Stereoelectronic Control in Addition of Nucleophiles to an Amidinium Ion

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Abstract: Nucleophilic addition to 1,3-dimethyl-5-phenyl-1,4,5,6-tetrahydropyrimidinium ion provides a quantitative measure of stereoelectronic control. This amidinium ion presents the nucleophile with two distinct paths for attack. Axial attack is favored by interaction between the orbital of the developing bond and antiperiplanar lone pairs on the nitrogens. Reaction of the amidinium salt with diverse nucleophiles (D^-, H_3C^-, *n*-Bu^-, $PhCH_2^-$, allyl$^-$, Ph^-, $C_5F_6^-$, $CH_2{=}CH^-$, $HC{\equiv}C^-$, $PhC{\equiv}C^-$, CN^-) produces mixtures of *cis* and *trans* stereoisomers. Both kinetic and thermodynamic product distributions were measured by ^1H NMR, before and after acid-catalyzed equilibration. The values provide insight into the roles of steric and stereoelectronic forces at the transition state and in products. Stereoelectronic effects on reactivity are found to be weak (ca. 1 kcal/mol).

Introduction

Antiperiplanar Lone Pairs. Stereoelectronic control, arising from the positioning of lone pairs, is a topic of much current interest.[1] The aspect relevant to thermodynamic stabilities is known as the anomeric effect.[2] In connection with reactivity it was first applied at the acetal level of oxidation, where an antiperiplanar lone pair is expected to facilitate bond cleavage.[3] This preference, often called the antiperiplanar lone-pair hypothesis (ALPH) or the kinetic anomeric effect, is supported by calculations.[4] Yet experimental evidence is weak or elusive,[5] except that an orthogonal lone pair is indisputably less effective than a periplanar one.[6] The ALPH was extended to tetrahedral intermediates by Deslongchamps, who hypothesized that cleavage is favored by two lone pairs antiperiplanar to the leaving group.[3]

The role of antiperiplanar lone pairs is a fundamental aspect of the dependence of chemical reactivity on structural features. It is still an area of considerable uncertainty and controversy,[7] with wide acceptance[8] and only occasional skepticism.[9]

To what extent does an antiperiplanar lone pair facilitate cleavage of a tetrahedral intermediate? Early evidence came from hydrolysis of a cyclic hemiorthoester, which opens to hydroxy ester, rather than lactone.[10] Nevertheless, a serious inconsistency is that the five-membered-ring hemiorthoester also gives hydroxy ester, even though it ought to have cleaved to

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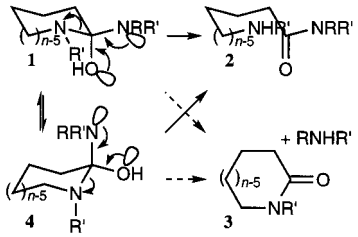
lactone. Therefore, it was proposed that the absence of lactones could be attributed to their destabilization, independently of ALPH.[11]

To reduce ambiguity, hydrolysis of cyclic amidines was studied. Reaction proceeds via a hemiorthoamide, with **1** as initial conformer. After rotation about the exocyclic C−N bond, two lone pairs are antiperiplanar to the endocyclic C−N, which can cleave to the aminoamide (**2**). Cleavage of the exocyclic C−N and formation of the lactam (**3**) could utilize an antiperiplanar lone pair on O but would require the *syn* lone pair on the ring N. Although ring inversion of **1** can produce conformer **4**, this too can cleave only the endocyclic C−N. Conformers that could cleave to the lactam are inaccessible because their formation requires nitrogen inversion, which is slow. Thus, if ALPH holds, aminoamide **2** (n = 5,6,7) is predicted to be the kinetic product. Yet when leaving abilities are balanced,[12] five- and seven-membered rings produce considerable lactam **3**, and even in six-membered rings stereoelectronic control is weak.[13] Similar results were obtained in hydrolysis of cyclic guanidines.[14]

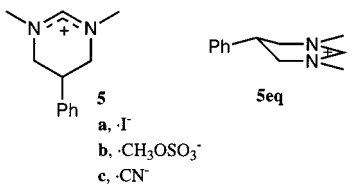


One explanation for these results is the involvement of a *syn* lone pair,[13] which is supported by some computations,[15] as well as by several other counterexamples to ALPH.[16] Although the proponents of ALPH have accepted synperiplanar lone pairs in some rigid acetals with obligatory eclipsing,[17] they reject a more general role for *syn* lone pairs in conformationally flexible systems or in tetrahedral intermediates.[18]

Much of the interest in ALPH is for purposes of synthesis, where it offers a novel method to control stereochemistry. Steric hindrance is the most common device for directing an incoming nucleophile along a path chosen to create a chiral center selectively. However, an alternative is to direct the nucleophile to a position antiperiplanar to a lone pair.[19] In some cases the high stereoselectivity observed (>99:1) implies a strong influence (>3 kcal/mol). It is important to understand the circumstances under which an antiperiplanar lone pair governs stereoselectivity.

Another System for Assessing ALPH. In the hydrolysis of cyclic amidines there are two possible steps where stereoelectronic control may operate. One is the cleavage of the hemiorthoamide intermediate. The other is the addition of hydroxide to form that intermediate. If cleavage is favored by two lone pairs antiperiplanar to the leaving group, then it follows from the principle of microscopic reversibility that addition is favored if the hydroxide enters antiperiplanar to the lone pairs. The counter-ALPH results could be due to the involvement of *syn* lone pairs in either step or in both. We have proposed that stereoelectronic control is reduced in the cleavage step because a lone pair on the oxyanion provides so strong a push that a *syn* lone pair on the nitrogen is adequate.[13] However, we would like to separate the two steps.

As part of an ongoing effort to assess ALPH, we here examine the stereochemistry of nucleophilic addition to an amidinium ion, 1,3-dimethyl-5-phenyl-1,4,5,6-tetrahydropyrimidinium ion (**5**). This study isolates the addition step and allows an independent assessment of its stereoselectivity. Moreover, in contrast to five- and seven-membered rings stereoelectronic control is expected to be stronger in this six-membered ring.



This amidinium ion is expected to adopt conformation **5-eq**, since the conjugated N−C−N system constrains the ring to a half-boat coplanar with both methyl groups, and since the phenyl will be preferentially pseudoequatorial, owing to steric effects. There are two possible addition paths, depending on whether the nucleophile enters *syn* or *anti* to the developing lone pairs on the nitrogens. According to ALPH, the latter path, leading to *cis* product, with the nucleophile axial, is favored by interactions between nitrogen lone pairs and the orbital of the incipient bond. The two transition states are shown in Figure 1. The product ratio then provides a measure of the relative stabilities of these two transition states, subject to the requirement that the products not interconvert under the reaction conditions.

A preference for *cis* product is counter-thermodynamic, since the axial substituent suffers destabilizing steric interactions. An independent experimental determination of the thermodynamics is available through equilibration and measurement of the *cis: trans* ratio.

Amidinium ion **5** can be reacted with a wide range of nucleophiles, but there are experimental constraints. One is that nucleophiles must be strong enough to form a covalent bond and not leave the amidinium ion as an ion pair. Even if a

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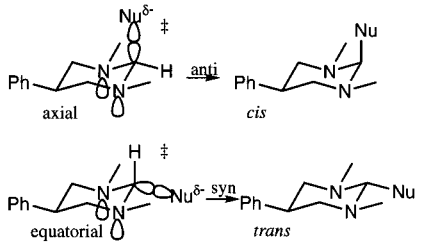
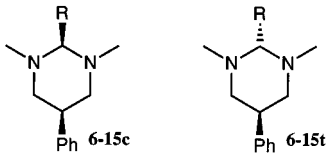


Figure 1. Transition states for axial or equatorial addition to **5**, *anti* or *syn* to N lone pairs.

covalent compound is formed, it may be in equilibrium with the ion pair, which permits interconversion of *cis* and *trans* and masks the kinetic product. Another constraint is that additional reactions must not intrude. Strong bases cannot be used, since they form an adduct that is exceedingly fragile,[20] or they deprotonate **5** at C2, giving the carbene, which dimerizes.[21] With some nucleophiles, such as hydroxide, the initial products are unstable tetrahedral intermediates that undergo rapid cleavage.[22] Nucleophiles that we have successfully reacted with **5** are $NaBD_4$, $LiAlD_4$, CH_3Li, *n*-BuLi, $PhCH_2MgCl$, $CH_2{=}CHCH_2$-MgCl, PhMgBr, C_6F_5MgCl, $CH_2{=}CHMgBr$, HC≡CMgBr, and PhC≡CMgBr, leading to products **6**−**15**.

Not only do these cyclic amidinium ions provide information about ALPH but they and their adducts are also of independent interest. Some 1,4,5,6-tetrahydropyrimidines show activity as neuromuscular blockers or antidepressant agents.[23] Imidazolinium ions are important precursors to carbenes.[20] Tetrahydropyrimidinium and imidazolinium salts have been treated with nucleophiles to create a wide variety of saturated heterocycles.[24] We now show that nucleophiles show a small but clear preference for addition antiperiplanar to the lone pairs on the two nitrogens of amidinium ion **5**. This is consistent with ALPH, whose influence though is weak.



6, R = D
7, R = CH_3
8, R = Bu
9, R = CH_2Ph
10, R = allyl

11, R = Ph
12, R = C_6F_5
13, R = $CH{=}CH_2$
14, R = C≡CH
15, R = C≡CPh

Experimental Section

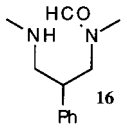
NMR Spectroscopy. All ^1H and ^{13}C NMR spectra were acquired on a Varian Unity 500, Varian Mercury 400, or Varian Mercury 300 spectrometer. Spectra were taken in benzene-d_6, chloroform-*d*, dimethyl sulfoxide-d_6, or DMF-d_7. NOE and COSY experiments were performed using the default sequence of the Varian software.

Integrations from ^1H NMR spectra were used to evaluate product ratios. If signals from *cis* and *trans* stereoisomers overlapped, other well-resolved signals were integrated to determine individual contributions to the total.

Synthesis. The synthesis of 5-phenyl-1,4,5,6-tetrahydropyrimidine was adapted from a published procedure starting from phenylacetonitrile and formamide.[25] The resulting 4-amino-5-phenylpyrimidine (mp 154.5−155.5 °C) was hydrolyzed to 5-phenyl-4-pyrimidinone: mp 176−177 °C (lit. mp 173−174 °C), ^1H NMR (DMSO) δ 7.37−7.45 (m, 3H), 7.71−7.73 (m, 2H), 8.17 (s, 1H), 8.21 (s, 1H). This was converted with $POCl_3$ to 4-chloro-5-phenylpyrimidine: mp 73−74 °C (lit. mp 71−72 °C), ^1H NMR (DMSO) 7.53−7.60 (m, 5H), 8.87 (s, 1H), 9.08 (s, 1H). Hydrogenation over 5% Pd/C converted this to the tetrahydropyrimidine hydrochloride: mp 165−168 °C, ^1H NMR (DMSO) δ 3.13 (sept, J = 5 Hz, 1H), 3.44 (t, J = 12 Hz, 2H), 3.52 (dd, J = 12, 5 Hz, 2H), 7.32−7.41 (m, 5H), 8.29 (s, 1H), 10.20−10.40 (bs, 1H).

Conversion to 1,3-dimethyl-5-phenyl-1,4,5,6-tetrahydropyrimidinium salts could be accomplished by using 2 equiv of NaH and slightly more than 2 equiv of methylating agent in dry THF, either methyl iodide at 0 °C for 1 h, then at room temperature for 1 h or dimethyl sulfate at 40 °C for 1 h. The mixture was filtered, and the resulting solid was taken up in dry CH_2Cl_2. The amidinium iodide **5a** was purified by recrystallization from dry CH_2Cl_2:THF (2:1). A colorless, hygroscopic solid was obtained in 35% yield: ^1H NMR (DMSO) δ 3.20 (s, 6H), 3.35 (m, 1H), 3.50 (m, 4H), 7.35−7.45 (m, 5H), 8.45 (s, 1H), ^{13}C NMR (DMSO) δ 152.8, 137.9, 128.9, 127.8, 127.7, 49.1, 41.1, 34.2. The amidinium methosulfate **5b** was obtained in 42% yield as an amorphous, hygroscopic solid: ^1H NMR (DMSO) δ 3.20 (s, 6H), 3.40 (s, 3H), 3.40−3.50 (m, 5H), 7.20−7.45 (m, 5H), 8.20 (s, 1H).

Addition of Nucleophiles. A sample of amidinium iodide **5a** was treated with excess 0.1 M NaOH. The reaction mixture was extracted with methylene chloride, dried, and concentrated under vacuum, yielding a colorless oil. The ring-opened aminoformamide (**16**) is the only product, obtained in 62% yield. It exists as a 2:1 mixture of amide stereoisomers: ^1H NMR (DMSO) δ 2.22 and 2.25 (s, 3H), 2.65 (m, 2H), 2.65 and 2.71 (s, 3H), 3.08 (m, 1H), 3.2−3.6 (m, 2H), 7.2−7.4 (m, 5H), 7.7 and 7.9 (s, 1H), ^{13}C NMR (DMSO) δ 163.8, 142.9, 129.9, 129.4, 128.1, 56.5, 54.0, 45.2, 38.0, 31.0 (major stereoisomer), δ 164.0, 143.1, 129.8, 129.6, 128.0, 56.9, 48.7, 44.4, 36.2 (minor stereoisomer).



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Reductions of amidinium salt **5a** were carried out at 0 °C with 3 equiv of $NaBD_4$ in methanol or with equimolar $LiAlD_4$ in dry THF. After 2 min the solution was shaken with saturated sodium carbonate and methylene chloride, and the organic layer was washed twice with water and dried. The solvent was removed under vacuum, and the residue was taken up in an NMR solvent.

For addition of RMgBr or RLi two different procedures were utilized, either to preserve kinetic product mixtures or to allow equilibration. For preservation extreme care was taken to exclude trace acid or water. Acid-free NMR solvents were prepared by adding 0.1 μg/mL 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU). All glassware was either flame-dried or rinsed with this solvent. To a dry sample of the amidinium ion **5** under dry N_2 were added dry reaction solvent and excess organometallic reagent. The mixture was stirred for a period of time ranging from two minutes to several hours. Solvents were then removed under vacuum. Acid-free NMR solvent was added to the reaction flask

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Table 1. ^{1}H NMR Data for *cis* and *trans* Hexahydropyrimidines **6**−**15**

assignment	**6c**	**7c**	**8c**	**9c**	**10c**
H2	3.30 (bs)	3.42 (q J = 6)	2.77 (t J = 6)	3.53 (t J = 6)	3.33 (t J = 6)
H4,6$_c$ (t J = 12 Hz)	1.84	2.86	2.90	2.98	2.85
H4,6$_t$ (dd J = 12,4 Hz)	2.74	2.58	2.71	2.64	2.59
H5 (tt J = 12,4 Hz)	3.20	3.29	3.31	3.27	3.24
N-CH$_3$ (s)	1.97	2.32	2.50	2.37	2.37
Ph (m)	7.2−7.4	7−7.2	7.2−7.4	7−7.4	7−7.2
other		1.09 (d)	1.7 (m), 1.3−1.5 (m), 0.94 (t)	2.84 (d)	*b*
	6t	**7t**	**8t**	**9t**	**10t**
H2	2.17 (bs)	2.87 (q J = 6)	2.42 (t J = 6)	3.21 (t J = 6)	2.81 (t J = 6)
H4,6$_c$ (dd J = 12,4 Hz)	2.74[a]	2.94	3.08	2.92	2.92
H4,6$_t$ (t J = 12 Hz)	1.82	2.48	2.55	2.49	2.45
H5 (tt J = 12,4 Hz)	3.20[a]	3.29	3.29	3.27	3.28
N-CH$_3$ (s)	1.96	2.10	2.32	2.21	2.18
Ph (m)	7.2−7.4	7−7.2	7.2−7.4	7−7.4	7−7.2
other		1.17 (d)	1.62 (m), 1.3−1.5 (m), 0.94 (t)	2.84 (d)	2.32 (tt), 5.13 (m), 6.08 (m)

assignment	**11c**	**12c**[d]	**13c**	**14c**	**15c**
H2	2.86 s		2.58 (d J = 4)	4.23 (s)	4.51 (s)[c]
H4,6$_c$ (t J = 12 Hz)	3.00 (dd J = 12,1)		2.82	2.73	2.88
H4,6$_t$ (dd J = 12,4 Hz)	2.36		2.72	2.63	2.72
H5 (tt J = 12,4 Hz)	2.68 (m)		3.34	3.23	3.32
N-CH$_3$ (s)	1.77		2.34	2.27	2.37
Ph (m)	7−7.6, 8.6		7−7.2	7−7.2	7−7.5
other			5.99[b]		
	11t	**12t**	**13t**	**14t**[d]	**15t**[d]
H2	2.92 (s)	3.72 s	2.66 (d J = 4)		
H4,6$_c$ (dd J = 12,4 Hz)	3.04	3.25	3.11		
H4,6$_t$ (t J = 12 Hz)	2.20	2.33	2.28		
H5 (tt J = 12,4 Hz)	3.48	3.34	3.34		
N-CH$_3$ (s)	1.88	2.14	2.25		
Ph (m)	7−7.6, 8.6	7.2−7.4	7−7.2		
other			5.87 (ddd J = 12,8,4), 5.17 (dd J = 12,2), 5.08 (dd J = 8,2)		

[a] Indistinguishable from **6c**. [b] Peak overlap precluded identification. [c] $^1J_{CH}$ = 153 Hz. [d] Not observed.

and stirred briefly. The resulting mixture was filtered through cotton into an NMR tube. Each experiment was repeated several times, and kinetic ratios were taken from samples with the highest proportion of the less stable stereoisomer. Alternatively, the mixture was treated with saturated aqueous NaCl solution and extracted with cyclohexane. The organic extract was washed several times with water and then dried. Solvent was removed under vacuum, and the residue was dissolved in an NMR solvent.

Additions of lithium acetylide or lithium phenylacetylide (excess) were also carried out in DMSO-d_6 and dried over 4 Å molecular sieves. Volatiles were removed under vacuum prior to NMR analysis. Kinetic product mixtures were obtained with acid-free solvents and glassware.

Tetrabutylammonium cyanide (0.1−10 equiv) was added to amidinium iodide **5a** in an appropriate NMR solvent. The resulting mixture was filtered through cotton and transferred to an NMR tube.

Equilibration of Hexahydropyrimidines. Conversion of kinetic product mixtures to thermodynamic mixtures was carried out with acetic acid or phenol and monitored by ^{1}H NMR. Samples that contained an unknown excess of DBU were first titrated with small quantities of acid until the start of stereoisomerization was detected, and then they were allowed to equilibrate for days.

Reductive Trapping of Iminium Ion Intermediates. Approximately 50 mg of hexahydropyrimidine was dissolved in 4 mL of acetonitrile/acetic acid (1:1) and stirred overnight with 3 equiv of $NaBH_3CN$ at 50 °C.[26] The resulting solution was neutralized with Na_2CO_3, extracted into $CHCl_3$, washed with saturated NaCl, and concentrated under vacuum.

Nucleophile Exchange. A sample of the 2-pentafluorophenyl hexahydropyrimidine (**12**) in benzene-d_6 was stirred briefly with excess lithium phenylacetylide. Solvent was removed under vacuum prior to NMR analysis. Decomposition of 2-pentafluorophenyl-2-propanol[27] (δ 1.73, t, J = 2 Hz) in DMSO-d_6 containing NaOD was followed by ^{1}H NMR at room temperature.

Molecular-Mechanics Calculations. Energies of the stereoisomers of $PhCH{=}NHCH_3^+$ were calculated with MM2 parametrization (CS Chem3D Pro 4.0).[28]

Results

Unsuccessful Reactions. *tert*-Butyl- and isopropyl-magnesium bromides produced complex mixtures in low yield. It is likely that these bulky reagents act as bases rather than nucleophiles. Reductions with milder reducing agents sodium cyanoborohydride and diisobutylaluminum hydride, even at high temperature, left amidinium salts unreacted. The addition of excess weak nucleophiles sodium azide or tetrabutylammonium fluoride to **5** in various organic solvents had no appreciable effect on the ^{1}H NMR spectrum.

Signal Assignments. Tables 1−2 list the ^{1}H and ^{13}C chemical shifts for *cis* and *trans* products **6**−**15**. Peak assignments for each stereoisomer were made on the basis of H−H couplings

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Table 2. ^{13}C NMR Data for *cis* and *trans* Hexahydropyrimidines **6**−**15**

assignment	**6c**	**7c**	**8c**	**9c**	**10c**
C2	77.5 t	*a*	79.5	80.1	80.0
C4,6	59.8	52.0	52.7	51.6	53.2
C5	37.8	37.0	35.5	34.8	42.5
N-CH_3	42.2	41.9	42.2	41.4	37.2
Ph	128.1, 127.2, 126.2	*a*	*a*	127.8, 127.2, 126.9, 126.0, 125.3, 124.4	128.3, 127.5, 126.3
ipso	141.8	*a*	*a*	140.8, 139.5	142.5
other	*a*	*a*	30.1, 26.8, 22.9, 14.2	27.1	136.6, 115.0, 35.8

	6t[b]	**7t**	**8t**	**9t**	**10t**
C2		78.6[c]	83.0	82.4	82.5
C4,6		62.1	62.5	61.5	62.9
C5		36.9	36.9	36.2	42.3
N-CH_3		39.1	38.9	38.1	38.8
Ph		128.1, 127.5, 126.8	128.2, 127.1, 126.9	127.6, 127.2, 127.0, 126.0, 125.3, 124.8	127.9, 127.9, 126.4
ipso		141.2	141.5	140.2, 137.6	142.1
other		18.7	29.9, 26.9, 23.1, 14.1	35.3	135.6, 115.2, 35.4

assignment	**11c**	**13c**	**14c**	**15c**
C2	84.0	82.0	73.6	73.9
C4,6	53.0	53.1	54.3	54.0
C5	40.1	38.4	40.6	40.1
N-CH_3	44.1	40.9	41.7	41.9
Ph	*a*	127.0, 126.0, 125.2	127.8, 127.6, 127.2	131.6, 128.2, 128.0, 127.9, 127.3, 126.4
ipso	*a*	*a*	142.0	141.4
other		119.1[a]	73.8, 76.7	89.9, 81.0

	11t	**13t**	**14t**[d]	**15t**[d]
C2	91.6	88.5		
C4,6	62.0	60.3		
C5	41.0	39.2		
N-CH_3	42.8	41.2		
Ph	128.3, 128.2, 128.1, 128.0, 127.1, 127.1	127.1, 126.3, 125.4		
ipso	141.4, 140.6	140.3		
other		137.5, 118.8		

[a] Peak overlap precluded identification. [b] Indistinguishable from **6c**. [c] $^1J_{CH}$ = 136 Hz. [d] Not detected.

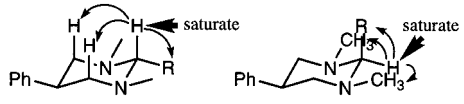

Figure 2. Observed NOE enhancements.

and by analogy to other hexahydropyrimidines in this study. Labels H4,6$_c$ and H4,6$_t$ designate *cis* or *trans* to the substituent at C2.

Stereoisomer assignments were made with NOE experiments. Observed enhancements for a typical set of hexahydropyrimidines are shown in Figure 2. Only with *trans* hexahydropyrimidines **6**−**13t** are NOEs observed between H2 and H4,6. The acetylenyl-substituted hexahydropyrimidine stereoisomers **14c**,**15c** were assigned from a 1−2 Hz W-coupling between H2 and H4,6$_t$,[29] detected by 2D COSY. The *cis* stereochemistry for **15c** is consistent with $^1J_{CH}$ = 153 Hz, higher than the 136 Hz in **7t**, where the CH is antiperiplanar to the lone pairs.[30]

The data in Tables 1−2 provide insight into the conformations of 2-substituted hexahydropyrimidines. Signals for substituents antiperiplanar to a nitrogen lone pair are shifted upfield. This is clearly the case with CHD isotopomers **6c** and **6t**. Moreover, H4,6$_t$ signals in *trans* isomers are always upfield of the corresponding H4,6$_c$ signals in the *cis*. This indicates that nitrogen lone pairs are less often axial in *cis* isomers, where the *N*-methyl can avoid gauche interactions by being axial. Similarly, the *N*-methyl is generally downfield in the *cis* isomers, because it is axial, which also generally leaves the *N*-methyl ^{13}C signal upfield in the *trans* isomers, owing to a γ-gauche interaction with the 2-substituent. These results are consistent with previous ones on some conformationally flexible hexahydropyrimidines.[31]

A further observation concerns the 2-phenyl-substituted *cis* isomer (**11c**), which shows only a 1-Hz coupling between H5 and H4,6$_c$, not the usual 12 Hz. Apparently this exists chiefly

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Table 3. Product Distributions from Addition of Nucleophiles to **5a**

nucleophile	solvent	% *cis* (kinetic)	% *cis* (equil)
$NaBD_4$	CH_3OH	88	50
$LiAlD_4$	THF	90	50
CH_3Li	DME	65	15
n-BuLi	DME	75	17
n-BuLi	DME[a]	75	17
n-BuLi	benzene	75	17
n-BuLi	THF	75	17
n-BuLi	DME[a]	75	17
$PhCH_2MgCl$	DME	65	35
$PhCH_2MgCl$	DME[b]	65	35
$PhCH_2MgCl$	DME[a]	65	35
$CH_2{=}CHCH_2MgCl$	DME	60	25
PhMgBr	DME[a,b]	80	<2
C_6F_5MgCl	DME	<2	<2
$CH_2{=}CHMgBr$	DME	15	15
HC≡CMgBr	DMSO	>98	>98
PhC≡CMgBr	DMSO	>98	>98
PhC≡CMgBr	DME	>98	>98
PhC≡CMgBr	DMSO[a]	>98	>98
PhC≡CMgBr	DMSO[c]	>98	>98

[a] **5b**. [b] With 0.5 equiv of tetramethylethylenediamine (TMEDA). [c] **5c**.

as the conformer where the C5 phenyl is axial, allowing the C2 phenyl to be equatorial. This is the opposite sense of ring inversion from the other 5-phenylhexahydropyrimidines because repulsions between the 5-phenyl and H4,6 or lone pairs are less severe than between the 2-phenyl and the *N*-methyls.

Tetrabutylammonium Cyanide Additions. Amidinium salt **5a** is soluble in polar solvents DMSO, acetonitrile, and DMF, slightly soluble in CH_2Cl_2 and $CHCl_3$, and insoluble in pyridine or THF. It readily dissolves in all of these solvents upon addition of tetrabutylammonium cyanide. We attribute this increased solubility in nonpolar solvents to a replacement of iodide by cyanide, which can form a covalent adduct.

The resulting species **5c** is a mixture of ionic and covalent forms. The existence of an equilibrium between them was detected by ^{1}H NMR in a number of solvents. The chemical shift of H2 responds to the change in hybridization at C2. The most drastic change was observed in DMF-d_7. Upon addition of 1 equiv of cyanide, the signal shifts from δ 8.6 to δ 6.8 and broadens. Addition of excess cyanide narrows the signal somewhat, with a further upfield shift to δ 5.5, aproaching the δ 4.2 or 4.5 of covalent acetylene adducts **14**−**15**. The spectral data for this sample are: ^{1}H NMR (DMF) δ 7.2−7.4 (m, 5H), 5.5 (bs, 1H, $^1J_{CH}$ = 164 Hz), 3.15 (tt, J = 12, 4 Hz, 1H), 3.00 (dd, J = 12, 4 Hz, 2H), 2.58 (t, J = 12 Hz, 2H), 2.54 (s, 6H). The resolution of H4,6$_c$ from H4,6$_t$ is like that of other covalent adducts in Tables 1−2, but the chemical shifts do not permit assignment as *cis* or *trans*.

The greater solubility of amidinium cyanide **5c** permits its application to addition reactions with nucleophiles, in the same manner as iodide or methosulfate salts (**5a**,**b**). Products and product distributions were identical in all cases tested. The exclusion of water from solvents containing **5c** made it easier to avoid hydrolysis to aminoamide (**16**).

Product Ratios. The results from ^{1}H NMR integrations are listed in Table 3. For most of these nucleophiles the kinetic product mixture contained mostly *cis* isomer, whereas thermodynamic mixtures were mostly *trans*. Exceptions are pentafluorophenyl- and vinyl-magnesium bromide and lithium acetylide and phenylacetylide, each of which produced a constant product mixture that did not show stereoisomerization.

Product Stability. Adducts **6**−**15** are generally stable to neutral or basic conditions, including aqueous alkali. Kinetic products could be maintained for days in organic solvents with an excess of DBU. Stereoisomerization of most samples occurred cleanly in the presence of trace acid. No other products were observed, except with the vinyl and allyl derivatives, which decomposed over several hours.

Rates of product stereoisomerization depend on the substituent at C2. In the presence of acetic acid kinetic mixtures of **6c** and **6t** established equilibrium after several days. In contrast, conversion of **7**−**11c** to **7**−**11t** occurred under these conditions before the sample could be introduced into the NMR spectrometer.

Rates of phenol-catalyzed stereoisomerization were assayed by NMR in an attempt to assess the effect of 2-substitution. Exact rate constants could not be obtained because the unknown amount of DBU neutralizes the added acid and renders its concentration uncertain. To restrict these stereoisomerization experiments to a narrow range of acidities, the samples were titrated with small aliquots of acid until stereoisomerization commenced. The time required for equilibration of any particular hexahydropyrimidine was then reproducible within a factor of 2. Alkyl and aryl hexahydropyrimidines **8**−**11** equilibrated in approximately 1 h, the same for all four species. In contrast, equilibration of **6** required >1 month.

The acid-catalyzed stereoisomerization is likely to occur by reversible ring-opening to an iminium ion (**17** in Figure 3). This intermediate could be trapped in mild acid with $NaBH_3CN$, as with some similar heterocycles.[26] The ^{1}H NMR data for the products (**18**, R = $PhCH_2$ or CCPh) from reduction of benzyl- and phenylacetylenyl-substituted hexahydropyrimidines (**9**,**15**) are given in Table 4.

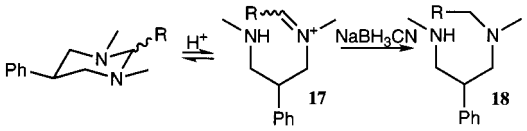


Figure 3. Stereoisomerization of hexahydropyrimidines and trapping of the intermediate (**17**).

Table 4. NMR Data for Products from Reduction of Iminium Ions **16**

assignment	**18**, R = $PhCH_2$	**18**, R = CCPh
CH_2Nu	3.42 (d J = 16 Hz), 3.58 (d J = 16 Hz)	3.56 (bs)
N-CH_3	2.29, 2.40	2.38, 2.39
CH_2N (m)	2.52, 2.74	2.98
CH_2NH (m)	2.82, 2.91	2.76
CH (m)	3.24	3.11

The *cis* pentafluorophenyl adduct could never be detected. With careful workup the *trans* adduct **12t** was obtained, but this was hydrolyzed to **16** within several hours, even in the presence of drying agents Na_2SO_4 or $MgSO_4$. This reactivity is surprising. It is quite similar to that of the ionic amidinium iodide **5a** or the weakly covalent cyanide **5c**, each of which undergoes exchange with nucleophiles such as cyanide or hydroxide. It is most unlikely that hydroxide or water is capable of S_N2 displacement of pentafluorophenyl anion at a tertiary center. It is more likely that hydrolysis occurs by reversion of **12** to **5**, the common cationic intermediate in all of these substitutions. The reversion must be reversible, allowing for the rapid stereoisomerization of **12c** to **12t** (Figure 4). When **12** was allowed to react with lithium phenylacetylide, adduct **15** was produced, with a ^{1}H NMR spectrum matching that of **15** created directly from **5**.

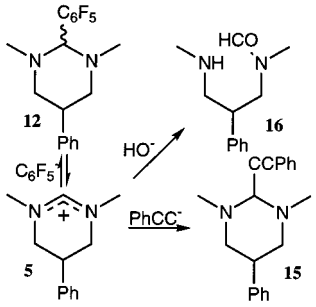


Figure 4. Trapping of amidinium ion **5**.

Discussion

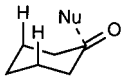
Product Distributions. The data in Table 3 show different kinetic and thermodynamic product mixtures for nucleophiles D^-, Me^-, *n*-Bu^-, $PhCH_2^-$, $allyl^-$, and Ph^-. Kinetics favors formation of the less stable *cis* isomer, which is converted to *trans* upon equilibration. These results are consistent with ALPH. However, there are cases where kinetic mixtures cannot be distinguished from thermodynamic. For some nucleophiles the major product is always *cis* (HCC^-, $PhCC^-$) or always *trans* ($C_6F_5^-$), or an unchanging mixture of the two ($H_2C{=}CH^-$), or else a product of indeterminate stereochemistry (CN^-). Such behavior could arise if the kinetic mixture is identical with the thermodynamic or if the kinetic product quickly stereoisomerizes to the thermodynamic. If the latter, the observed products do not reflect stereoelectronic control.

This ambiguity can be resolved by considering two mechanisms for stereoisomerization, reversible dissociation of the nucleophile and reversible ring opening. The amidinium ion (**5**) forms covalent adducts with CN^- and $C_6F_5^-$, but both nucleophiles can then be replaced by others (HO^-, $PhCC^-$). Thus, there must be a rapid equilibrium between covalent and ionic forms, as is also consistent with the variation of chemical shift of **5c** with the concentration of cyanide. This interconversion then provides a mechanism for rapid stereoisomerization, and the exclusively *trans* product **12t** from $C_6F_5^-$ must be the equilibrium mixture.

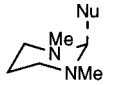
Acid-catalyzed stereoisomerization of hexahydropyrimidines **6**−**11** does convert kinetic product mixtures into thermodynamic ones, whereas these are stable in base. These are in equilibrium with open-chain iminium ions (**17**),[26,32] which could be trapped with $NaBH_3CN$. Reversal of the ring opening then allows for stereoisomerization. Since iminium ion **17** (R = CCPh) could also be trapped, this mechanism, catalyzed by unknown acid, is probably responsible for stereoisomerizations of **13**−**15**, whose observed product distributions are equilibrium values. The reason this is so rapid is addressed below.

In contrast to the nucleophiles where equilibration is rapid, with D^-, Me^-, *n*-Bu^-, $PhCH_2^-$, $allyl^-$, and Ph^- stereoisomerization could be made slow enough that initial products are kinetically determined. The predominance of the *cis* isomer in the kinetic products in Table 3 is consistent with ALPH.

The aggregation state of the nucleophile, as moderated by solvent or added TMEDA, has no appreciable effect on product distribution. Nor does the counterion of the amidinium salt, whether iodide or methosulfate. There is little variation with the size of the nucleophile, although the smallest nucleophile, D^-, gives the largest percent of axial substitution. This parallels the stereoselectivity in reactions of cyclohexanones, where axial approach of bulky nucleophiles is hindered.[33] However, addition to ketones is not a good model, since approach is at an angle of ca. 110° to the C−O,[34] passing near H3,5 (**19**), whereas approach to an amidinium ion is more external (**20**). This is a distinction between inter-exo-trig and inter-endo-trig, analogous to Baldwin's rules for ring-closure.[35] Therefore, steric effects on the kinetic product distributions in Table 3 are minimal.



19



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Rates of Stereoisomerization. The rates of hexahydropyrimidine stereoisomerization are interesting in their own right, since two mechanisms operate, depending on substituent. The variation of ring-opening rates can be attributed to the ability of substituents R to stabilize the positive charge in **17**. The greater reactivity of substituted hexahydropyrimidines **7**−**11**, relative to the parent **6**, is analogous to substituent effects on rates of hydrolysis of 1,3-dioxolanes and on ring-chain equilibria in some tetrahydropyrimidines.[36] The rapid stereoisomerization of **13**−**15**, even in the absence of added acid, then must be due to further stabilization of **17** by conjugation with $CH{=}CH_2$, C≡CH, or C≡CPh. Yet the rate of ring-opening stereoisomerization for **11** is comparable to that of alkyl derivatives (**8**−**10**) and thus low enough to permit isolation of the kinetic mixture, even though the phenyl substituent ought to stabilize **17** as vinyl and acetylenyl do. The reason it does not is that conjugation between phenyl and $C{=}N^+$ induces steric crowding between an ortho hydrogen and the *cis* methyl or alkyl. Indeed, a molecular mechanics calculation indicates that the *trans* isomer of $PhCH{=}NHCH_3^+$ is 5 kcal/mol more stable than the *cis*. Stabilization by phenyl is variable, since it does accelerate stereoisomerization ca. 10^3-fold, relative to D, whereas no such effect was observed with 1,3-imidazolidines.[37]

As for the other mechanism, it is not surprising that CN^- binds only weakly to the amidinium ion, since it is the least basic nucleophile studied ($pK_a^{HCN} = 9.2$, $pK_a^{C_6F_5H} = 25$, $pK_a^{RCCH} = 24$ or 25.2).[38] When a solution of **5c** is washed with water, it reverts to the ion and is hydrolyzed. The pentafluorophenyl adduct is covalent, as expected and as demonstrated by its stability to aqueous workup, but it does slowly undergo dissociation to an ion pair, allowing stereoisomerization or capture by water or PhCCLi. Yet the acetylenyl adducts do not hydrolyze in base, even though the leaving abilities are comparable. It is likely that the leaving ability of $C_6F_5^-$ is enhanced by relief of steric repulsions, whereas that of the acetylides is reduced by the strength of the sp−sp^3 C−C bond. Neither of these features is reflected in the pK_a's.

The ease of dissociation of $C_6F_5^-$ from a neutral molecule is surprising, but not unreasonable in light of the electron-withdrawing fluorines. Carbanions are known to dissociate from

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highly substituted tertiary alkoxides.[39] As evidence that $C_6F_5^-$ can dissociate even from a simple alkoxide, we find that base converts 2-pentafluorophenyl-2-propanol to acetone partially within 10 min and completely within 24 h.

Thermodynamic Product Ratios. The product distributions, after equilibration, are listed in Table 3. The 50:50 mixture for **6** is evidence that the CHD group has equilibrated. Impurities precluded accurate integration that might have indicated a greater proportion of equatorial D.[40]

For the other groups the more stable product stereoisomer is the *trans*, except for the acetylenes. This preference is quite large for phenyl and pentafluorophenyl, as expected from the steric repulsions with an axial aryl. These are so large that the phenyl-substituted *cis* isomer (**11c**) exists chiefly as the ring-inverted conformer, with the C5 phenyl axial. For alkyl groups the equatorial preference is small, with a ratio ranging from 2:1 to 6:1, appreciably less than in cyclohexanes.[41] This is because of repulsion between an equatorial alkyl and one *N*-methyl that is predominantly axial.[31]

It is remarkable that the acetylenes strongly favor the *cis* isomer, with C≡CR axial, contrary to the behavior in cyclohexanes. This is likely to be an anomeric effect, analogous to the 2 kcal/mol preference in 2-cyanopiperidine.[42] It also requires that the 5-phenyl greatly favors equatorial.

Contribution of Stereoelectronic Control. With nucleophiles D^-, Me^-, *n*-Bu^-, $PhCH_2^-$, $allyl^-$, and Ph^- products are stable enough that the kinetic mixtures provide a measure of stereoelectronic control. The excess of *cis* product is good evidence that the nucleophile prefers to add antiperiplanar to the lone pairs on the two nitrogens. This excess is opposite to that seen in the equilibrium mixture, which is governed by steric effects. However, in the transition state steric effects are minimal, owing to a trajectory (**20**) that avoids axial hydrogens. Yet the influence of stereoelectronic control is also minimal. The *anti* preference, varying from 60 to 90%, corresponds to a free-energy difference of ca. 1 kcal/mol. Even in the most selective case, reaction of $LiAlD_4$ or $NaBD_4$, the preference is only 1.3 kcal/mol.

An alternative measure of stereoelectronic control might be the excess of the kinetic preference for *cis* over the thermodynamic, since stereoelectronic control must overcome the preference for *trans*. This excess varies from 0.75 to 1.6 kcal/mol, except for R = Ph (**11**), where it is >3 kcal/mol. This exception shows that such a correction is not warranted, since the contribution of stereoelectronic control ought not increase with the steric bulk of the nucleophile. Steric interactions are not comparable in the products, because the conformations are different, one of the *N*-methyls being predominantly axial. In the transition state both are equatorial to allow the nucleophile to add antiperiplanar to the lone pairs, and those might even have been expected to hinder equatorial approach. Nevertheless, axial approach is not strongly favored.

We had proposed that stereoelectronic control is reduced in the cleavage step of amidine hydrolysis, rather than in the addition of hydroxide.[13] Now that the two steps can be separated, it becomes clear that addition does not show strong stereoelectronic control. The nucleophiles here may not be comparable to hydroxide in the amidine reactions, and it is unfortunate that alkoxide addition could not be studied. The weakness of stereoelectronic control in the addition step can be attributed to a transition state that is early along the reaction coordinate, with little interaction between the lone pair and the bond that is forming, whose stereochemistry then does not matter. This reverses the argument from the earlier proposal, where the transition state was assumed to be early for the cleavage. Such an assumption can always be made, but it weakens ALPH by reducing its predictive power.

Conclusions

Kinetic products from reaction of nucleophiles D^-, Me^-, *n*-Bu^-, $PhCH_2^-$, $allyl^-$, and Ph^- with amidinium ion **5** show a clear preference for addition antiperiplanar to the lone pairs on the two nitrogens. This is counter to the thermodynamic preference and is good evidence for stereoelectronic control. However, its influence is weak, contributing ca. 1 kcal/mol.

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