**, *7*, 599. Mikolajczyk, M.; Graczyk, P.; Kabachnik, M. I.; Baranov, A. P. *J. Org. Chem.* **1989**, *54*, 2859.
(19) Morino, Y. In *Constants of Organic Compounds*; Kotake, M.; Eds.; Asakura: Tokyo, 1963; pp 500 and 504.
(20) Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley-Interscience: New York, 1972; p 238.
(21) Irwin, J. J.; Ha, T.-K.; Dunitz, J. D. *Helv. Chim. Acta* **1990**, *73*, 1805. Carballeira, L.; Fernández, B.; Mosquera, R. A.; Ríos, M. A. *J. Mol. Struct. (THEOCHEM 64)* **1990**, *205*, 235.
(22) Wiberg, K. B.; Rablen, P. R. *J. Am. Chem. Soc.* **1993**, *115*, 614.
(23) Rahman, M. M.; Lemal, D. M.; Dailey, W. P. *J. Am. Chem. Soc.* **1988**, *110*, 1964.
(24) Senderowitz, H.; Aped, P.; Fuchs, B. *Helv. Chim. Acta* **1990**, *73*, 2113.
(25) Fernández, B.; Ríos, M. A.; Carballeira, L. *J. Comput. Chem.* **1991**, *12*, 78.
(26) Pinto, M. B.; Wolfe, S. *Tetrahedron Lett.* **1982**, *23*, 3687.

both oxygens equatorial by only 3.8 kJ mol^{-1},[27] and part of this is due to the fact that an ether group is less bulky than a tertiary amine. Here the anomeric effect must be <1.9 kJ mol^{-1} per N–C–O, and so small an anomeric effect is consistent with an electrostatic origin.

Therefore we have prepared 2-methoxy-1,3-dimethylhexahydropyrimidine (**3**) and determined its conformational equilibrium. The *N*-methyls are essential to prevent elimination to an amidine. There are several conformers (**3Eee, 3Eae, 3Aae, 3Aee**) permitting equilibration of axial and equatorial methoxy groups by successive



ring inversions and nitrogen inversions. The comparison is the conformational equilibrium of 2-methoxy-1,3-dioxane (**4**), studied by Nader and Eliel.[28] The n–σ^* interactions are stronger in **3** than in **4**, whereas dipole–dipole interactions are weaker. Therefore a larger proportion of axial conformer for **3** than for **4** would suggest that orbital interactions are the primary origin



of the anomeric effect, whereas a smaller proportion would suggest that electrostatic interactions are dominant. Through comparison of the conformational equilibria for **3** and **4** we have determined which of these alternative explanations is more compelling.

Experimental Section

Synthesis. A patented method[29] was adapted for the preparation of 2-methoxy-1,3-dimethylhexahydropyrimidine (**3**). *N,N'*-Dimethyl-1,3-propanediamine (2.04 g, 20 mmol, Aldrich) was combined with α,α-dimethoxytrimethylamine (2.62 g, 22 mmol, Lancaster) in 30 mL of dry benzene containing 20 mg of *p*-toluenesulfonic acid. The resulting mixture was heated to 80-85 °C for 2–3 days with stirring under N_2 in a Dean-Stark apparatus. Heating was discontinued when a ^{1}H NMR spectrum of the reaction mixture no longer showed the δ 4.2 methine signal of reactant. Quinoline (0.2 mL) was added, solvent was removed at 10 mmHg, and product was distilled in vacuum: up to 52% yield, bp 12–15 °C/1 Torr (lit.[29] bp 62–66 °C/25 Torr).

The material is quite unstable. In most solvents, especially wet or polar ones, it reacts or decomposes instantly. This is a severe limitation on the studies that can be performed. When kept neat or in nonpolar solvent and under N_2, **3** can last for weeks at 0 °C without much deterioration.

Sample Preparation. Deuterated solvents were obtained from Cambridge Isotope Laboratories. Diethyl ether and tetrahydrofuran (undeuterated) were distilled under N_2 from benzophenone ketyl, and 10% benzene-d_6 was added for spectrometer lock and reference. Samples in ether, THF, or acetone-d_6 were prepared by adding **3** to solvent cooled below –66 °C. Samples, approximately 0.5 M in **3**, were flushed with N_2.

NMR Methods. Experiments were carried out on either a GE QE-300 NMR spectrometer (300 MHz ^{1}H, 75.4 MHz ^{13}C) or a Varian Unity-500 spectrometer (500 MHz ^{1}H, 125.7 MHz ^{13}C). Chemical shifts are referenced to a solvent signal as internal standard (pentane-d_{12}—^{13}C δ 12.4, trace benzene ^{1}H δ 7.15; toluene-d_8—^{13}C δ 20.4, ^{1}H δ 7.09; methylene chloride-d_2—^{13}C δ 53.8, ^{1}H δ 5.32; acetone-d_6—^{13}C δ 29.8, ^{1}H δ 2.04). Saturation-transfer difference spectra compared a spectrum where one ^{1}H peak was irradiated during interpulse delay with a control in which a baseline frequency was irradiated. For ^{13}C intensities the decoupler was gated off during the interpulse delay and on during acquisition. Heteronuclear ^{13}C–^{1}H correlation spectra[30] were obtained using standard pulse sequence CSCMB4 of the QE300 spectrometer, as described previously.[8]

Temperatures were calibrated with a 1:1 methanol–methanol-d_4 sample.[31] Spectra were obtained as the probe temperature was lowered in 10 °C steps, and the coalescence temperature T_c was noted. Despite unequal populations $\Delta G^{\ddagger}$ was approximated by $4.57T_c(\log(T_c/\Delta\nu) + 9.97)$,[32] where $\Delta\nu$ is the separation in hertz between the two signals from the pure conformers.

Ratios of conformers at low temperature were evaluated by integrating appropriate ^{1}H signals or sums of overlapping signals. The ratios were also evaluated from integrations of all pairs of ^{13}C signals. In diethyl ether ratios were evaluated from Lorentzian fittings of the ^{13}C signals. Errors were obtained as standard deviations of at least two separate measurements, each made on different samples on separate occasions. The free energy changes for the conformational equilibrium were calculated from the observed ratios according to $\Delta G°_{A\rightarrow E} = -RT \ln([3E]/[3A])$.

Molecular Orbital and Molecular Mechanics Calculations. AM1 calculations[33] of the most stable structure of cyclohexane, ee and ea conformers of 1,3-dimethylhexahydropyrimidine, and 1,3-dioxane (**5**), plus their axial methyl and methoxy derivatives, were done using MOPAC Version 6.0. Energies of the axial and equatorial conformers (**6**) of 2-methyl-, 2-ethyl-, and 2-methoxycyclohexanes, 1,3-dimethylcyclohexanes, and 1,3-dimethylhexahydropyrimidines were calculated with MMX (PCMODEL).[34] Standard parameters were used, but in addition, to isolate the steric interactions, without any anomeric effect, the torsional parameters V_1 and V_2 for lone pairs on N–C–O bonds were set to zero and the dielectric constant was set to 80.

Results

Room-Temperature ^{13}C NMR Spectra. The ^{13}C spectrum of 2-methoxy-1,3-dimethylhexahydropyrimidine (**3**) at room temperature in toluene-d_8 is displayed in Figure 1. It is quite simple, with only five peaks, all well-separated. Chemical shifts are listed in Table 1, along with peak assignments based on established shift correlations. Moreover, a ^{1}H-coupled ^{13}C spectrum shows the multiplicity expected for each CH, CH_2, and CH_3.

Low-Temperature ^{13}C NMR Spectra. Figure 2 shows the ^{13}C spectrum of **3** at –98 °C. As the temperature is lowered, each of the signals broadens and decoalesces. Except for the NCH_3 signal, whose T_c is ca. –82 °C, all T_c are near –70 °C, corresponding to a $\Delta G^{\ddagger}$ value for ring inversion of 36 ± 1 kJ mol^{-1}. At –98 °C each of the signals has resharpened into two signals of unequal proportion. Except for the OCH_3 signals the minor one is downfield of the major. Since compression by an axial substituent usually shifts all ^{13}C signals upfield,[35] the major conformer is assigned as **3A**. These chemical shifts and peak assignments are listed in Table 2.

Assignment of the two conformers may also be made on the basis of $^1J_{CH}$ for C2, which should be larger for **3A** than for **3E**.[36] Such a trend is seen in other N–CH systems, as well as in carbohydrates, and has been attributed to a weakening of the axial C–H bond. The $^1J_{C_2H}$ values of the major, upfield signal and of the minor, downfield signal are 164 and 159 Hz,

(27) Alcaide, B.; Jimenez-Barbero, J.; Plumet, J.; Rodriguez-Campos, I. M. *Tetrahedron* **1992**, *48*, 2715.
(28) Nader, F. W.; Eliel, E. L. *J. Am. Chem. Soc.* **1970**, *92*, 3050.
(29) Winberg, H. E., E. I. du Pont de Nemours & Co. U.S. Patent No. 3239518, 1966; *Chem. Abstr.* **1966**, *64*, P15898c.
(30) Sanders, J. K. M.; Hunter, B. K. *Modern NMR Spectroscopy*; Oxford University Press: New York, 1987; p 100.
(31) Raiford, D. S.; Fisk, C. L.; Becker, E. D. *Anal. Chem.* **1979**, *51*, 2050.
(32) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228.
(33) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. Stewart, J. J. P. *QCPE Bull.* **1983**, *3*, 101.
(34) Serena Software, Box 3076, Bloomington, IN 47402.
(35) Whitesell, J. K.; Minton, M. A. *J. Am. Chem. Soc.* **1987**, *109*, 225.
(36) Perlin, A. S.; Casu, B. *Tetrahedron Lett.* **1969**, 2921. Jennings, W. B.; Boyd, D. R.; Watson, C. G.; Becker, E. D.; Bradley, R. B.; Jerina, D. M. *J. Am. Chem. Soc.* **1972**, *94*, 8501. Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. II* **1974**, 293. Fraser, R. R.; Bresse, M. *Can. J. Chem.* **1983**, *61*, 576.

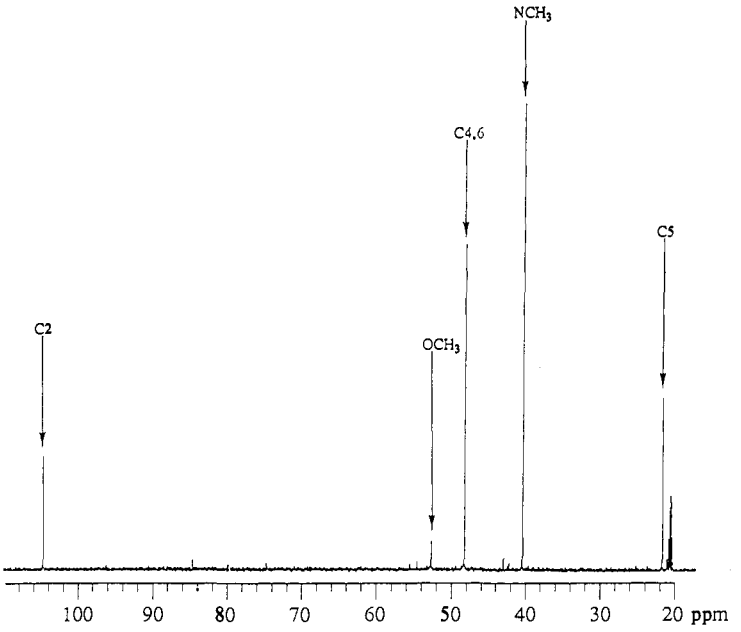


Figure 1. Room-temperature 125-MHz ^{13}C NMR spectrum of 2-methoxy-1,3-dimethylhexahydropyrimidine (**3**) in toluene-d_8.

Table 1. Averaged ^{13}C NMR Chemical Shifts and Assignments of **3**

	solvent (T, °C)					
	C_5D_{12} (24)	toluene-d_8 (27)	Et_2O (25)	THF (25)	CD_2Cl_2 (27)	acetone-d_6 (−38)
OCH_3	51.5	52.2	52.1	52.2	*a*	52.3
NCH_3	39.7	40.1	40.1	40.0	40.3	29.7
C2	104.1	104.3	104.6	104.4	104.9	103.8
C4,6	47.7	48.0	48.1	48.0	48.0	47.0
C5	20.9	21.4	21.3	21.3	21.9	20.1

[a] Under $CDHCl_2$ signal.

respectively. This evidence is the strongest for assigning the major conformer as **3A**.

Room-Temperature ^1H NMR Spectra. Figure 3 shows the room-temperature ^1H NMR spectrum of **3** in toluene-d_8. This too is so simple that gross assignments, without stereochemistry, could be made on the basis of the chemical shift, intensity, and multiplicity of each of the signals, and by comparison to the starting materials. To further substantiate the peak assignments, a room-temperature ^{13}C–^1H 2D correlation spectrum was obtained. For example, a cross-peak between the ^{13}C signal at δ 52.2 and the ^1H signal at δ 3.27 confirms their assignments to the OCH_3.

The stereochemistry is more problematic. Each CH_2 has diastereotopic protons, since one is cis to OCH_3 and the other is trans. No nuclear Overhauser enhancements could be detected between OCH_3 and either H4, so the assignment as cis and trans is indirect. Sequential selective decoupling of each of these four signals in benzene-d_6 simplified the remaining three and provided all the coupling constants: $^2J_{4t4c} = -11.7$ Hz, $^3J_{4t5c} = 4.9$ Hz, $^3J_{4t5t} = 4.4$ Hz, $^3J_{4c5t} = 9.8$ Hz, $^3J_{4c5c} = 3.4$ Hz, $^2J_{5c5t} = -12.7$ Hz. The large 9.8-Hz anti coupling can be seen in the greater width of the downfield signal of each pair in Figure 3. This is the basis for assigning the downfield H4,6 and H5 as axial. It reverses the usual[37] assignment of upfield protons as axial, but there are exceptions, even in nitrogen heterocycles.[27,38] Then from the above assignment of axial methoxy in the major isomer, it follows that the axial H4 is cis, etc. Table 3 lists all assignments.

Low-Temperature ^1H NMR Spectra. As the temperature is lowered below -30 °C, each of the signals of **3** broadens and begins to decoalesce, until at −98 °C decoalescence is complete. For H2 T_c is near −70 °C, indicating a $\Delta G^{\ddagger}$ value of ca. 38 kJ mol^{-1}, which agrees with the value from ^{13}C NMR. Two sets of signals in unequal proportion are apparent in the spectrum shown in Figure 4. The ones due to H2 and OCH_3 are most informative, since they are the most isolated, especially the well-resolved major H2 signal at δ 4.05, furthest downfield. Assignments of the low-temperature spectra are listed in Table 4. Correlation of exchanging sites could be confirmed by saturation transfer at −96 °C.

The assignment of the H2 protons is consistent with the general observation that axial protons are upfield of equatorial.[39] Although we have reversed this assignment at H4,6 and H5, the generalization is stronger for protons antiperiplanar to two nitrogen lone pairs.[37b] Therefore the H2 chemical shifts also identify the major conformer as **3A** and the minor as **3E**. The behavior of other signals is consistent with ring inversion but does not provide further information. The *N*-methyl signal decoalesces into two peaks of similar chemical shifts, since their environments are nearly the same in the two conformers. In contrast, the two sets of CH_2 signals each decoalesce into separate axial and equatorial signals that are up to 1 ppm apart, as expected for axial and equatorial protons.

Intermediate-Temperature Spectra. Just below room temperature there is also a poorly reproducible decoalescence that is difficult to characterize. It is more common in samples that contain more impurities. The peak at δ 3.7 in Figure 4 is a manifestation. A clue is that the IR spectrum of **3** sometimes shows an intense peak at 1680 cm^{-1}, probably due to the hydrolysis product *N*-formyl-*N*,*N*′-dimethyl-1,3-propanediamine. Thus a small amount of methanol may be produced. This decoalescence could then be the result of a ring-opening equilibrium between **3** plus CH_3OH and $CH_3NH(CH_2)_3N(CH_3)CH(OCH_3)_2$. However, this process does not interfere with the low-temperature decoalescence, which involves equilibrium between **3A** and **3E**.

Integration. The percentage of the minor conformer **3E**, as

(37) (a) Franklin, N. C.; Feltkamp, H. *Angew. Chem., Int. Ed. Engl.* **1956**, *4*, 774. (b) Riddell, F. G. *J. Chem. Soc. B* **1967**, 560. (c) Lambert, J. B.; Bailey, D. S.; Michel, B. F. *J. Am. Chem. Soc.* **1972**, *94*, 3812. (d) Vierhapper, F. W.; Eliel, E. L. *J. Org. Chem.* **1975**, *40*, 2734. (e) Eliel, E. L.; Kandasamy, D.; Yen, C.-y.; Hargrave, K. D. *J. Am. Chem. Soc.* **1980**, *102*, 3698.

(38) (a) Eliel, E. L.; Rao, V. S.; Vierhapper, F. W.; Juaristi, G. *Z. Tetrahedron Lett.* **1975**, 4339. (b) Katritzky, A. R.; Baker, V. J.; Ferguson, I. J.; Patel, R. C. *J. Chem. Soc., Perkin Trans. II* **1979**, 143.

(39) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 5th ed.; Wiley: New York, 1991; p 175.

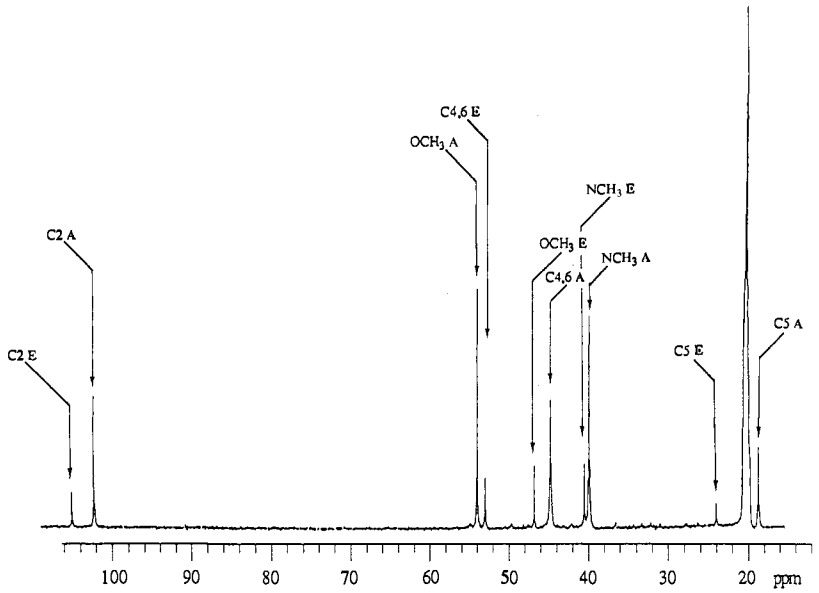


Figure 2. 125-MHz ^{13}C NMR spectrum of 2-methoxy-1,3-dimethylhexahydropyrimidine (**3**) in toluene-d_8 at −98 °C.

Table 2. Low-Temperature ^{13}C NMR Chemical Shifts (δ_{major}, δ_{minor}) and Assignments of **3**

	solvent (T, °C)					
	C_5D_{12} (−101)	toluene-d_8 (−98)	Et_2O (−101)	THF (−101)	CD_2Cl_2 (−96)	acetone-d_6 (−96)
OCH_3	53.9, 46.9	54.0, 46.8	53.8,[a] 46.4	53.8, 46.3	56.1, 46.4	54.7, 46.4
NCH_3	39.9, 41.2	40.0, 40.3	39.9, 40.5	39.7, 40.4	39.7, 40.0	39.9, 40.5
C2	103.3, 106.1	102.2, 105.5	102.6, 105.8	102.6, 105.9	102.7, 105.2	102.8, 105.9
C4,6	45.6, 54.5	44.9, 53.1	44.9, 53.6[a]	44.8, 53.4	44.3, 53.0	44.8, 53.4
C5	19.6, *a*	18.9, 24.1	19.0, 24.4	19.0, 24.4	20.3, 23.7	19.7, 24.3

[a] Incompletely resolved.

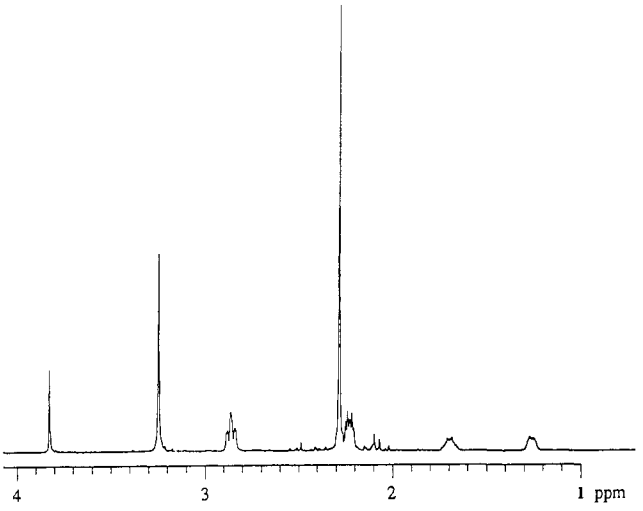


Figure 3. Room-temperature 500-MHz ^1H NMR spectrum of 2-methoxy-1,3-dimethylhexahydropyrimidine (**3**) in toluene-d_8.

evaluated from each of the reporter nuclei and in six solvents, is listed in Table 5. Results in acetone-d_6 containing 4% methanol, which was the most polar medium viable, were the same as those in acetone-d_6. Table 6 includes the corresponding $\Delta G°_{A\rightarrow E}$. There is good agreement among all reporter nuclei, and the values of $\Delta G°_{A\rightarrow E}$, averaged over all reporter nuclei, are included in Table 6.

Computed Structural and Steric Parameters. Table 7 lists AM1 structural parameters for cyclohexanes, 1,3-dimethylhexahydropyrimidines, and 1,3-dioxanes (**5**). Whenever two distances were within 0.03 Å of one another, the average is reported. The data show that despite the shorter C–N and C–O bonds in both heterocycles, the opening of the NCN angle flattens the ring and

(40) Profeta, S., Jr.; Allinger, N. L. *J. Am. Chem. Soc.* **1985**, *107*, 1907.

Table 3. Averaged ^1H NMR Chemical Shifts, Relative Intensities, Multiplicites, and Assignments of 2-Methoxy-1,3-dimethylhexahydropyrimidine (**3**)

	solvent (T, °C)				
	C_5D_{12} (24)	toluene-d_8 (27)	Et_2O (25)	CD_2Cl_2 (25)	acetone-d_6 (−38)
OCH_3 (s, 3H)	3.09	3.26	3.06	3.16	3.22
NCH_3 (s, 6H)	2.17	2.28	2.12	2.17	2.25
H2 (s, 1H)	3.70	3.82	3.65	3.77	3.90
$H4,6_{trans}$ (m, 2H)	2.21	2.22	2.15	2.25	2.33
$H4,6_{cis}$ (bt, 2H)	2.79	2.87	2.72	2.70	2.79
$H5_{cis}$ (m, 1H)	1.25	1.26	1.02	1.37	1.35
$H5_{trans}$ (m, 1H)	1.72	1.69	1.64	1.64	1.79

increases the distance d_{ax} between an axial substituent and axial hydrogens. A similar flattening was seen in MM2 calculations on piperidines.[40] The distances in 1,3-dimethylhexahydropyrimidine are close to those in cyclohexane and considerably larger than those in 1,3-dioxane.

Table 8 lists MMX-calculated heats of formation and A values, or energy differences between axial and equatorial conformers (**6**) of 2-methyl-, 2-ethyl-, and 2-methoxycyclohexanes, 1,3-dimethylcyclohexanes, and 1,3-dimethylhexahydropyrimidines, such that a positive value represents a stabilization of the equatorial form relative to the axial. The values for methylcyclohexane and methoxycyclohexane agree with experiment, since the method had been parameterized to do so. A flanking pair of equatorial methyls either on C2 and C6 or on nitrogens replacing those carbons decreases A_{CH_3}. However, either pair substantially increases $A_{C_2H_5}$, and the latter pair of methyls increases A_{OCH_3} slightly. This last is what is needed to estimate the steric interactions in **3**, especially with reparametrizing to eliminate any anomeric effect.

Discussion

Conformational Equilibrium. The behavior of the NMR chemical shifts of **3** is consistent with the interconversion of its

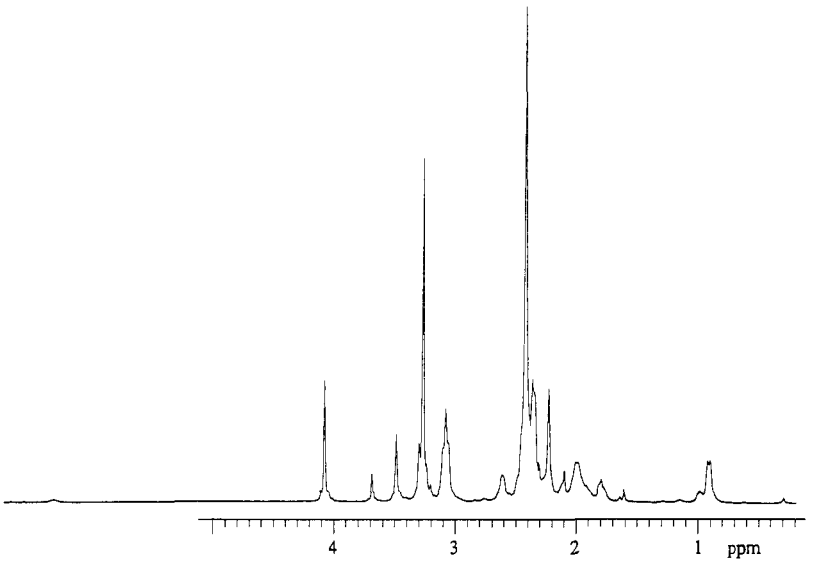


Figure 4. 500-MHz ^{1}H NMR spectrum of 2-methoxy-1,3-dimethylhexahydropyrimidine (**3**) in toluene-d_8 at −98 °C.

Table 4. Low-Temperature ^{1}H NMR Chemical Shifts and Assignments of **3**

	solvent; (T, °C)							
	C_5D_{12} (−101)		C_7D_8 (−98)		CD_2Cl_2 (−96)		C_3D_6O (−96)	
	δ_{major}	δ_{minor}	δ_{major}	δ_{minor}	δ_{major}	δ_{minor}	δ_{major}	δ_{minor}
OCH_3	3.10	2.99	3.24	3.47	3.19	3.04	3.24	3.14
NCH_3	2.17	*a*	2.21	2.40	2.20	2.03	2.31	2.10
H2	3.87	2.98	4.05	3.29	4.12	3.06	4.27	3.13
$H4,6_{trans}$	2.29	1.98	2.32	*a*	2.34	2.03	2.43	2.11
$H4,6_{cis}$	2.83	2.69	3.05	2.59	2.57	2.78	2.76	2.85
$H5_{cis}$	1.14[a]	1.63	0.89	1.78	1.20	1.60	1.19	1.70
$H5_{trans}$	1.86	1.35	1.97	0.98	1.79	1.34	1.95	1.43

[a] Incompletely resolved.

Table 5. Percent[a] **3E** in Six Solvents

signal integrated	C_5H_{12}	C_7D_8	Et_2O	THF	CD_2Cl_2	C_3D_6O
A-$^1H_2$/E-OC^1H_3	19[b]	20(1)			24.4[b]	18.7[b]
NCH_3 + $H4,6_{trans}$	21.5[c]	*d*			25(1)	20.7
$^1H5_{trans}$	21	*d*			27.5(5)	19.8
$^{13}C2$	17	18(1)	20	23	26(1)	17(1)
O$^{13}CH_3$	16	19(3.5)	*d*	18	265(2)	*d*
N$^{13}CH_3$	21	20(2)	24	21	24	19.0(1)
$^{13}C4,6$	21	18(2)	*d*	22	27(2)	18.4(1)
$^{13}C5$	*d*	18(4)	23	20	27(3)	18.3(1)

[a] Standard deviation of the last digit in parentheses. [b] H2 + OCH_3. [c] $H4,6_{cis}$. [d] Signal coincidences prevented reliable integration.

Table 6. $\Delta G°_{A\rightarrow E}$ (kJ mol^{-1})[a] for **3** in Six Solvents

signal integrated	C_5H_{12}	C_7D_8	Et_2O	THF	CD_2Cl_2	C_3D_6O
A-$^1H_2$/E-OC^1H_3	2.1(1)[b]	2.0(1)			1.7[b]	2.2(1)[b]
NCH_3 + $H4,6_{trans}$	1.85(10)[c]				1.6(1)	2.0(1)
$^1H5_{trans}$	1.9(1)				1.4(4)	2.1(1)
$^{13}C2$	2.3(1)	2.2(1)	2.0(1)	1.7(1)	1.5(1)	2.3(1)
O$^{13}CH_3$	2.4(1)	2.1(3)		2.2(1)	1.6(2)	
N$^{13}CH_3$	1.9(1)	2.0(2)	1.65(10)	1.9(1)	1.7	2.1(1)
$^{13}C4,6$	1.9(1)	2.2(2)		1.8(1)	1.5(2)	2.2(1)
$^{13}C5$		2.2(4)	1.7(1)	2.0(1)	1.5(2)	2.2(1)
av	2.0(2)	2.1(1)	1.8(2)	1.9(2)	1.6(1)	2.15(10)

[a] Standard deviation of the last digit in parentheses. [b] H2 + OCH_3. [c] $H4,6_{cis}$.

two chair conformers. The average chemical shift is close to the weighted average of the two separate chemical shifts or simply to δ_{major}. Moreover, the $\Delta G^‡$ value of 36–38 kJ mol^{-1} agrees with the $\Delta G^‡$ for inversions of other six-membered rings subject to an anomeric effect,[6] and it is well above the <28 kJ mol^{-1} value of $\Delta G^‡$ for nitrogen inversion.[41]

Table 7. Structural Parameters in **5** from AM1 Calculations

Y	X	θ, deg	d_{ax}, Å
CH_2	H	111.3	2.63
CH_2	OCH_3	111.3	2.74, 2.68
CH_2	CH_3	110.2	2.92
NCH_3 (eq + eq)	H	116.3	2.86
NCH_3 (eq + ax)	H	116.5	2.55, 2.72
NCH_3 (eq + eq)	OCH_3	114.8	2.88
NCH_3 (eq + ax)	OCH_3	115.1	2.76, 2.66
NCH_3 (eq + eq)	CH_3	112.3	2.99
NCH_3 (eq + ax)	CH_3	114.0	2.79, 2.96
O	H	108.0	2.49
O	OCH_3	111.4	2.47, 2.53
O	CH_3	108.1	2.75

Table 8. MMX Heats of Formation (kJ mol^{-1}) and A Values ($\Delta H_{f,ax} - \Delta H_{f,eq}$) for Axial and Equatorial Conformers of **6**

Y	X	$\Delta H_{f,ax}$	$\Delta H_{f,eq}$	A_X
CH_2	CH_3	−144.9	−152.3	7.4
$CHCH_3$ (eq)	CH_3	−192.4	−197.4	5.0
NCH_3 (eq)	CH_3	−11.8	−14.6	2.8
CH_2	C_2H_5	−164.6	−172.2	7.6
$CHCH_3$ (eq)	C_2H_5	−203.6	−215.9	12.3
NCH_3 (eq)	C_2H_5	−19.7	−34.9	15.2
CH_2	OCH_3	−270.4	−272.8	2.4
$CHCH_3$ (eq)	OCH_3	−320.9	−322.5	1.6
NCH_3 (eq)	OCH_3	−172.5	−177.4	4.9
NCH_3 (eq)	OCH_3	−180.0[a]	−184.0[a]	3.9[a]

[a] With N–C–O torsional $V_1 = 0 = V_2$ and dielectric constant 80.

Comparison of the proportion of axial methoxy in **3** with that in **4** provides an assessment of the relative importance of the factors responsible for the anomeric effect. We find that the axial conformer of **3** is favored by up to 2.1 kJ mol^{-1} and by at least 1.6 kJ mol^{-1}. The average over the six solvents is 1.9 ± 0.2 kJ mol^{-1}. In comparison the axial conformer of **4** is favored by 2.6 ± 0.6 kJ mol^{-1}.[28] Thus substitution of N for O has *not* resulted in a substantial increase in the proportion of axial conformer.

In view of the popularity of the molecular orbital interpretation, this result is surprising. The stronger n–σ^* interactions with nitrogen lone pairs ought to have led to more axial conformer for **3**. This suggests that n–σ^* interactions are not dominant for the anomeric effect.

This result does not depend on the assignments of H4,6 and H5 but only on the assignment of axial and equatorial methoxy.

(41) Ferguson, I. J.; Katritzky, A. R.; Read, D. M. *J. Chem. Soc., Perkin Trans. II* **1977**, 818.

This is based on the low-temperature chemical shifts of C2 and H2 and the $^1J_{CH}$s. However, if it is reversed, the dominant conformer of **3** would have OCH_3 equatorial, despite the increased n–σ^* interactions, so that the conclusion becomes even stronger.

Correction for Steric Effects. According to the data in Table 6, $\Delta G°_{A\rightarrow E}$ is nearly the same for **3** as the 2.6 ± 0.6 kJ mol^{-1} value for **4**. However, comparison of anomeric effects requires correction for the differential steric effects according to eq 1. Steric effects are greater in a heterocycle where shorter bonds compress axial–axial distances. Therefore A_{OCH_3} from cyclohexanes is an underestimate, but it can be corrected by using A_{CH_3} values for heterocycle and for cyclohexane, as in eq 2.[32]

$$A_{OCH_3}{}^{Het} = (A_{CH_3}{}^{Het}/A_{CH_3}{}^{cHx})A_{OCH_3}{}^{cHx} \qquad (2)$$

From $A_{CH_3}{}^{Diox}$ = 16.6 ± 0.4 kJ mol^{-1},[28] $A_{CH_3}{}^{cHx}$ = 7.3 ± 0.3 kJ mol^{-1},[43] and $A_{OCH_3}{}^{cHx}$ = 3.1 ± 0.2 kJ mol^{-1},[44] $A_{OCH_3}{}^{Diox}$ can be estimated as 7.0 ± 0.6 kJ mol^{-1}. For **3** we take $A_{CH_3}{}^{HPym}$ as 4.3 kJ mol^{-1} from the equilibrium in 1,2,3-trimethylhexahydropyrimidine.[38b] This is in good agreement with the 4.5 kJ mol^{-1} value from MM2 calculations.[45] Then eq 2 leads to $A_{OCH_3}{}^{HPym}$ = 1.83 kJ mol^{-1}. Alternatively, since AM1 calculations suggest that interatomic distances in a hexahydropyrimidine are quite similar to those in a cyclohexane and considerably longer than those in a 1,3-dioxane, we might ignore eq 2 and simply approximate the steric effects in a hexahydropyrimidine as identical to those in a cyclohexane, or $A_{OCH_3}{}^{HPym}$ = 3.1 kJ mol^{-1}. To be conservative we take the average, 2.5 ± 0.6 kJ mol^{-1}.

From eq 1 these steric corrections lead to E_{An} in **4** as 9.6 ± 0.9 kJ mol^{-1}. For **3** E_{An} is 4.4 ± 0.6 kJ mol^{-1}, averaged over the six solvents. Thus the anomeric effect has decreased roughly by half on substituting N for O. It did not increase, as required it it were due to n–σ^* interactions. Therefore we conclude that the anomeric effect in these systems instead arises primarily from electrostatic interactions.

Other Possibilities. There are several assumptions in the above analysis. These need to be addressed in order to determine whether the conclusion is valid or whether there is some other reason for the apparent decrease in anomeric effect. The assumptions are the reliability of steric corrections, the conformations of the *N*-methyls, the transferability of steric parameters, the magnitude of dipole–dipole interactions, and the contribution from the exo-anomeric effect. We must be sure that the reduced anomeric effect in **3** cannot be accounted for in terms of n–σ^* overlap.

The lower E_{An} in **3** arises not from the measured conformational equilibrium, which is the same as in **4**, but from the smaller correction for steric effects. These are estimated from 1,2,3-trimethylhexahydropyrimidine but they are in conflict with the $A_{CH_3}{}^{Het}$ in 2-methylpiperidine of 10.5 kJ mol^{-1},[37e] which would lead to a far larger correction. We ignore this as a more distant model, since it has only one nitrogen, which moreover is unmethylated. Besides, the AM1 results in Table 7 suggest that steric repulsions in a 1,3-dimethylhexahydropyrimidine are close to those in cyclohexane and considerably less than those in a 1,3-dioxane. To salvage the n–σ^* interpretation, E_{An} in **3** would need to be greater than in **4**. This would require axial repulsions in a hexahydropyrimidine to be even larger than in a 1,3-dioxane, despite the relative lengths of C–N and C–O bonds.

Another possible rationalization for the reduced anomeric effect in **3** is that steric and lone pair repulsions may force one of the *N*-methyls to be axial, so that its lone pair cannot be antiperiplanar to the C–O bond. The configuration of the *N*-methyls could not be determined since nitrogen inversion is too fast. However, **3A** ought to exist chiefly as **3Aee** since the ee form is preferred by 2.7 kJ mol^{-1} in 1,3-dimethylhexahydropyrimidine.[38b] The steric repulsion from the OCH_3 group must reduce this preference, but according to the calculated[45] repulsion from an even larger CH_3 group, steric effects are not sufficient to disfavor **3Aee**. Besides, any enhanced anomeric effect should increase the preference for this conformer, and the rationalization that it is not preferred contradicts a claim of enhancement due to stronger n–σ^* interactions.

Still another rationalization for the low proportion of **3A** is a reversal of the steric sizes of methoxy and methyl. Ordinarily methoxy is intermediate in size between hydrogen and methyl, as we have assumed above. Yet here the equatorial methyls at the two adjacent positions may interact more strongly with a methoxy than with a methyl, since the former corresponds to a 1,3-diaxial repulsion, whereas the latter corresponds to a gauche-butane repulsion, which is weaker. To gauge these repulsions, MMX calculations are most suitable, since they can be modified to omit the orientation-dependent anomeric effects for N–C–O fragments. For comparison, 2-ethyl is included, since this is ordinarily the same size as methyl. The calculated *A* values in Table 8 indicate that a 2-ethyl group on a 1,3-dimethylcyclohexane or a 1,3-dimethylhexahydropyrimidine is indeed much larger than a methyl, but that a 2-methoxy group on such a ring remains smaller than a methyl. (Inspection of the geometry reveals that the van der Waals repulsion is relieved by rotating about the C–OCH_3 bond.) With $A_{OCH_3}{}^{HPym}$ equal to the maximum 4.9 kJ mol^{-1}, eq 1 then leads to an upper limit of 6.8 kJ mol^{-1} for E_{An} of **3**. It would have been less ambiguous to avoid these steric interactions with 2-hydroxy-1,3-dimethylhexahydropyrimidine, but this would rapidly cleave to the amino amide. Nevertheless, these estimates suggest that the steric repulsions between methoxy and *N*-methyls are not what is responsible for the low proportion of **3A**, and the anomeric effect in **3** remains less than that in **4**. However, this conclusion does depend on the adequacy of molecular mechanics calculations to assess the steric interactions, and therein may lie the chief weakness of this entire argument.

Although the dipole moment associated with an oxygen is greater than that for a nitrogen, the angles are different, so that the dipole moments alone are not the measure of the magnitude of electrostatic interactions. Only the axial lone pair on oxygen contributes to the anomeric effect, since the equatorial lone pair is disposed equivalently with respect to axial and equatorial methoxyls. This reduces the dipole–dipole energy by the ratio of one lone pair dipole moment to the molecular dipole moment, which is the resultant of the two lone pair dipoles. With tetrahedral angles between lone pairs this factor is $^1/_2\cos(109.5°/2)$, or 0.866. Relative to the large difference in observed dipole moments this is too small a correction to make dipole–dipole interactions in **4** smaller than those in **3**.

The exo-anomeric effect[46] usually favors equatorial conformer **1E**, where the reduced steric congestion permits conformers about the C–X bond with a lone pair antiperiplanar to the C–Y bond. This is especially important for **4**, where only the equatorial conformer permits both lone pairs of the methoxy oxygen to be antiperiplanar to ring C–O bonds. If the exo-anomeric effect too is to be ascribed to n–σ^* interactions, it will be less important for **3**, since $\sigma_{C-N}{}^*$ is less interactive than $\sigma_{C-O}{}^*$. Then there would be less preference for **3E**, and the proportion of **3A** ought to have been increased even further, contrary to observation.

Lone Pair Repulsions. The anomeric effect has also been attributed to mutual repulsion of lone pairs.[1c] This is a quantum mechanical phenomenon arising from orbital overlap and distinct from the classical electrostatic repulsion of those lone pairs. Yet both **3Eee** and **3Aee** have conformations available that avoid overlap of oxygen orbitals with nitrogen orbitals. (There is repulsive overlap of nitrogen lone pairs, but the greater stability of the ee form of 1,3-dimethylhexahydropyrimidine[38b] also shows that this is not important.) Therefore there is no anomeric effect

(42) Franck, R. W. *Tetrahedron* **1983**, *39*, 3251.
(43) Booth, H.; Everett, J. R. *J. Chem. Soc., Chem. Commun.* **1976**, 278.
(44) Schneider, H.-J.; Hoppen, V. *Tetrahedron Lett.* **1974**, 579.
(45) Carballeira, L.; Mosquera, R. A.; Ríos, M. A. *J. Mol. Struct.* **1988**, *176*, 89.
(46) Lemieux, R. U.; Pavia, A. A.; Martin, J. C.; Watanabe, K. A. *Can. J. Chem.* **1969**, *47*, 4427. Lemieux, R. U.; Koto, S. *Tetrahedron* **1979**, *30*, 1933. Lemieux, R. U.; Koto, S.; Voisin, D. In ref 1c, p 17.

due to this repulsion. If this were the origin of the anomeric effect, **3E** ought to predominate owing to the steric effect alone. Since it does not, we conclude that this result is further[1a,3] evidence against lone pair overlap being responsible for the anomeric effect.

Solvent Dependence. The data in Tables 5 and 6 show small variations of the proportion of conformer **3E**, of $\Delta G°_{A\rightarrow E}$, and of E_{An} with solvent. This is independent of any correction for steric repulsions. In the five less polar solvents there may be a systematic decrease of $\Delta G°_{A\rightarrow E}$ with increasing solvent polarity. This is consisent with an electrostatic origin of the anomeric effect. However, in the most polar solvent, acetone, $\Delta G°_{A\rightarrow E}$ increases, and it may be that the electrostatic interactions have become so weak that the n–σ^* interactions dominate.

It is unfortunate that these studies are limited to nonpolar solvents. In polar solvents, where electrostatic effects are reduced, the anomeric effect may be due to orbital overlap. This seems to be the case for aqueous nojirimycin,[26] where the anomeric effect is larger than for its oxygen analog, although the magnitude is uncertain owing to steric differences. Therefore the conclusion that the anomeric effect in **3** and **4** is due primilarly to electrostatics cannot be universal.

Structural Changes. It is still necessary to account for the bond length changes that have been considered the best evidence for the molecular orbital interpretation and that the electrostatic explanation is claimed[1a,d,f] to be incapable of rationalizing. As a simplified model system we take **1** (Y = O), with two dipoles, one associated with the C–X bond and the other associated with the oxygen lone pairs and the C–O bonds. The electrostatic energy is given by eq 3, where μ_{CX} and μ_O are these dipole moments,

$$E_{dd} = \frac{\mu_{CX}\mu_O[\cos\phi_{12} + 3\cos\theta_1\cos\theta_2]}{r_{CO}^3} \qquad (3)$$

assumed situated at carbon and at oxygen, ϕ_{12} is the angle between them, and θ_1 and θ_2 is the angle between a dipole moment and the vector to the other atom, located a distance r_{CO} away. For an axial conformer **1A** with exact tetrahedral bond angles and exactly staggered bonds the angular factor is zero. For the equatorial conformer **1E** the angular factor makes this dipole–dipole energy positive, accounting for its destabilization. Equation 4 gives the derivative of this energy with respect to the C–O bond

$$\frac{\partial E_{dd}}{\partial r_{CO}} = -3\frac{\mu_{CX}\mu_O[\cos\phi_{12} + 3\cos\theta_1\cos\theta_2]}{r_{CO}^4} \qquad (4)$$

length, subject to the simplification that μ_O arises primarily from oxygen lone pairs and does not vary with r_{CO}. This derivative is negative for **1E**, so that its energy is lowered by lengthening the C–O bond. Equation 5 gives the derivative of the dipole–dipole

$$\frac{\partial E_{dd}}{\partial r_{CX}} = \frac{\mu_O[\cos\phi_{12} + 3\cos\theta_1\cos\theta_2]}{r_{CO}^3}\frac{\partial\mu_{CX}}{\partial r_{CX}} \qquad (5)$$

energy with respect to the C–X bond length. In methyl fluoride $\partial\mu/\partial r_{CF}$ is positive, both experimentally and theoretically,[47] and this should be general for all C–X. Then the derivative in eq 5 is positive for **1E**, so that its energy is raised by lengthening the C–X bond.

Thus according to simple electrostatics, the C–O bond of the equatorial conformer **1E** must be lengthened and its C–X bond shortened. This means that relative to **1E**, the C–O bond of the axial conformer **1A** is shorter and its C–X bond longer. These are the observed geometric changes attributed to n–σ^* interactions, but they are equally well accounted for by dipole–dipole interactions.

Nevertheless there are other geometric changes that cannot be accounted for by dipole–dipole interactions. There is a systematic twist of the dihedral angle about the C–O bond, which has been attributed[5c,d] to improvement of the overlap in **1A** between the σ^* orbital of the C–X bond and the 2p lone pair of oxygen. Equation 6 gives the derivative of the dipole–dipole energy with

$$\frac{\partial E_{dd}}{\partial\chi_{COCX}} = \frac{\mu_{CX}\mu_O}{r_{CO}^3}\frac{\partial\cos\phi_{12}}{\partial\chi_{COCX}} \qquad (6)$$

respect to that dihedral angle. By analytic geometry it is readily shown that $\partial\cos\phi_{12}/\partial\chi_{COCX}$ is zero for **1E** and positive for **1A**. Therefore the energy of **1A** ought to be lowered by decreasing this dihedral angle. This had been noted previously[6] in connection with the anomeric effect on the barrier to ring inversion. Yet this is not the twist that is observed. Nor does dipole–dipole repulsion account for the opening of the OCX angle in the axial conformer. If these discrepancies are not due to some other factor, such as relief of steric repulsions, which are thought to be responsible for the bond angle variation,[48] it may be the strongest evidence for n–σ^* interactions, even though it contradicts the other results presented here.

Summary and Conclusions

Experimentally there is as much axial conformer for **3** as for **4**. Yet the reduced steric interactions in a hexahydropyrimidine ought to have permitted more of **3A**. Were there a stronger anomeric effect in **3** due to the better donor ability of nitrogen there would be even more of **3A**, so much so that there would be hardly any **3E**. Yet the presence of appreciable **3E** is quite apparent in the low-temperature NMR spectra of Figures 2 and 4. Were n–σ^* interactions dominant for the anomeric effect the stronger n–σ^* interactions with nitrogen lone pairs would have led to a contrary result.

Alternatively, the anomeric effect E_{An} in **3** is appreciably smaller than that in **4**. Since the stronger n–σ^* interactions that accompany substitution of nitrogen for oxygen do not result in an increase in the anomeric effect, these cannot be the dominant interactions. We therefore conclude that the anomeric effect arises primarily from electrostatic interactions. However, this conclusion is limited to nonpolar solvents.

Moreover, the bond length changes that have been considered as strong evidence for n–σ^* interactions can equally well be accounted for on the basis of dipole–dipole interactions. These results ought to stimulate a rethinking of the origins of the anomeric effect, and more attention should be paid to electrostatics.

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(47) Newton, J. H.; Levine, R. A.; Person, W. B. *J. Chem. Phys.* **1977**, *67*, 3282. Kim, K.; Park, C. W. *J. Mol. Struct.* **1987**, *161*, 297.

(48) Gorenstein, D. G.; Kar, D. *J. Am. Chem. Soc.* **1977**, *99*, 672. Wiberg, K. B.; Murcko, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4821.