Preference for Axial *N*-Alkylation of Tetrahydro-1,3-oxazines and Hexahydropyrimidines: Manifestation of a Kinetic Anomeric Effect

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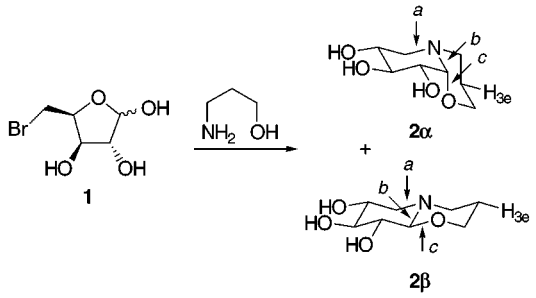
Reaction of 3-amino-1-propanol with 5-bromo-5-deoxy-D-xylose in aqueous solution gives anomeric hexahydropyrido[2,1-*b*][1,3]oxazine-7,8,9-triols **2**α and **2***β*. When this reaction was monitored by ^{1}H NMR, it was observed that the α-anomer formed 20 times faster but the *β*-anomer was more stable ($K_{\beta/\alpha} = 7.3$). The reaction pathways for formation of these products are assessed, and it is determined that *N*-alkylation of diastereomeric tetrahydro-1,3-oxazine intermediates is the discriminatory step. The faster formation of the α-anomer is ascribed principally to a kinetic anomeric effect that destabilizes the transition state for equatorial *N*-alkylation and formation of the *β*-anomer. The α-anomer is principally formed by axial *N*-alkylation. Reaction of *meso*-2,4-pentanediamine with 5-bromo-5-deoxy-D-xylose in aqueous solution gives octahydropyrido[1,2-*a*]-pyrimidine-7,8,9-triols **16**α and **17***β*, which cannot interconvert. In this case, formation of **16**α is twice as fast as formation of **17***β*. This rate differential is ascribed to a similar but weaker kinetic anomeric effect in the *N*-alkylation of hexahydropyrimidines.

Introduction

It is widely accepted that the anomeric effect[1] is due to a stereoelectronic preference for an antiperiplanar arrangement of a doubly occupied, nonbonding sp^3-orbital and a bond to a heteroatom that permits a no bond−double bond resonance effect.[2] On similar grounds, it is predicted that a heteroatom antiperiplanar to a doubly occupied, nonbonding sp^3-orbital is made more basic and nucleophilic because the resonance effect increases the electron density on the heteroatom.[3] The latter is considered to be a kinetic anomeric effect.[1b,1f] Many observations of kinetic anomeric effects have been with acetals[1b] and in the field of carbohydrate chemistry,[1c] but examples in other compound classes such as imidate and phosphate esters also have been reported.[1b,1e] Examples of kinetic anomeric effects with nitrogen heterocycles are much less common, and instances in *N*-alkylation reactions of heterocycles apparently have not been reported.

In following by NMR the reaction of 5-bromo-5-deoxy-D-xylose (**1**) with 3-amino-1-propanol to produce the two anomers of hexahydropyrido[2,1-*b*][1,3]oxazine-7,8,9-triol **2**,[4] it was observed that the α-anomer forms more rapidly but the *β*-anomer is more stable.[5] Herein is described a mechanistic study that attributes the faster formation of the less stable anomer to a kinetic anomeric effect in the *N*-alkylation of tetrahydro-1,3-oxazine intermediates that favors axial attack over equatorial. Also discussed is a much smaller effect observed in the formation of related octahydropyrido[1,2-*a*]pyrimidine-7,8,9-triol diastereomers, which cannot interconvert. These observations may find application in the stereoselective synthesis of some classes of heterocycles.



Results and Discussion

Determination of the Reaction Pathway to Hexahydropyrido[2,1-*b*][1,3]oxazine-7,8,9-triol Products. Production of bicyclic anomers **2**α and **2***β* from **1** and 3-amino-1-propanol involves formation of three new bonds, *a*−*c*, with the last being reversible and involved in anomeric equilibration. Determination of the pathways of formation of these two products requires learning which new bond, *a* or *b*, to the nitrogen atom is formed first. This was initially addressed by determining the relative reactivities of model compounds **3** and **4**. After

(1) For reviews, see: (a) *Anomeric Effect, Origin and Consequences*; Szarek, W. A., Horton, D., Eds.; ACS Symposium Series 87; American Chemical Society: Washington, DC, 1979. (b) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983. (c) Tvaroška, I.; Bleha, T. *Adv. Carbohydr. Chem. Biochem.* **1989**, *47*, 45−123. (d) *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series 593; American Chemical Society: Washington, DC, 1993. (e) Graczyk, P. P.; Mikołajczyk, M. *Top. Stereochem.* **1994**, *21*, 159−349. (f) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC: Boca Raton, FL, 1995.

(2) Romers, C.; Altona, C.; Buys, H. R.; Havinga, E. *Top. Stereochem.* **1969**, *4*, 39−97.

(3) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; p 31.

(4) Berges, D. A.; Fan, J.; Devinck, S.; Liu, N.; Dalley, N. K. *Tetrahedron* **1999**, *55*, 6759−6770.

(5) The conformations shown for **2**α and **2***β* were determined to strongly predominate in D_2O solution by comparison of the ^{1}H−^{1}H three-bond coupling constants observed for these products with those predicted for various chair conformational possibilities for these compounds.[6]

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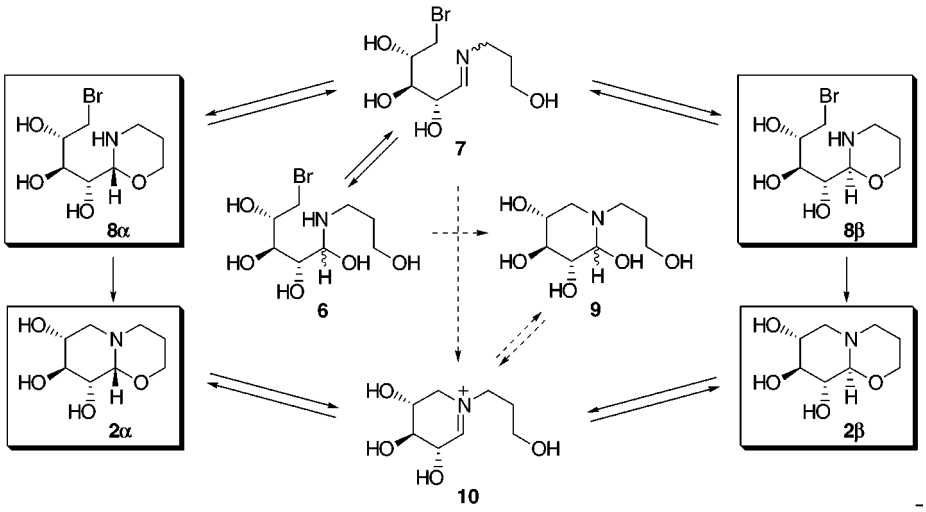
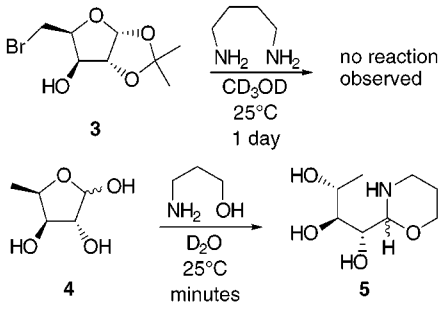
Scheme 1



standing 1 day at room temperature in CD_3OD with excess 1,4-butanediamine, bromide **3** was essentially unchanged as judged by both ^1H and ^{13}C NMR analysis, but 5-deoxy-D-xylose (**4**) reacted within minutes with 3-amino-1-propanol in D_2O to form an equilibrium mixture of epimeric tetrahydrooxazines (**5**) and unreacted **4** as determined by ^1H NMR.[7] Rapid formation of tetrahydrooxazines was also observed when **1** reacted with 3-amino-1-propanol in D_2O (vide infra). On the basis of these three results, it was concluded that bond *b* forms before bond *a*.



Scheme 1 summarizes pathways to bicyclic products **2**α and **2**β in which formation of bond *b* precedes formation of bond *a*. The epimeric amines **6** are formed by addition of the 3-amino-1-propanol to the aldehyde function of the ring-opened form of **1**. Dehydration of **6** to stereoisomeric imines **7** followed by cyclization would give tetrahydrooxazines **8**α and **8**β that could be precursors to **2**α and **2**β, respectively. Since rapid formation and then depletion of tetrahydrooxazine intermediates is observed, intramolecular *N*-alkylation of the tetrahydrooxazines **8**α and **8**β is likely to be the major process leading to the final products. An alternative process involves cyclization of imine **6** to piperidine **9** followed by water loss to give iminium ion **10**, which upon ring-closure would give both **2**α and **2**β. Another alternative involves cyclization of **7** to **10**, which would then go to products. The latter two processes pass through iminium ion **10**, which must be the intermediate involved in equilibration of the anomeric products **2**α and **2**β. In order for **10** to also be responsible for kinetic control, the rate of conversion of **10** to **2**α must be considerably greater than the rate to **2**β, and this is not expected.[8] It will be shown later that formation of the major products in the octahydropyrido[1,2-*a*]pyrimidine example cannot involve a single iminium ion corresponding to **10**.

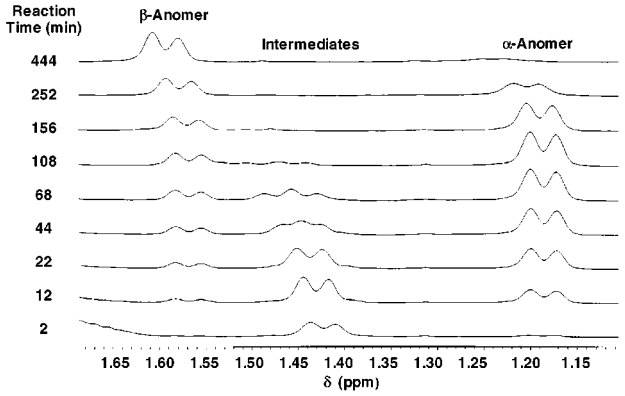


Figure 1. ^1H NMR kinetic analysis of the reaction of 5-bromo-5-deoxy-D-xylose with 1 equiv of 3-amino-1-propanol in D_2O.

Kinetic Analysis of the Formation of Hexahydropyrido[2,1-*b*][1,3]oxazine-7,8,9-triol Products. A kinetic ^1H NMR study was undertaken to gain evidence of the processes that are operative and to determine the relative rates of formation of **2**α and **2**β. Figure 1 illustrates, for different reaction times, the portion of the spectrum containing the signals of the H_{3e} protons of products **2**α and **2**β as well as the H_{5e} protons of tetrahydrooxazines that are reaction intermediates. Figure 2, a plot of percent conversion to products over time, shows that complete conversion of starting bromide to tetrahydrooxazine compounds (intermediates and prod-

(6) The prediction of $^1H-^1H$ three-bond coupling constants in bicyclic azasugars follows very well an empirical method developed for pyranose rings: Altona, C.; Haasnoot, C. A. G. *Org. Magn. Reson.* **1980**, *13*, 417−429.

(7) The formation of tetrahydrooxazines is readily observed by the appearance at high fields of the equatorial proton at oxazine ring position 5 (overlapping signals at δ 1.34 in epimeric mixture **5** and broad doublets at δ 1.19 and 1.57 in D_2O for H_{3e} in **2**α and **2**β, respectively). The high-field appearance of this proton has been reported previously: Booth, H.; Lemieux, R. U. *Can. J. Chem.* **1971**, *49*, 777−788.

(8) To have kinetic control involving intermediate **10**, the transition states for cyclization cannot be productlike since **2**β is more stable than **2**α. Therefore, they must resemble **10**, and there should be little difference in the rates of formation of **2**α and **2**β if **10** is their precursor.

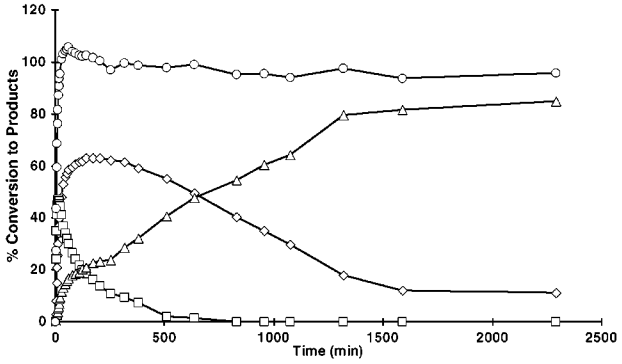


Figure 2. Plot of percent conversion to intermediates and products over time for the reaction of 5-bromo-5-deoxy-D-xylose with $2^1/_2$ equiv of 3-amino-1-propanol in D_2O. Symbols: □ is the amount of tetrahydrooxazine intermediates; ◇ is the amount of **2**α; △ is the amount of **2**β; ○ is the sum of the amounts of intermediates **8**α and **8**β and products **2**α and **2**β.

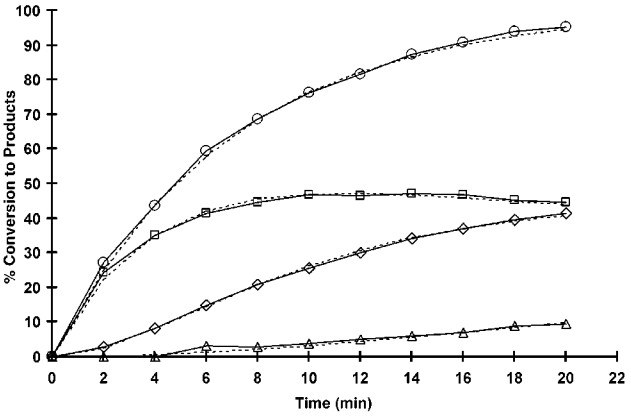
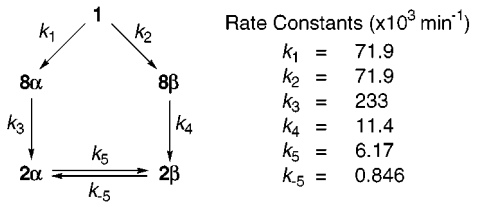
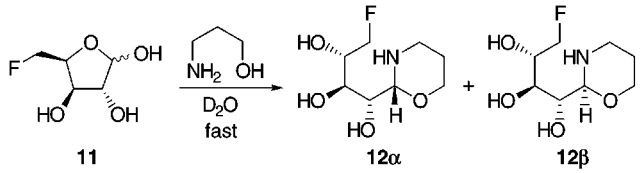


Figure 3. Initial rates of the reaction of 5-bromo-5-deoxy-D-xylose with $2^1/_2$ equiv of 3-amino-1-propanol in D_2O. Symbols: □ is the amount of tetrahydrooxazine intermediates; ◇ is the amount of **2**α; △ is the amount of **2**β; ○ is the sum of the amounts of intermediates **8**α and **8**β and products **2**α and **2**β. Solid lines are the observed results, and dashed lines are those obtained from curve-fitting.

ucts) is extremely fast (~20 min) and is accompanied by slower buildup and then loss of most of the α-anomer with concomitant formation of the β-anomer. An equilibrium between the anomeric products is established after about 1 day. Figure 3 shows percent conversion to intermediates and products for the initial 20 min along with curves generated to match the experimental data from which rate constants were obtained. Implicit in the rate determinations was the assumption that intermediates **8**α and **8**β form at comparable rates[9] and are equally stable in terms of conformational energy. This assumption seemed well-justified on the basis of studies with 5-deoxy-5-fluoro-D-xylose (**11**), which rapidly forms the epimeric tetrahydrooxazines **12**α and **12**β at very similar rates and in essentially equal amounts;[10] **12**α and **12**β undergo cyclization to **2**α and **2**β, respectively, much more slowly than do **8**α and **8**β, which allowed the relative rates of formation of **12**α and **12**β to be assessed.

Scheme 2





Initial rate information obtained from curve-fitting of the kinetic study is shown in Scheme 2. In the fitting process, constants k_1 and k_2 were required to be equal on the basis of previous arguments and were derived from the overall rates of formation of **8**α and **8**β from **1**. They were obtained from the plot of the sum of the amounts of intermediates **8**α and **8**β and products **2**α and **2**β versus time. Although intermediates must form between **1** and **8**α and **8**β, only the rate constants for overall formation of **8**α and **8**β were necessary for determining the other rate constants shown in Scheme 2.[11] These additional rate constants were determined from the plots of the amounts of **2**α and **2**β versus time and took into account the formation of **2**α and **2**β from **8**α and **8**β, respectively, and also the interconversion of the final products. Although intermediate **10** undoubtedly is involved in the interconversion process, it was not observed by ^{1}H NMR even when crystalline **2**β was allowed to equilibrate in D_2O.[12] This indicates that the rate of opening of the bicyclic products to **10** is much slower than the subsequent recyclization. The rate constants k_5 and k_{-5} are for the overall process of interconversion and combine two steps in each direction. The ratio k_5/k_{-5}, the equilibrium constant for the interconversion, is 7.3 and was obtained from the equilibration experiment; this ratio was held constant during curve-fitting. The ratio k_3/k_4 of 20.5 shows that **8**α is considerably more reactive than **8**β with respect to cyclization.

Transition-State Analysis of the *N*-Alkylation Reactions. The competitive pathways for *N*-alkylation are illustrated by the potential energy diagram of Figure 4. This diagram ignores proton-transfer steps and does not distinguish between isomers of **7**. It does include organizational steps to produce conformations **8**α***** and **8**β*****, which are arranged to allow reaction to occur. The following discussion delineates the reasoning behind the relative energies shown for various states. Three reasonable chairlike conformational states that might represent

(9) As seen in Figure 1, a single signal for tetrahydrooxazine intermediates is present during the first 22 min, but at 44 min a second is also apparent. On the basis of the assumption that **8**α and **8**β form at similar rates, then the original signal is a composite of peaks from both **8**α and **8**β. The subsequent separation that occurs may be due to production by the reaction of hydrogen bromide, which protonates the intermediates and causes a chemical shift difference. The effect of acid on the chemical shifts of the H_{3e} protons of the products is apparent at the later times in Figure 1.

(10) The formation of **12**α and **12**β was best followed by ^{13}C NMR observing peaks at approximately δ 25.5 and 25.4 for the tetrahydrooxazine carbon at ring position 5 for the two epimers.

(11) Additional intermediates were observed during the initial stages of the reaction, but their structures and amounts could not ascertained because their ^{1}H NMR signals overlapped with those of other species.

(12) Equilibrium was reached from **2**β after about 2.5 days. An equilibrium constant $K_{\beta/\alpha}$ for the equilibration of 7.3 means that $\Delta G_{2\beta-2\alpha}$ is −1.2 kcal/mol at 25 °C. ($\Delta G = -RT \ln K$; $R = 0.001\ 99$ kcal K^{-1} mol^{-1} and $T = 298$ K).

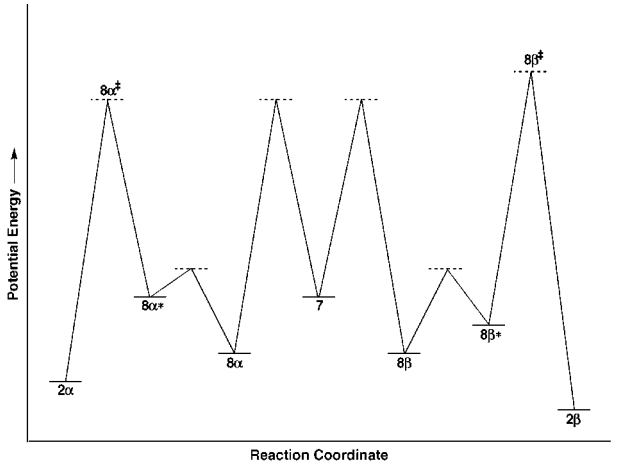
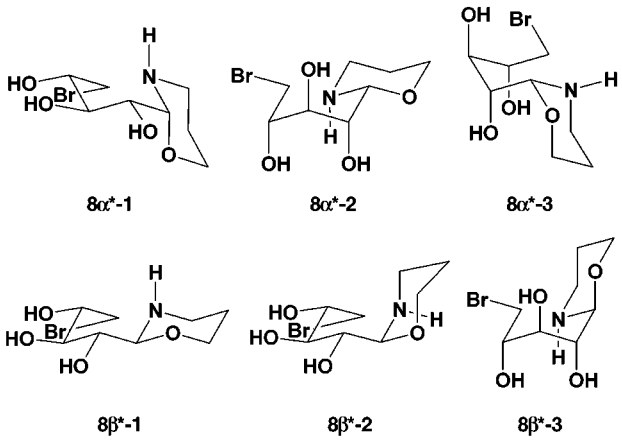


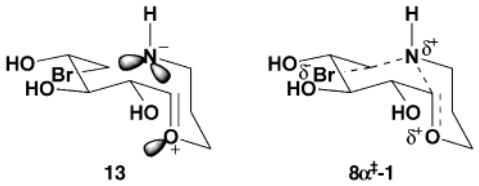
Figure 4. Potential energy diagram for the production of **2**α and **2**β from common imine intermediates **7**. Transition states are represented by dashed horizontal lines, and solid lines are used for intermediates and products.

8α***** are shown by structures **8**α***-1** through **8**α***-3**; a fourth chairlike conformation that has the lone pair on nitrogen and the side chain in a trans-diaxial relationship cannot lead to product. The three conformational possibilities differ in terms of electronic factors (anomeric effects), steric factors, and approach of attack on the tetrahydrooxazine nitrogen atom. The transition state derived from **8**α***-1** involves axial attack, but the other two involve equatorial attack. Likewise, there are three reasonable chairlike conformational states that might represent **8**β*, which are shown by structures **8**β***-1** through **8**β***-3**. The first two lead to transition states involving equatorial attack on the tetrahydrooxazine nitrogen atom, while the last would result in axial attack.[13]

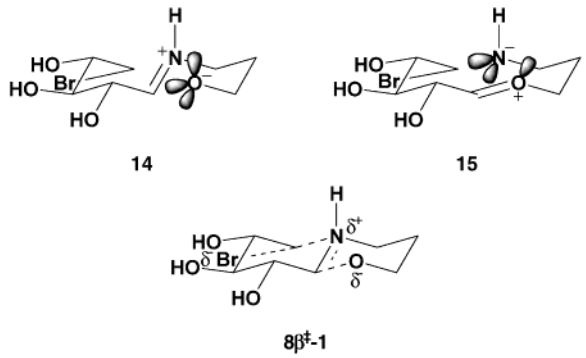


Comparison of the possible pathways leading to **2**α and **2**β requires an assessment of the influence of steric and anomeric effects on the ground states just enumerated and the transition states that result from them. If anomeric effects on ground states and transition states were not important and only steric effects were operative, then formation of **2**β would be favored over production of **2**α because the energy of activation required to go from **8**β***-1** to its transition state would be less than any other **8**β***** or **8**α***** possibility; going from **8**β***-1** to its transition state introduces the least amount of additional steric strain as interatomic distances shorten in the transition state. Since formation of **2**α is faster than that of **2**β, then anomeric effects must be important for these reactions.

Influence of Anomeric Effects on Energies of Ground and Transition States. Further analysis of ground states **8**α***-1** and **8**β***-3** for axial *N*-alkylation reveals that only an anomeric effect involving a lone pair of electrons on oxygen can be operative in these cases (see structure **13** for an illustration of the effect for **8**α***-1**). This would stabilize these conformations weakly since electron flow would go counter to the electronegativity difference between nitrogen and oxygen; an alternative view of this effect is that it increases electron density on the nitrogen atom and thereby increases its reactivity for alkylation reactions. On the other hand, the transition states (illustrated by **8**α‡**-1**) derived from these ground states should also be stabilized by the same kind of anomeric effect since the forming positive charge would be carried by both the nitrogen and oxygen atoms.[14]



The various ground states for equatorial alkylation would experience two kinds of anomeric effects. Using conformation **8**β***-1** as an example, these effects are illustrated by **14** and **15**, respectively. On the basis of the electronegativity difference between oxygen and nitrogen, the effect illustrated by **14** should result in more significant stabilization of the ground state **8**β***-1** than that shown by **15**. This should cause a substantial reduction in the nucleophilicity of its nitrogen atom. On the other hand, the transition states derived from these ground states should be stabilized by anomeric effects such as that shown with **8**α‡**-1**, but the other more powerful anomeric effect (illustrated by **8**β‡**-1**) should be destabilizing.



(13) The fact that the conformations of the products **2**α and **2**β resemble those of conformational states **8**α***-1** and **8**β***-1** does not necessarily mean that these conformational states are precursors to the products since any other conformations of the products arising directly from cyclization may rapidly deprotonate and flip a ring with concomitant nitrogen inversion to give the favored conformations. The process of rapid flipping has been observed with the related compounds and will be reported separately.

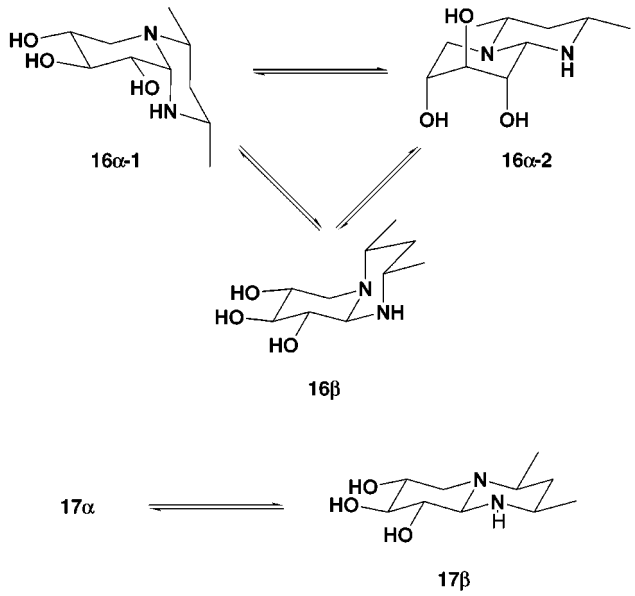
(14) It is likely that such an anomeric effect would produce more stabilization for the transition state than for the ground state because the former involves a sharing of charge and the latter a separation of charge.

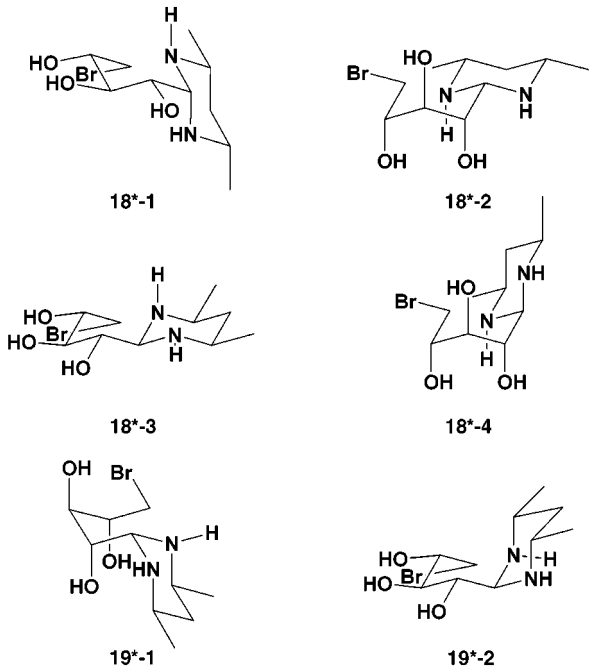
The consequences of involvement of anomeric effects are greater stabilization of the ground states for equatorial *N*-alkylation relative to axial and greater stabilization of the transition states for axial alkylation than for equatorial. In the absence of other effects, this would result in a smaller activation energy for the axial process compared with the equatorial. A relatively higher rate for axial *N*-alkylation than for equatorial can then be ascribed to a kinetic anomeric effect.

Steric and anomeric effects work in opposite directions in these cases. The anomeric effects must dominate; otherwise, **2***β* would form faster than **2**α. Formation of **2**α must necessarily then involve axial *N*-alkylation and transition state **8**α‡**-1**; however, the mechanism for formation of **2***β* is unresolved and may involve axial alkylation from ground state **8***β******-3 followed by very rapid ring-flipping with nitrogen inversion or equatorial alkylation from ground state **8***β******-1, the former favored by anomeric effects and the latter by steric effects.

Observation of a Small Kinetic Anomeric Effect in the Formation of Octahydropyrido[1,2-*a*]pyrimidine-7,8,9-triols. Analysis of the rates of formation of **2**α and **2***β* was complicated by their equilibration. Observation of a kinetic anomeric effect would be more straightforward in a system where interconversion of anomeric products is not possible. Certain interconversions can be prohibited by introducing two or more new stereogenic centers in the cyclization process. One such instance occurs in the reaction of **1** with *meso*-2,4-pentanediamine, which could give rise to four diastereomeric products, **16**α, **16***β*, **17**α, and **17***β*. Although anomeric isomerization can occur between **16**α and **16***β* and between **17**α and **17***β*, it is not possible between **16**α and **17***β* and between **17**α and **16***β*. In fact, reaction of **1** with *meso*-2,4-pentanediamine produces **16**α and **17***β* in a 2:1 ratio, and the products are separable. The structures and conformations of the products were determined by analysis of their $^1H-^1H$ three-bond coupling constants. Although **17***β* exists in a single major conformation and does not undergo detectable configurational isomerization at the anomeric center, **16**α is conformationally complex, consisting of primarily conformer **16**α**-1** with some of **16**α**-2** also present; **16**α also slowly configurationally isomerizes to an anomeric mixture containing about 10% of **16***β*.[15] No **16***β* is detectable during the first 2 h of the reaction of **1** with *meso*-2,3-pentanediamine, and therefore this isomer is not a significant initial product that contributes much to the formation of **16**α.[16]

Following the rationale given in the tetrahydrooxazine explanation and adding the condition that the two methyl groups on the hexahydropyrimidine ring cannot be axial, there are two reasonable chairlike conformations (**18*-1**, **18*-2**) for the hexahydropyrimidine intermediate leading to **16**α and two (**18*-3** and **18*-4**) that could produce **17***β*. Reaction via conformer **18*-3** giving **17***β* should be favored overall on steric grounds, but since **16**α forms faster, anomeric effects must be important in this instance also. In contrast, **17**α and **16***β* each can form from only one reasonable chairlike conformation (**19*-1** and **19*-2**, respectively). Since the side chain of **19** is axial to the hexahydropyrimidine ring, this isomer should be present in a relatively small amount compared with diastereomer **18** in which the side chain is equatorial. Consequently, **19** does not give rise to detectable initial products.





In contrast with **2**α and **2***β*, which form from separate intermediates and can interconvert, **16**α and **17***β* arise from the same intermediate and cannot interconvert. This simplifies analysis of the hexahydropyrimidine case relative to that of the tetrahydrooxazines. Anomeric effects should be more important in stabilizing ground states of **18** and **19** than they were for the corresponding tetrahydrooxazines since electron flow no longer can go counter to electronegativity. Likewise, transition states should also be more stabilized by anomeric effects. However, the anomeric effect, which was so powerful in destabilizing the transition state derived from **8***β****-1**, should not be as significant for **18*-3** because the

(15) Details about these NMR assignments and conformational and configurational equilibria will be published separately.

(16) The rate of conversion of **16***β* to **16**α ought to be about 9 times that of the reverse reaction, which reaches equilibrium over about 3 days. Therefore, conversion of **16***β* to **16**α is a relatively slow process compared with the rate of formation of **16**α, and **16***β* cannot be a significant source of **16**α.

electronegativity difference between oxygen and nitrogen is not present. The smaller difference between the rates of formation of **16**α and **17**β than was observed between **2**α and **2**β can then be ascribed principally to a less significant destabilizing anomeric effect in the case of the transition state derived from **18**β***-3** than that derived from **8**β***-1**.

In conclusion, the faster rate of formation of α- than β-anomers in the *N*-alkylation of tetrahydrooxazines and hexahydropyrimidines has been ascribed principally to an anomeric effect that destabilizes the transition state leading to equatorial alkylation and thereby favors axial alkylation.

Experimental Section

Kinetic NMR experiments were done at 25 °C. The preacquisition delay (PAD) parameter was arrayed to automatically control the acquisition times. Kinetic and curve-fitting data are given in Supporting Information. Assignments for **16**α, **16**β, and **17**β were made using COSY and HETCOR (heteronuclear chemical shift correlation) and, when needed, selective ^{1}H−^{1}H decoupling and NOE experiments. Elemental analysis was performed by M-H-W Laboratories in Phoenix, AZ.

^{1}H NMR Kinetic Analysis of the Reaction of 5-Bromo-5-deoxy-D-xylofuranose with 3-Amino-1-propanol. A solution of 5-bromo-5-deoxy-D-xylofuranose[4] (8.4 mg, 0.039 mmol) and 3-amino-1-propanol (7.54 μL, 0.0986 mmol) in D_2O (0.8 mL) containing sodium pivalate (2.2 mg, 0.018 mmol) as integration reference was monitored by ^{1}H NMR. After a delay of 84 s, acquisition of spectra began. The acquisition time for each spectrum was 72 s. Delays were used so that spectra were acquired at the following average time intervals and repetition times: 2 min × 10, 4 min × 10, 8 min × 10, 16 min × 5, 32 min × 5, 64 min × 5, and 128 min × 2 to give a total of 47 spectra. Peaks at approximately δ 1.00 (reference), 1.20 (**2**α), 1.44 (hexahydro-1,3-oxazine intermediates), and 1.58 (**2**β) were integrated. The data acquired from the first 10 spectra and selected data thereafter are plotted in Figures 2 and 3.

^{13}C NMR Kinetic Analysis of the Reaction of 5-Fluoro-5-deoxy-D-xylose with 3-Amino-1-propanol. A solution of 5-fluoro-5-deoxy-D-xylose[17] (25.6 mg, 0.120 mmol) and 3-amino-1-propanol (9.23 μL, 0.120 mmol) in D_2O (0.7 mL) was monitored by ^{13}C NMR. Spectra were recorded over the following time intervals (min) from the start of the reaction: 3−5, 3−10, 3−15, 15−25, 15−38, 39−65, and 65−102. Peaks at δ 25.5 and 25.4 belonging to the tetrahydrooxazine products were monitored. Throughout the entire time course, the ratio of these two peaks was about 1 to 1. After 8 h, no bicyclic products were observed. However, after about 4 days, conversion to bicyclic products **2**α and **2**β was complete.

[2*S*-(2α,4α,7α,8β,9α,9aβ)]-Octahydro-2,4-dimethylpyrido-[1,2-*a*]pyrimidine-7,8,9-triol (16α), [2*S*-(2α,4α,7α,8β,9α,9aα)]−Octahydro-2,4-dimethylpyrido[1,2-*a*]pyrimidine-7,8,9-triol (16β), and [2*R*-(2α,4α,7β,8α,9β,9aβ)]−Octahydro-2,4-dimethylpyrido[1,2-*a*]pyrimidine-7,8,9-triol (17β). A solution of **1** (189 mg, 0.89 mmol) and *meso*-2,4-diaminopentane[18] (91 mg, 0.89 mmol) in water (2 mL) was stirred for 10 min and then treated with Amberlite CG-400 ion-exchange resin (hydroxide form) to remove HBr. ^{1}H NMR showed the presence of **16**α and **17**β in a ratio of 2:1. Evaporation under vacuum gave a slightly yellow syrup, which upon crystallization from ethanol gave colorless crystals that were only the α-anomer **16**α (95 mg, 49%, mp 163−164 °C); upon standing for several days in D_2O, **16**α equilibrated with a second β-anomer, **16**β. The filtrate from the crystallization of **16**α was purified by chromatography on silica gel eluting first with 5% CH_3OH in CH_2Cl_2 containing 1% ammonium hydroxide followed by 7.5%, 10%, 15%, 20%, and 30% CH_3OH in CH_2Cl_2 containing 1% ammonium hydroxide to give **17**β (51 mg, 27%) as a syrup. **16**α: ^{1}H NMR (D_2O, reference CH_3CN δ 1.95, at 90 °C) δ 3.59 (d, J = 3.9 Hz, 1H, H-9a), 3.59 (dd, J = 7.3, 7.3 Hz, 1H, H-8), 3.52 (ddd, J = 4.4, 7.3, 7.3 Hz, 1H, H-7), 3.50 (dd, J = 3.9, 7.3 Hz, 1H, H-9), ∼2.7 (m, 3H, H-2, H-4, H-6a), 2.51 (dd, J = 4.4, 11.7 Hz, 1H, H-6b), 1.35 (dt, J = 2.9, 13.5, 1H, H-3eq), 1.07 (ddd, J = 11.7, 11.7, 13.5, 1H, H-3ax), 0.98 (d, J = 6.8 Hz, 3H, 2- or 4-CH_3), 0.97 (d, J = 6.4 Hz, 3H, 2- or 4-CH_3); ^{13}C NMR (D_2O, reference CH_3CN δ 1.39, at 90 °C) δ 75.2 (C-9a or C-8), 73.1 (C-9a or C-8), 72.2 (C-9), 70.8 (C-7), 56.6 (C-2 or C-4), 51.2 (C-2 or C-4), 44.8 (C-6), 37.3 (C-3), 21.4 and 19.1 (2- and 4-CH_3). **16**β: ^{1}H NMR (D_2O, reference CH_3CN δ 1.95, at 90 °C)[19] δ 3.85 (dd, J = 9.3, 10.3 Hz, 1H, H-9), 3.67 (ddd, J = 4.9, 9.3, 11.2 Hz, 1H, H-7), 3.44 (d, J = 10.3 Hz, 1H, H-9a), 3.21 (t, J = 9.3 Hz, 1H, H-8), 3.17 (dd, J = 4.9, 14.2 Hz, 1H, H-6eq), 2.90 (m, 2H, H-2 and 4), 2.29 (dd, J = 11.2, 14.2 Hz, 1H, H-6ax), 1.59 (dt, J = 2.9, 13.2 Hz, 1H, H-3eq), 0.96 (d, J = 6.0 Hz, 3H, 2- or 4-CH_3), 0.92 (d, J = 6.3 Hz, 3H, 2- or 4-CH_3), 0.86 (dt, J = 11.2, 13.2 Hz, 1H, H-3ax); ^{13}C NMR (D_2O, reference CH_3CN δ 1.39, at 90 °C) δ 79.6, 73.5, 67.3, 66.6, 49.8, 48.7, 44.1, 42.4, 21.6, 19.4. Anal. Calcd for $C_{10}H_{20}N_2O_3$: C, 55.53; H, 9.32; N, 12.95. Found: C, 55.53; H, 9.16; N, 12.79. **17**β: ^{1}H NMR (D_2O containing 1 drop of concentrated NH_4OH,[20] reference CH_3CN δ 1.94) δ 3.42 (ddd, J = 4.9, 9.3, 11.2 Hz, 1H, H-7), 3.20 (dd, J = 4.9, 11.2 Hz, 1H, H-6eq), 3.19 (t, J = 9.3 Hz, 1H, H-8), 3.03 (t, J = 9.3 Hz, 1H, H-9), 2.75 (d, J = 9.3 Hz, 1H, H-9a), 2.62 (m, J = 2.9, 6.4, 12.0 Hz, 1H, H-2), 2.20 (m, J = 2.9, 6.4, 12.0 Hz, 1H, H-4), 1.76 (t, J = 11.2 Hz, 1H, H-6ax), 1.58 (dt, J = 2.9, 14.6, 1H, H-3eq), 1.00 (d, J = 6.4 Hz, 3H, 4-CH_3), 0.95 (d, J = 6.4 Hz, 3H, 2-CH_3), 0.93 (dt, J = 12.0, 14.6 Hz, 1H, H-3ax);[21] ^{13}C NMR (75 MHz, D_2O containing 1 drop of concentrated NH_4OH, reference CH_3CN δ 1.39) δ 78.8 (C-9a), 77.3 (C-8), 74.2 (C-9), 69.3 (C-7), 57.7 (C-4), 52.6 (C-6), 50.0 (C-2), 41.8 (C-3), 21.1 (2-CH_3), 19.4 (4-CH_3). HRMS (CI): calcd for $C_{10}H_{20}N_2O_3$, 216.1469 (M), found 216.1463.

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Supporting Information Available: The curve-fitting results and the data for Figures 2 and 3 (PDF) and ^{1}H NMR spectra of compound **17**β. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Kent, P. W.; Young, R. C. *Tetrahedron* **1971**, *27*, 4057−4064.
(18) Hutchins, R. O.; Maryanoff, B. E. *J. Org. Chem*. **1972**, *37*, 1829−1830.
(19) A HETCOR experiment was run at room temperature and consequently cross-peaks were not observed in all cases owing to extreme broadness of ^{13}C NMR signals. In these cases, definitive assignments could not be made.
(20) Addition of a drop of concentrated NH_4OH caused a change in chemical shift, which separated some overlapping signals and allowed coupling constants to be determined.
(21) Coupling constants for this signal were obtained from a spectrum without NH_4OH added.