Mechanistic Evaluation of the Halocyclization of 4-Penten-1-ol by Some Bis(2-substituted pyridine) and Bis(2,6-disubstituted pyridine)bromonium Triflates

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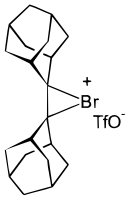
Received March 24, 2000

The halocyclization reaction of 4-penten-1-ol mediated by various bis(2-substituted pyridine) and (2,6- disubstituted pyridine)bromonium triflates ($P_2Br^+OTf^-$) was investigated to determine the influence of the substituents on the mechanism of reaction. In all cases, the reaction proceeds via a two-step process where the starting P_2Br^+ reversibly dissociates to a reactive monosubstituted PBr^+, which then is captured by 4-penten-1-ol to form halocyclized product (2-bromomethyltetrahydrofuran). The dissociation rate constant of P_2Br^+ (k_d) is sensitive to the steric bulk at the 2- and 6-positions, and in the case of the 2,6-dicyclohexylpyridine or 2,6-dicyclopentylpyridine, the P_2Br^+ species are too unstable to isolate. The partitioning ratio of the reactive intermediate (PBr^+) between reversal and product formation (k_{-d}/k_2) is not particularly sensitive to the nature of the pyridine, the limiting values being 3−7 except in the case of bis(2(−)-menthylpyridine)bromonium triflate where the k_{-d}/k_2 ratio is ∼80. The reaction of 4-penten-1-ol and its OD isotopomer with bis(lutidine)bromonium triflate was investigated to determine the deuterium kinetic isotope effect (dkie) on the bromocyclization reaction. The $(k_{-d}/k_2)^{H/D}$ ratio is 1.0, indicating that the rate-limiting step for the bromocyclization is probably formation of a PBr^+−4-penten-1-ol complex which does not involve substantial changes in the bonding of the OH. The cyclization of 4-penten-1-ol and 4-pentenoic acid mediated by bis(2(−)-menthylpyridine)bromonium triflate produces an enantiomeric excess in the cyclized products of only 2.4% and 4.8% respectively.

Introduction

In recent reports from these laboratories, we have described mechanistic details of Br^+-transfer from the bromonium triflate of adamantylideneadamantane (Ad = Ad-Br^+, **1**)[1] and bis(*sym*-collidine)bromonium triflate (**2**)[2] to acceptor alkenes. Bis(collidine) halonium species



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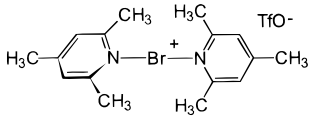

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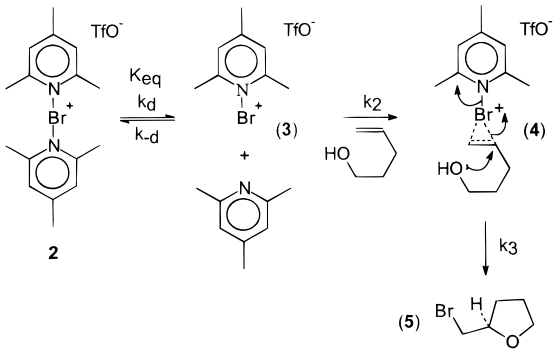
have been used as sources of electrophilic halogen to effect a variety of halocyclization reactions of 1,ω-alkenoic acids and amides[3] and various alkenols.[3a,d] For the latter process with 4-penten-1-ol, it has been established that

Scheme 1



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the mechanism proceeds as in Scheme 1, where dissociation of one collidine from **2** yields a reversibly formed bromocollidinium ion (**3**) which is subsequently captured by the alkene leading to cyclized products.[2] There are mechanistic uncertainties remaining for this reaction, namely which of step 2 or 3 is rate-limiting and whether the bromocollidinium−alkenol species (**4**) is better described as a π-complex[4] or a bromonium ion complexed to the amine. Existing ^{13}C NMR evidence for the bromocollidinum−Ad═Ad system certainly favors the latter.[2]

The fact that the mechanism of these halocyclizations proceeds through complexes such as **4** suggests that it may be possible to transfer stereochemical information from some chiral pyridine analogue to the cyclized

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10.1021/jo000449a CCC: $19.00
Published on Web 08/12/2000

products. One of the simplest approaches involves cyclization reactions initiated by bromonium or iodonium complexes of pyridines having chiral groups at the 2 and/or 6 position. Herein we describe the syntheses of some simple 2-substituted and 2,6-disubstituted pyridine derivatives (**6**−**10**) and the kinetics of the reaction of their bromonium ions with 4-penten-1-ol. In particular, we are interested in the effects of the substituents on the kinetics of the reaction and whether there is a deuterium kinetic isotope effect (dkie) on the cyclization reaction with 4-penten-1-ol-OD. In the case of the bromonium ion of 2-(−)-menthylpyridine, we describe the preliminary results of its effectiveness in promoting asymmetric cyclizations of 4-penten-1-ol and 4-pentenoic acid.

Experimental Section

Materials and Methods. Dichloromethane and hexane were purified as described.[5] 1,2-Dichloroethane (Aldrich, HPLC grade) was used as supplied. Chemicals, including pyridine halides, (−)-menthol, Ni(dppp)Cl_2 [1,3-bis(diphenylphosphino)-propane]dichloronickel (II), and all the unsaturated alcohols and acids used in this study, were purchased from Aldrich and used without further purification. 4-Penten-1-ol-OD was prepared as previously described;[1c] ^{1}H NMR analyses indicated less than 2% residual H in the hydroxyl group.

Spectrophotometric kinetic measurements were obtained using an OLIS modified Cary 17 UV−vis spectrophotometer or an Applied Photophysics SX-17MV stopped-flow reaction analyzer. GC analyses were carried on a Helwett-Packed 6890 gas chromatograph with a 30-m Supelco β-Dex 390 column or a Chiraldex γ-Dex BP column.

Synthesis. Grignard reagents were prepared in a standard manner by adding a solution of an organic halide to magnesium ribbons which had been dried under nitrogen by flaming. Magnesium was usually used in 20% excess over the halide to exhaust the latter. After completion of the addition, the mixture was refluxed for another 1 h to ensure the reaction.

A general procedure for the cross-coupling reaction of alkyl Grignard reagents with pyridine halides was used.[6] In a 100 mL two-necked flask, equipped with a pressure-equalizing dropping funnel, a reflux condenser attached to a nitrogen line and a stirring bar, were placed 30 mg (0.055 mmol) of Ni(dppp)Cl_2, 5 mmol of pyridine halide, and 50 mL of dried THF; the nickel complex was insoluble in the mixture. The freshly prepared Grignard reagent (5.5 mmol in THF, prepared as above) was added to the mixture with stirring under nitrogen at room temperature over 30 min. The mixture changed from brown-red to dark black. After refluxing for a given period of time (based on the TLC), the mixture was hydrolyzed with dilute hydrochloric acid under ice bath cooling. The organic layer and ether extracts of the aqueous layer were combined, washed with water, $NaHCO_3$ solution, and water, and then dried over anhydrous Na_2CO_3. After evaporation of solvent the crude product was purified further by silica gel column chromatography using ethyl acetate and hexane. Physical data for the following compounds are given in the Supporting Information.

2,6-Dicyclohexylpyridine: yield 85%, from 2,6-dichloropyridine and cyclohexylmagnesium bromide; pale yellow oil; HRMS calcd for $C_{17}H_{25}N$ 243.1987, found 243.1981.

2,6-Dicyclopentylpyridine: yield 78%, from 2,6-dichloropyridine and cyclopentylmagnesium bromide; pale brown oil; HRMS calcd for $C_{15}H_{21}N$ 215.1674; found 215.1678.

2-Methyl-6-cyclohexylpyridine: yield 54%, from 2-methyl-6-bromopyridine and cyclohexylmagnesium bromide; oil; HRMS calcd for $C_{12}H_{17}N$ 175.1361, found 175.1341. The major isolated byproduct was 2,2′-dimethyl bipyridine (yield 20%).

2-Methyl-6-cyclopentylpyridine: yield 46%, from 2-methyl-6-bromopyridine and cyclopentylmagnesium bromide; oil; HRMS calcd for $C_{11}H_{15}N$ 161.1204, found 161.1192. The major isolated byproduct was 2,2′-dimethylbipyridine (yield 30%).

2-Cyclohexylpyridine: yield 72%, from 2-bromopyridine and cyclohexylmagnesium bromide; oil; HRMS calcd for $C_{11}H_{15}N$ 161.1204, found 161.1185.

2-Cyclopentylpyridine: yield 80% from 2-bromopyridine and cyclopentylmagnesium bromide; oil; HRMS calcd for $C_{10}H_{13}N$ 147.1048, found 147.1037.

(−)-2-Menthylpyridine.[7] Magnesium turnings (0.5 g, 20 mmol) in dry THF (15 mL) were activated by stirring with a few drops of 1,2-dibromoethane under nitrogen. After 5 min, a few drops of a solution of 1.87 mL of (−)-menthyl chloride (10 mmol) in THF (10 mL) was added, and warming to about 60 °C started the reaction. The remaining (−)-menthyl chloride solution was added dropwise and the mixture heated at 60 °C with stirring for another 6 h. After cooling, unreacted magnesium was filtered under nitrogen, rinsed with THF, and dried. From the weight of the residual magnesium, the theoretical amount of (−)-menthylmagnesium chloride Grignard reagent was estimated to be 9 mmol (90%). It was then added over 30 min to a stirred solution of 2-bromopyridine (0.7 g, 5 mmol) and 20 mg of Ni(dppp)Cl_2 in THF (35 mL) at 0 °C under nitrogen. The mixture was then stirred at room temperature for 40 h. The reaction was quenched with saturated aqueous NH_4Cl and diluted with enough water to dissolve precipitated magnesium salts. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2CO_3 and the solvent evaporated. The remaining brown oil was purified by column chromatography (hexane/EtOAc: 5/1, R_f = 0.45): yield 25%; HRMS calcd for $C_{15}H_{23}N$ 217.1830, found 217.1832.

The (−)-menthyl chloride used above was prepared in 93% yield from (−)-menthol as described:[8] oil; bp 56.0−56.5 °C/2.0 mmHg.

2,6-Di(−)-menthylpyridine: oil; yield 7%, from 2,6-dichloropyridine and (−)-menthylmagnesium chloride; R_f = 0.72 (silica gel TLC hexane/EtOAc: 5/1); HRMS calcd for $C_{25}H_{41}N$ 355.3239, found 355.3212. The major isolated byproducts are 2-menthylpyridine (10%) and 2-chloro-6-menthylpyridine (5%): HRMS calcd for $C_{15}H_{22}NCl$ 251.1441, found 251.1429.

The bis(2-substitutedpyridine)bromonium triflates (P_2-BrOTf) were prepared according to our previous method.[2] Unfortunately, the dicyclohexyl and dicyclopentyl pyridines gave the corresponding protonated pyridinium triflate salts instead of the desired bromonium triflate complexes through this process.

General Procedure for the Reaction of Bis((−)-2-menthylpyridine)bromonium Triflate with Unsaturated Alcohols and Acids. To a flame-dried 50 mL flask, was added bis(2(−)-menthylpyridine)bromonium triflate (0.2 mmol) and 20 mL of freshly distilled CH_2Cl_2 under nitrogen. The flask was then cooled to −78 °C, and a solution of unsaturated alcohol or acid (0.18 mmol) in dry CH_2Cl_2 (5 mL) was added via a Sage-pump over 1 h. The solution was stirred for another 3 h at −78 °C and then quenched by addition of saturated NH_4Cl aqueous solution. The organic layer was washed with H_2SO_4 (10%, 3 × 30 mL), saturated $NaHCO_3$ solution (3 × 30 mL), brine (3 × 30 mL) and then dried over anhydrous Na_2CO_3. After filtration, the solvent was evaporated carefully to afford the product.

The corresponding racemic compounds were prepared with bis(collidine)bromonium triflate through a similar procedure at room temperature.

The aqueous acidic washes were made basic with NaOH (3 M) and extracted with CH_2Cl_2. The combined organic layer was dried over $NaCO_3$ and evaporated to recover (−)-2-menthylpyridine (about 95% recovery) as a pale yellow oil.

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Table 1. Pseudo-First-Order Rate Constants for the Reaction of Bis(2-cyclopentylpyridine)bromonium Triflate ((6)$_2$BrOTf) with 4-Penten-1-ol in $C_2H_4Cl_2$, t = 25.0 °C

[4-penten-1-ol] (10^{-3} M)	k_{obs} (s^{-1})
[(**6**)$_2$BrOTf] = 1.0×10^{-4} M, [**6**] = 1.0×10^{-4} M	
2.0	34.82 ± 0.38
2.5	36.12 ± 0.31
3.0	39.41 ± 0.30
4.0	43.71 ± 0.29
5.0	47.23 ± 0.23
7.0	54.32 ± 0.33

Table 2. Pseudo-First-Order Rate Constants for the Reaction of Bis(2-cyclohexylpyridine)bromonium Triflate ((7)$_2$BrOTf) with 4-Penten-1-ol in $C_2H_4Cl_2$, t = 25.0 °C

[4-penten-1-ol] (10^{-3} M)	k_{obs} (s^{-1})
[(**7**)$_2$BrOTf] = 1.0×10^{-4} M, [**7**] = 1.0×10^{-4} M	
2.0	28.17 ± 0.25
2.5	29.44 ± 0.28
3.0	30.74 ± 0.33
4.0	33.33 ± 0.41
5.0	34.86 ± 0.62
7.0	37.52 ± 0.60
[(**7**)$_2$BrOTf] = 1.0×10^{-4} M, [**7**] = 2.0×10^{-4} M	
1.0	24.93 ± 0.46
1.5	25.97 ± 0.58
2.0	27.30 ± 0.59
2.5	27.95 ± 0.70
3.0	29.76 ± 0.81
4.0	32.01 ± 0.81
5.0	33.55 ± 1.04
7.0	35.96 ± 1.38

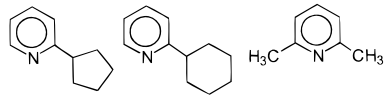
2-(Bromomethyl)tetrahydrofuran. Prepared from 4-penten-1-ol: GC (100 °C, 30m Supelco β-Dex 390 column), 2.4% ee (retention time: 21.29 min, 22.85 min).

5-Bromomethyldihydrofuran-2-one. Prepared from 4-pentenoic acid: GC (120 °C, 30m Chiraldex γ-Dex BP column), 4.8% ee (retention time: 16.04 min, 16.88 min).

Kinetics. The kinetics of the reactions of the various bis-(2-substituted pyridine)bromonium triflates (P_2BrOTf) with 4-penten-1-ol and its OD isotopomer were monitored by observing the rate disappearance of the bromonium ion at 240 nm (the wavelength of maximum change) in 1,2-dichloroethane at 25.0 °C under conditions of excess olefin and different concentrations of added substituted pyridines (P). The pseudo-first-order rate constants were evaluated by NLLSQ fitting of the absorbance vs time traces for disappearance of P_2BrOTf to a standard exponential model ($A_t = A_\infty + (A_0 - A_\infty)\exp(-k_{obs}t)$). The k_{obs} values reported in the tables are the averages of five to six runs.

Results

Given in Tables 1−6 are the pseudo-first-order rate constants (k_{obs}) for the reaction of excess 4-penten-1-ol with the bis(substituted pyridine)bromonium ions, (P_2-Br^+), of **6**−**10** in dichloroethane containing added parent pyridine at 25 °C. The k_{obs} vs [4-penten-1-ol] data in Table 3 for reaction of the bromonium ion of lutidine (**8**) can be



6 **7** **8**

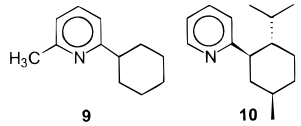


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Table 3. Pseudo-First-Order Rate Constants for the Reaction of Bis(lutidine)bromonium Triflate ((8)$_2$BrOTf) with 4-Penten-1-ol in $C_2H_4Cl_2$, t = 25.0 °C

[4-penten-1-ol] (10^{-3} M)	k_{obs} (s^{-1})
[(**8**)$_2$BrOTf] = 5.0×10^{-5} M, [**8**] = 5.0×10^{-5} M	
0.5	80.85 ± 0.70
0.6	87.64 ± 0.73
0.8	98.18 ± 1.01
1.5	121.12 ± 1.48
4.0	150.59 ± 2.99
[(**8**)$_2$BrOTf] = 5.0×10^{-5} M, [**8**] = 1.5×10^{-4} M	
0.5	53.20 ± 0.48
0.6	61.86 ± 0.60
1.5	98.92 ± 1.29
2.0	108.63 ± 1.22
4.0	133.07 ± 2.30
[(**8**)$_2$BrOTf] = 5.0×10^{-5} M, [**8**] = 3.0×10^{-4} M	
0.5	37.06 ± 0.44
0.6	43.64 ± 0.49
0.8	50.57 ± 0.48
1.0	59.01 ± 0.69
1.5	77.77 ± 0.80
2.0	91.18 ± 1.25
4.0	121.5 ± 1.70

Table 4. Pseudo-First-Order Rate Constants for the Reaction of Bis(lutidine)bromonium Triflate ((8)$_2$BrOTf) with 4-Penten-1-ol-OD in $C_2H_4Cl_2$, t = 25.0 °C

[4-penten-1-ol-OD] (10^{-3} M)	k_{obs} (s^{-1})
[(**8**)$_2$BrOTf] = 5.0×10^{-5} M, [**8**] = 5.0×10^{-5} M	
0.5	82.54 ± 0.89
0.6	91.23 ± 0.87
0.8	95.04 ± 1.19
1.0	105.69 ± 1.80
1.5	123.46 ± 1.35
2.0	136.82 ± 1.99
4.0	161.15 ± 2.91
[(**8**)$_2$BrOTf] = 5.0×10^{-5} M, [**8**] = 3.0×10^{-4} M	
0.6	47.17 ± 1.04
0.8	59.72 ± 0.84
1.0	64.89 ± 1.17
1.5	79.25 ± 1.29
2.0	99.35 ± 2.06
4.0	130.03 ± 2.77

compared with those in Table 4 for its reaction with 4-penten-1-ol-OD. All of the available data are consistent with the process given in Scheme 1 for which can be derived the kinetic expression for disappearance of bromonium ion given in eq 1 assuming a steady state in [P-Br^+ ion, (**3**)] and rate-limiting product formation via k_2.

$$k_{obs} = k_d k_2[\text{4-penten-1-ol}]/(k_{-d}[P] + k_2[\text{4-penten-1-ol}]) \quad (1)$$

Equation 1 can be linearized to give eq 2 so that a plot of $1/k_{obs}$ vs 1/[4-penten-1-ol] gives an intercept of $1/k_d$ and slope of $k_{-d}[P]/k_d k_2$. Shown in Figure 1 are representative

$$1/k_{obs} = (k_{-d}[P]/k_d k_2)(1/[\text{4-penten-1-ol}]) + 1/k_d \quad (2)$$

plots of the so-transformed kinetic data for the reaction of bis(2-methyl-6-cyclohexylpyridine)bromonium triflate ((**9**)$_2$-Br^+/TfO^-) and 4-penten-1-ol which clearly show the inverse first order dependence on added [2-methyl-6-cyclohexylpyridine]. Similar plots for the other bis-(substituted pyridine)bromonium ions, (not shown) generate slopes and intercepts which yield the k_d and k_{-d}/k_2 values collected in Table 7.

Table 5. Pseudo-First-Order Rate Constants for the Reaction of Bis(2-methyl-6-cyclohexylpyridine)bromonium Triflate ($(\mathbf{9})_2$BrOTf) with 4-Penten-1-ol in $C_2H_4Cl_2$, t = 25.0 °C

[4-penten-1-ol] (10^{-3} M)	k_{obs} (s^{-1})
[$(\mathbf{9})_2$BrOTf] = 1.5×10^{-4} M, [**9**] = 1.5×10^{-4} M	
1.5	448.1 ± 8.45
2.0	503.2 ± 13.08
2.5	529.2 ± 15.11
3.0	541.8 ± 17.86
4.0	594.1 ± 19.69
5.0	617.9 ± 31.79
[$(\mathbf{9})_2$BrOTf] = 1.5×10^{-4} M, [**9**] = 4.5×10^{-4} M	
1.0	259.5 ± 9.63
1.5	323.1 ± 6.03
2.0	364.4 ± 6.83
2.5	396.4 ± 14.36
3.0	440.8 ± 12.97
4.0	462.0 ± 15.81
5.0	500.0 ± 18.61
7.0	571.4 ± 19.71
[$(\mathbf{9})_2$BrOTf] = 1.5×10^{-4} M, [**9**] = 7.5×10^{-4} M	
1.0	186.2 ± 10.66
1.5	234.0 ± 17.65
2.0	296.6 ± 22.81
2.5	323.0 ± 25.82
4.0	413.6 ± 33.31

Table 6. Pseudo-First-Order Rate Constants for the Reaction of Bis(2-(−)menthylpyridine)bromonium Triflate ($(\mathbf{10})_2$BrOTf) with 4-Penten-1-ol in $C_2H_4Cl_2$, t = 25.0 °C

[4-penten-1-ol] (10^{-3} M)	k_{obs} (s^{-1})
[$(\mathbf{10})_2$BrOTf] = 1.0×10^{-4} M, [**10**] = 1.0×10^{-4} M	
2.5	11.94 ± 0.16
3.0	13.72 ± 0.24
4.0	17.43 ± 0.24
5.0	22.04 ± 0.43
7.0	30.11 ± 0.60
10.0	40.19 ± 1.47
[$(\mathbf{10})_2$BrOTf] = 1.0×10^{-4} M, [**10**] = 3.0×10^{-4} M	
2.0	8.36 ± 0.07
2.5	9.68 ± 0.11
3.0	11.73 ± 0.22
4.0	14.82 ± 0.29
5.0	19.61 ± 0.56
7.0	27.35 ± 0.69
10.0	32.57 ± 1.10
[$(\mathbf{10})_2$BrOTf] = 1.0×10^{-4} M, [**10**] = 5.0×10^{-4} M	
2.0	6.47 ± 0.14
2.5	7.97 ± 0.19
3.0	10.20 ± 0.30
4.0	11.68 ± 0.46
5.0	16.08 ± 1.11
7.0	21.78 ± 0.85
10.0	25.27 ± 1.52

Discussion

The k_{obs} vs [4-penten-1-ol] data in Tables 1−6 indicate that the reaction rate asymptotically approaches a limiting value as the [olefin] increases, thereby verifying the simple two-step reaction mechanism passing through a reversibly formed intermediate. When manipulated in the double reciprocal form of eq 2, the data yield the dissociation rate constant of the complex (k_d) and partitioning of the intermediate, P-Br^+, between product formation and reverse capture by P (k_{-d}/k_2). The k_d values in Table 7 represent the maximum that these bromonium ions can react with any acceptor olefin. Strictly speaking, the partitioning of the intermediate, k_{-d}/k_2, should be insensitive to the presence of added substituted pyridine,

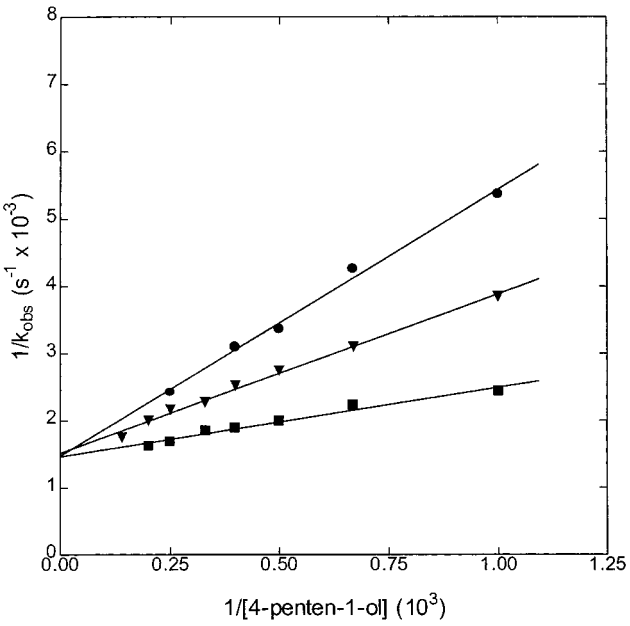


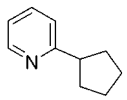
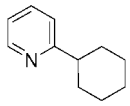
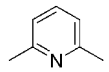
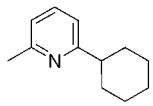
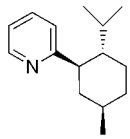
Figure 1. Plots of $1/k_{obs}$ for the reaction of bis(2-methyl-6-cyclohexylpyridine)bromonium triflate (1.5×10^{-4} M) vs 1/[4-penten-1ol] at three different concentrations of 2-methyl-6-cyclohexylpyridine in 1,2-dichloroethane at 25.0 °C (■, 1.5×10^{-4} M; ▼, 4.5×10^{-4}M; ●, 7.4×10^{-4} M). Lines through the data computed by fits to eq 2.

although the data for the latter ratio in Table 7 indicate an apparent decrease in the ratio as [P] increases. Given that parent pyridine and pyridinuim triflate are produced during the reaction, maintaining pseudo-first-order conditions requires that the added [**6**−**10**] must be sufficiently large that their concentrations do not change appreciably during the reaction. This was not possible for technical reasons associated with high solution absorbancies due to added pyridine, so the reported values for k_{-d}/k_2 are upper limits with those obtained at the highest [**6**−**10**] being most reliable.

The rate constants presented in Table 7 can be compared with those found earlier[2] for bis(*sym*-collidine)-bromonium triflate (**2**), $k_d = 205 \pm 10$ s^{-1} and $k_{-d}/k_2 = 2.6$. Evaluation of all the data in Table 7 indicates that the dissociation constant of P_2-Br^+ (k_d) is slowest for the mono substituted derivatives and further substitution increases the rate showing that the initial separation is quite sensitive to steric acceleration (compare **6** with **9** and **10**). This explains our inability to make the bromonium ions of 2,6-dicyclopentyl- or 2,6-dicyclohexylpyridine, the only isolable species from their reaction with Br_2/AgOTf being the corresponding HOTf salts. Inspection of the limiting k_{-d}/k_2 data for the various bromonium ions indicates that this ratio is relatively insensitive to the nature of the pyridine substituent, the upper limits for all these lying in the range of ∼3−7 except in the case of **10**−Br^+ for which the upper limit is ∼80 for reasons that are not clear.

The data in Table 7 for the reaction of bis(lutidine)-Br^+ with 4-penten-1-ol and its OD isotopomer shed light on the details of the cyclization process. Shown in Figure 2 are plots of this reaction at two different added [lutidine]. From the ratio of the slopes of these lines, the dkie. can be computed as $(k_{-d}/k_2)^{H/D} = 0.96$ and 1.11, values which are indistinguishable from unity. Given that the k_{-d} process should be independent of alkene, the

Table 7. Kinetic Data for Reaction of 4-Penten-1-ol with Various P_2BrOTf in 1,2-Dichloroethane at 25.0 °C Computed from Fits of Data in Tables 1−6 to Eq 2

	[P] (10^{-4} M)	[P2BrOTf] (10^{-4} M)	intercept (10^{-3})	slope (10^{-6}) (k_{-d}[P]/k_dk_2)	k_d (s^{-1})	k_{-d}/k_2
	1.0	1.0	15.22 ± 0.95	29.07 ± 2.92	65.7	19.1
	5.0	1.0	15.51 ± 1.15	57.77 ± 5.24	64.5	7.4
	1.0	1.0	23.67 ± 0.60	24.91 ± 1.82	42.2	10.5
	2.0	1.0	23.63 ± 0.10	30.35 ± 0.37	42.3	6.4
	0.5	0.5	5.97 ± 0.14	3.26 ± 0.10	167.5	10.9
	0.5	0.5[a]	5.78 ± 0.33[a]	3.30 ± 0.27[a]	173.0[a]	11.4[a]
	1.5	0.5	5.97 ± 0.22	6.34 ± 0.18	167.5	7.1
	3.0	0.5	5.84 ± 0.38	10.60 ± 0.32	171.2	6.0
	3.0	0.5[a]	5.68 ± 0.47[a]	9.29 ± 0.46[a]	176.0[a]	5.4[a]
	1.5	1.5	1.46 ± 0.04	1.03 ± 0.08	684.9	4.7
	4.5	1.5	1.52 ± 0.04	2.37 ± 0.07	657.9	3.5
	7.5	1.5	1.47 ± 0.12	3.96 ± 0.19	680.3	3.6
	1.0	1.0	7.43 ± 0.74	190.7 ± 5.7	134.6	256.7
	3.0	1.0	7.57 ± 0.40	230.9 ± 7.8	132.1	101.7
	5.0	1.0	7.14 ± 0.69	292.4 ± 12.1	140.0	81.9

[a] 4-Penten-1-ol-OD.

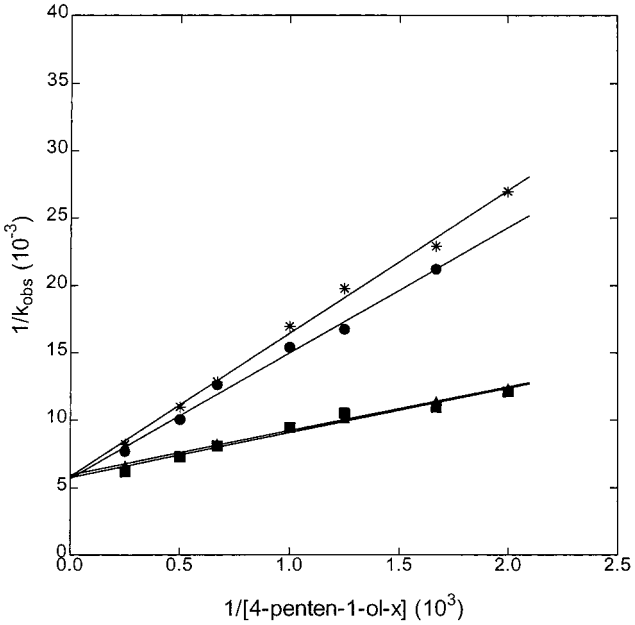
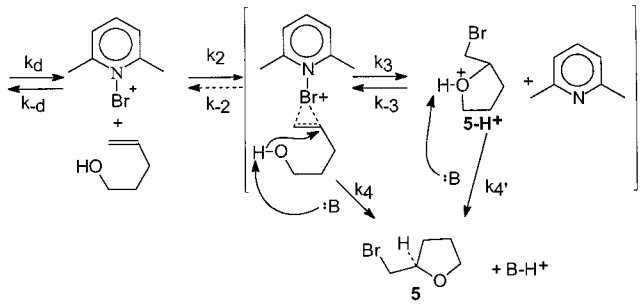


Figure 2. Plots of $1/k_{obs}$ for reaction of bis(lutidine)bromonium triflate (0.5×10^{-4}M) vs 1/[4-penten-1-ol] and 1/[4-penten-1-ol OD] at two concentrations of added lutidine in dichloroethane at 25 °C (∗, HOC_5H_9, ●, DOC_5H_9; [lutidine] = 3×10^{-4}M; ▲, HOC_5H_9, ■, DOC_5H_9; [lutidine] = 5×10^{-5}M). Lines through the data computed from fits to eq 2.

dkie of unity refers exclusively to reaction with the alkene and possibly subsequent steps concerning cyclization to form 2-bromomethyltetrahydrofuran (**5**). Any of these steps could be rate-limiting, with some predictably being subject to a dkie. Shown in Scheme 2 is a possible mechanism where the reaction of lutidine-Br^+ with alkene yields a lutidineBr^+−ol complex from which the cyclization proceeds. That complex could react directly with lutidine (k_4) to form **5**, or could spontaneously cyclize (k_3) to form **5**-H^+ which is then deprotonated by lutidine ($k_{4'}$). Of all the steps leading to cyclized product, only the

Scheme 2

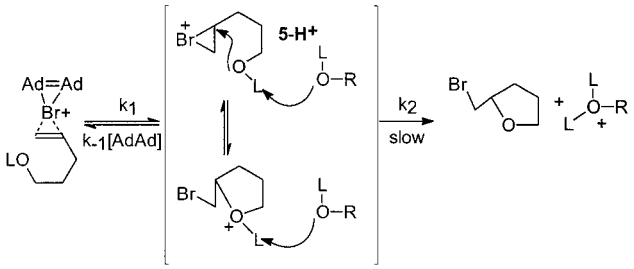


k_2 step leading to the P-Br^+−ol complex should yield a dkie of 1.0 since all other steps involve a proton in flight ($k_4$or $k_{4'}$) or one undergoing change in its bonding (e.g., the formation of **5**-H^+ via k_3).[9]

In an earlier study[1c] concerning the cyclization of 4-penten-1-ol mediated by the bromonium ion of adamantylideneadamantane (**1**) we observed a dkie of 2.0 for the cyclization. The mechanism for that reaction is similar to the ones described here with the important exception that the overall process is second order in [4-penten-1-ol]. Added 1-pentanol was observed to accelerate the reaction, a plot of k_{obs} vs [pentanol] showing

(9) For the formation of **5**-H^+, the O−H bond should have an associated fractionation factor of 1.0 for the noncyclized form and 0.69 for **5**-H^+ leading to an equilibrium isotope effect of $(k_3 \backslash k_{-3})^{H/D} = 1.4-1.5$. Should the k_3 step be rate limiting, we can assume that the transition state would be late, resembling the closed ion **5**-H^+, leading to a somewhat reduced dkie, but not as low as 1.0. Steps k_4 or $k_{4'}$ should have associated dkie's of $k_H/k_D > 2.0$ for a normal primary effect. For a discussion of fractionation factor analysis, see: (a) Schowen, R. L. In *Isotope Effects on Enzyme-Catalyzed Reactions;* Cleland, W. W., O'Leary, M. H., Northrop, D. B., Eds.; University Park Press: Baltimore, 1977. (b) Alvarez, F. J.; Schowen, R. L. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol. 7, pp 1−60. (c) Kresge, A. J.; More-O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Elsevier: Amsterdam, 1987; Vol. 7, pp 177−274. (d) Alvarez, F. J.; Schowen, R. L. In *Isotopes in Organic Chemistry*; Buncel, E., Lee, C. C., Eds.; Vol.7., Elsevier: Amsterdam, 1987; pp 1−60. (e) Kresge, A. J. *J. Am. Chem. Soc.* **1973**, *95*, 3065.

Scheme 3



saturation kinetics. The role of the second molecule of alcohol is to deprotonate the intermediate as in Scheme 3. The rate-limiting step for the reaction thus involves abstraction of the proton from either the open bromonium ion or the closed **5**-H^+ by ROH. The shift in the rate-limiting step from cyclization, in the case of Ad═Ad, to P−Br^+−ol complex formation in the cases of the bromopyridiniums described above is probably attributable to the presence of a poor abstracting base (ROH) for the former process, and a good base (P) in the latter process.

Enantioselectivity in Reactions of Bis((−)2-menthylpyridine)bromonium Triflate with 4-Penten-1-ol and Pentenoic Acid. Aside from the mechanistic questions associated with changes in the nature of the 2- and 6-pyridine substituents and the dkie for partitioning of the intermediate, a major aim of this study was to determine whether stereochemical information could be transferred from the bromonium complexes to the halocyclization process. The preliminary results afforded by the halocyclizations of 4-penten-1-ol and 4-pentenoic acid mediated by the 2(−)-menthylpyridine complex **10**$_2$−Br^+-OTf^- are disappointing, the enantiomeric excesses being only 2.4% and 4.8%, respectively. This suggests that the cyclization event in the P-Br^+−ol complex occurs too far from the pyridine to be influenced by the presence of the 2-menthyl substituent and that future pyridine-based systems utilizing this approach must ensure that the chiral substituent is positioned such that it better encapsulates the Br^+ to form a pocket into which the alkene is coordinated.

Conclusions

In the above study, we have shown that halocyclization of 4-penten-1-ol mediated by bis(2-substitutedpyridine) bromonium triflates follows a two step mechanism involving a reversibly formed intermediate (P-Br^+) which partitions between reversal and product formation. The rate of dissociation of the P_2-Br^+ is sensitive to the steric bulk of the substituents on the pyridine. In our hands, if the 2- and 6-substituents are both secondary (such as cyclohexyl or cyclopentyl), the ions are too unstable to be isolated. The partitioning of the P-Br^+ intermediate between reversal and halocyclization with 4-penten-1-ol is relatively insensitive to the nature of the of 2- and 6-substituents except for 2(−)-menthylpyridine where k_{-d}/k_2 is about 80. The halocyclization of 4-penten-1-ol and its OD isotopomer mediated by bis(lutidene)bromonium triflate gives a dkie of ∼1.0, which indicates that the rate limiting step for the cyclization is probably formation of a P-Br^+−4-penten-1-ol complex which undergoes rapid cyclization.

Disappointingly, reaction of the chiral **10**$_2Br^+$ ion with 4-penten-1-ol or 4-pentenoic acid does not give appreciable enantiomeric excess in the cyclized product. Further elaboration of the substituents at the 2-and 6-position of pyridine will need to take due account of steric considerations and placement of the chiral groups closer to the cyclization event.

Acknowledgment. The authors gratefully acknowledge the financial support of the Natural Sciences and Engineering Research Council of Canada. In addition, they thank Dr. Ping Cao of the Department of Chemistry, Pennsylvania State University, for determining the ee for the bromocyclization of 4-penten-1-ol.

Supporting Information Available: ^1H and ^{13}C NMR and mass spectral data for ligands **6**−**10**, 2,6-dimenthylpyridine, 2,6-dicyclopentylpyridine, and 2,6-dicyclohexylpyridine. This material is available free of charge via the Internet at http://pubs.acs.org.

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