Reexamination of a Putative [1s,4s] Sigmatropic Rearrangement

by

Yihhuang Hsieh

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Name : Yihhuang Hsieh

Degree : Master of Science

Title of thesis : Reexamination of a Putative [1s,4s] Sigmatropic Rearrangement

Examining Committee :

Chair : Dr. D. Sutton, Professor
Department of Chemistry

Dr. S. Wolfe, University Professor
Senior Supervisor
Department of Chemistry

Dr. E. Kiehlmann, Internal Examiner
Department of Chemistry

Dr. K. N. Slessor, Professor
Department of Chemistry

Dr. A. J. Bennet, Associate Professor
Department of Chemistry

Dr. Y. L. Chow, Professor
Department of Chemistry

Abstract

The thermal rearrangement of a 2-alkoxypyridine-1-oxide to a 1-alkoxy-2-pyridone, which has been reported to proceed by an intramolecular [1s,4s] sigmatropic migration of the alkyl group with retention of configuration and first order kinetics, has been reexamined. The intramolecular barrier found computationally by Dr. C.-K. Kim, Dr. K. Yang and Dr. Z. Shi is at least 20 kcal/mol higher than the reported experimental barrier. An alternative bimolecular mechanism, discovered computationally in our laboratory, has been confirmed by a variety of experiments, including crossover studies, determination of solvent effects and secondary H/D isotope effects as well as new kinetic and stereochemical studies. In the new mechanism, there is an initial intermolecular transfer of the alkyl group, with inversion of configuration, to the N-oxide. Depending on the nature of the alkyl group and the solvent, this is followed by a second transfer, also with inversion of configuration, of one of the alkyl groups of the cationic intermediate to one of the oxygens of the anionic intermediate. The product is then formed, without crossover, by a double inversion of one alkyl group, or, with crossover, by two single inversions of different alkyl groups. The intermediates of this mechanism have been synthesized, and are found to exhibit the predicted behavior.

Dedication

To my grandmother

Acknowledgments

I am deeply in debt to Professor Saul Wolfe who provided me with a great opportunity to study at Simon Fraser University under his guidance. His intellectual and financial support as well as his enthusiasm for organic chemistry cannot be described properly here by me. It would be inappropriate for me not to include the many people who have aided and made this thesis a reality. Firstly, I would like to thank Dr. C.-K. Kim, Dr. K. Yang, Dr. Z. Shi and Dr. N. Weinberg for their computational works and helpful discussions. Their efforts and interest in this research topic are appreciated. I would also like to thank Dr. R. D. Sharma and Dr. J. C. Brodovitch for their advice and experimental suggestions, both Dr. Alan Tracey and Marcey Tracey for their assistance in obtaining and interpreting nmr spectra, Dr. G. Eigendorf (University of British Columbia) and Greg Owen for providing mass spectra, and M. K. Yang for the microanalyses.

As for my laboratory colleagues, Stephen and Christiana, their friendship and helpful discussion over the past two years is gratefully acknowledged. And finally, I wish to express my gratitude to those members of the Department of Chemistry who have taught and shared their knowledge with me thoughout the years.

Table of Contents

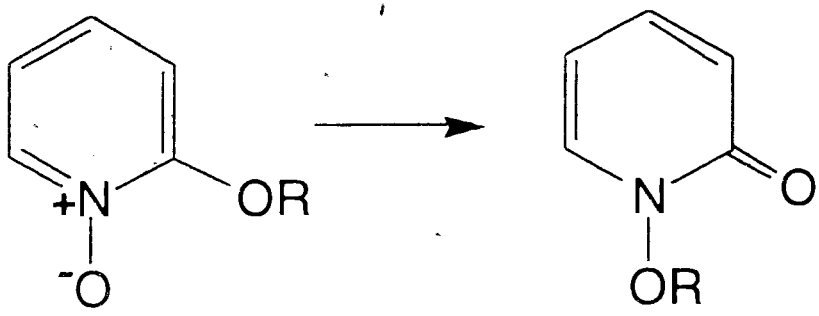
List of Figures

List of Tables

Chapter 1

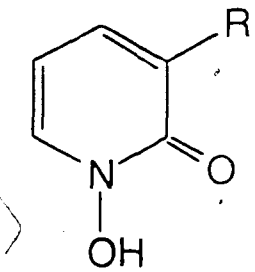
Introduction

The thermal rearrangement of a 2-alkoxypyridine-1-oxide (**1**) to a 1-alkoxy-2-pyridone (**2**) was first reported by Dinan and Tieckelmann in 1964.[1]



1 **2**

They found that heating **1** (R = methyl, ethyl, benzyl, allyl) neat at 100-140 ^{0}C led to complete rearrangement to **2** within 1.5-3.5 h. The addition of the free radical scavenger, p-benzoquinone, did not inhibit the reaction. In a second study,[2] it was observed that a 2-alkenyloxypyridine-1-oxide (**1**, R = $CHR_1CH=CHR_2$) rearranged to **2** (R = $CHR_1CH=CHR_2$) in diglyme solvent without a 1,3-allylic double bond shift. Higher temperatures led to *ortho*-Claisen rearrangement, to give **3** (R = $CHR_2CH=CHR_1$) as a major product. Crossover products were observed in competition experiments with substituted and unsubstituted alkenyloxy compounds. The cyclopropylcarbinyloxy compound yielded, in addition to 96% of 1-cyclopropylcarbinyloxy-2-pyridone, about 4% of the skeletally rearranged 1-cyclobutyloxy-2-pyridone. In refluxing carbon tetrachloride, the optically active N-oxide **4**, $[\alpha]_{340}^{28}$ $+35.0^0$, rearranged to **5**, $[\alpha]_{340}^{28}$ -169^0.



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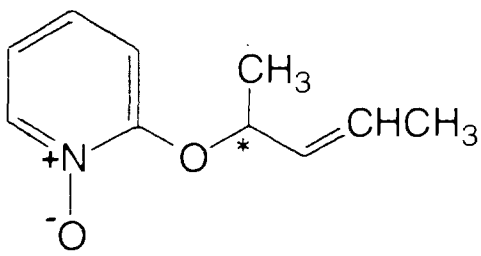

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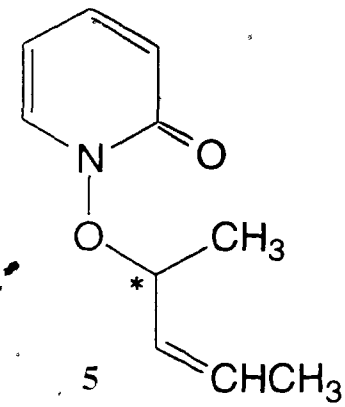

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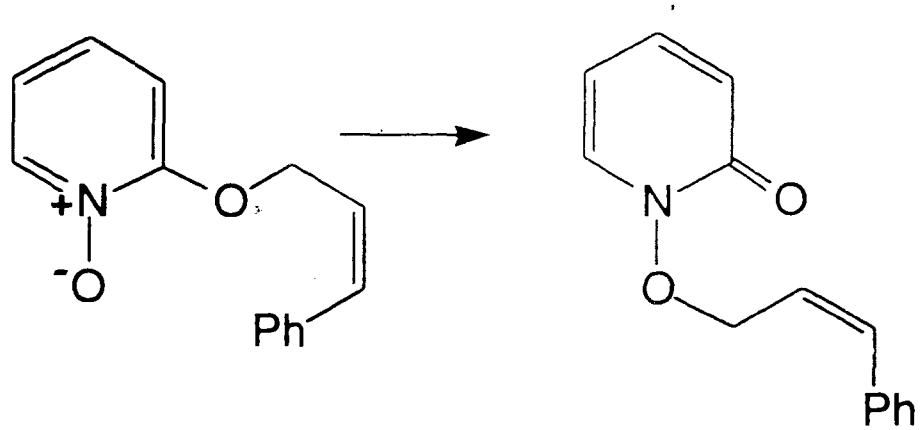
It was concluded that the reaction is not radical in nature, and a mechanism involving inter- or intramolecular displacement of R by the N-oxide was considered. Since the transition state required for an intramolecular substitution reaction would involve a rather unlikely front-side displacement on the alkyl group, Lister and Tieckelmann[2] proposed that the rearrangement proceeded via internal return of an ion-pair intermediate.

Some of these results could not be confirmed. Schöllkopf and Hoppe[3] found no skeletal isomerization in the rearrangement of **1**, R = cyclopropylcarbinyl, and the α-methallyl compound (**1**, R = $CH(CH_3)CH=CH_2$) gave only the Claisen rearrangement product, with skeletal isomerization of the alkenyl substituent, and not the reported **2**, R = $CH(CH_3)CH=CH_2$. Ollis and coworkers[4] have made similar observations concerning the competition between the O → O (Tieckelmann) and O → C (Claisen) rearrangement pathways. They also found[4b] that heating the cis-cinnamyl ether **6** for 60 h at 53 ^{0}C led to the 1-cis-cinnamyloxy-2-pyridone **7** exclusively.



6 **7**

Schöllkopf and Hoppe[3,5] studied the rearrangement of substituted 2-benzyloxypyridine-1-oxides[5] and obtained a Hammett σp plot with slope -0.26 (Figure 1).[6] This was taken to indicate absence of ionic character in the transition state.

Using about 0.5 M solutions in chloroform-*d* solvent, Hoppe[5] reported first order kinetics in the temperature range 130-150 ^{0}C for R = CH_3, C_2H_5, *i*-C_3H_7 and $CH_2CH_2OC_2H_5$. For R = C_2H_5 and *i*-C_3H_7, 3-point Arrhenius plots yielded $\Delta H^{\neq}$ 11-12 kcal/mol and $\Delta S^{\neq}$ -52 - -56 cal/mol-deg. The reaction of 2-chloropyridine-1-oxide with α-deuteriobenzyl alcohol, $[\alpha]_{546}^{25}$ -0.556^0, gave **1**, R = CHDPh, $[\alpha]_{546}^{25}$ -1.133^0. This rearranged to **2**, R = CHDPh, $[\alpha]_{546}^{25}$ -0.899^0, which, upon refluxing with zinc and 30% acetic acid, yielded α-deuteriobenzyl alcohol, $[\alpha]_{546}^{25}$ -0.423^0. In a control experiment, the optically active alcohol underwent 18% racemization when refluxed with zinc and 30% acetic acid.

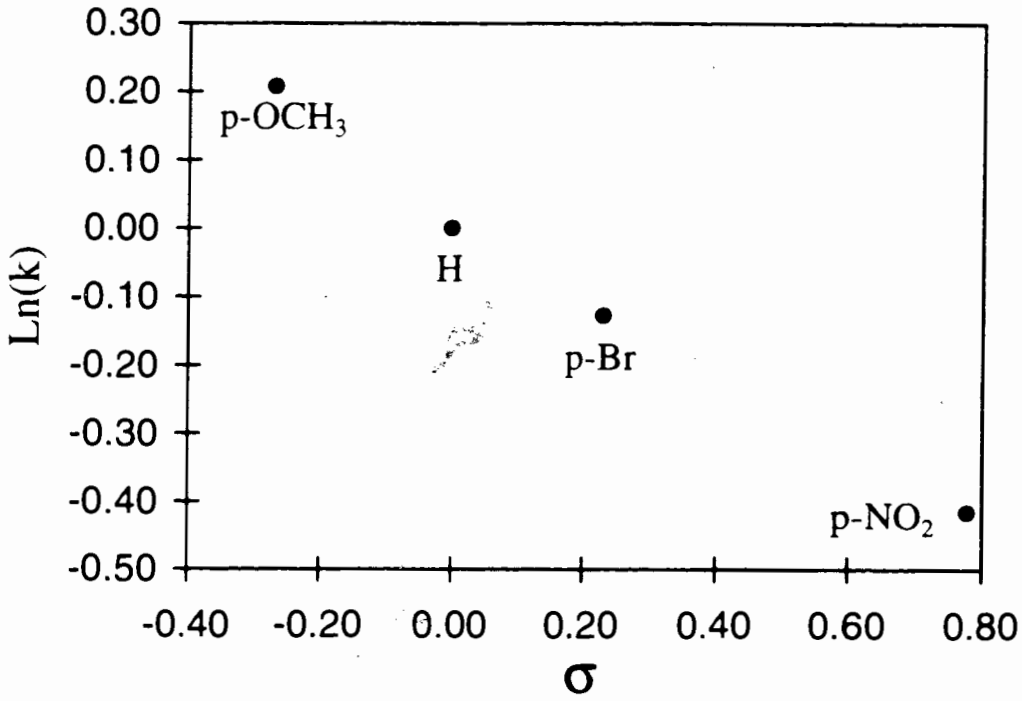
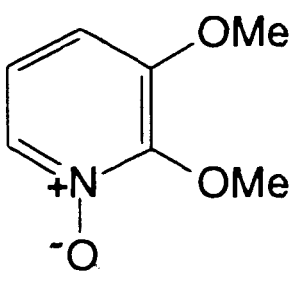


Figure 1 : Hammett σρ plot (from Ref. 5):

The combination of first order kinetics, a low enthalpy of activation, a high negative entropy of activation and, most importantly, rearrangement of the benzyl substituent with retention of configuration led Schöllkopf and Hoppe to propose a concerted intramolecular [1s, 4s] sigmatropic rearrangement mechanism (Figure 2).[7] This conclusion has been supported by, and is consistent with the results of Ollis and coworkers[4] for the rearrangement **6** $\rightarrow$ **7**.

However, a [1s, 4s] sigmatropic rearrangement mechanism cannot account for the results of Tieckelmann's crossover experiments. Crossover has also been observed by Ballesteros et al.[8] Heating a mixture of **1** (R = benzyl) and **8** at 140 ^{0}C in the absence of solvent led to a mixture of **2** (R = CH_3), **2** (R = benzyl), **9** and **10**. In dimethylformamide-d_7 (DMF), the rearrangement of **8** at 110 ^{0}C showed an "induction-period" and an "acceleration of the reaction rate" as the concentration increased from 0.128 M to 0.453 M. The reported first order activation parameters are $\Delta H^{\neq}$ 24.0 kcal/mol and $\Delta S^{\neq}$ -17.7 eu. In refluxing toluene-d_8, neither **1** (R = CH_3) nor **8** underwent significant rearrangement during 20 h.



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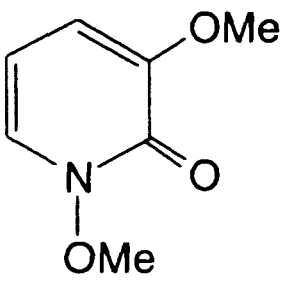

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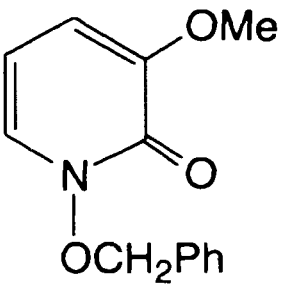

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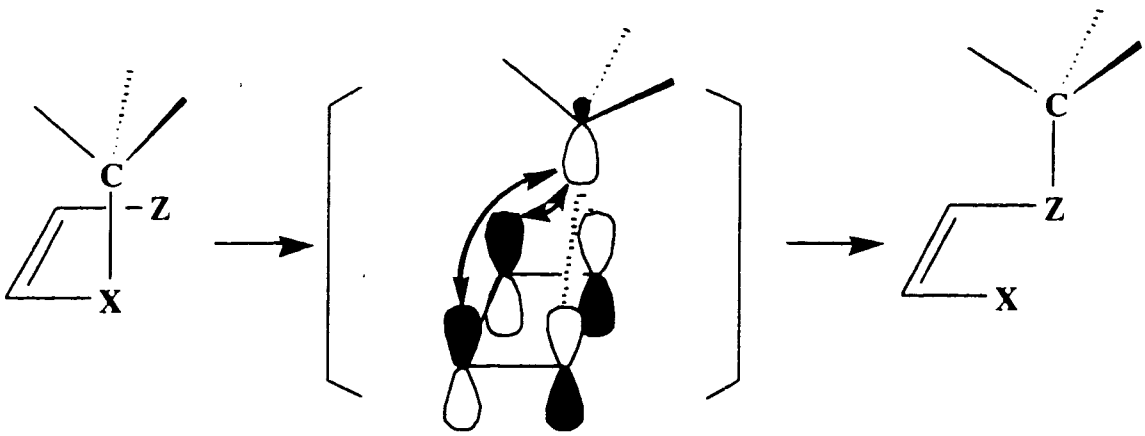
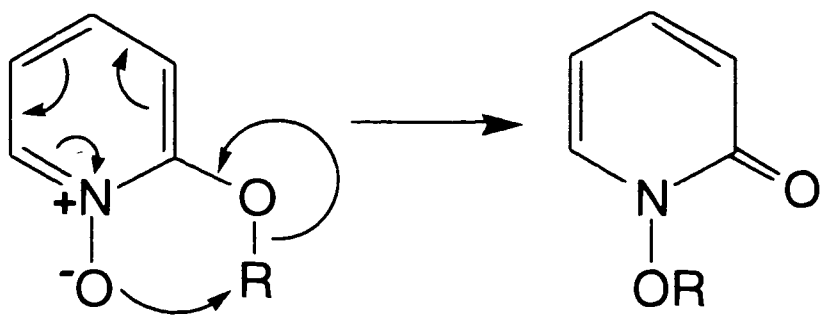


Figure 2 : Schematic representation of a [1s,4s] sigmatropic rearrangement of an alkyl group, as proposed by Schöllkopf and Hoppe (double-headed arrows have been added).

The Spanish workers concluded that the solvent effects and the results of the crossover experiments were consistent with an ionic mechanism, and not sigmatropic rearrangement.

The effect of pressure on the rearrangement of **1** (R = benzyl) in diglyme solution at 100 ^{0}C has been investigated by le Noble and Daka.[9] Since the reaction exhibits $\Delta V^{\neq}$ -30 ± 5 cm^3/mol, these workers concluded that the sign of $\Delta V^{\neq}$ "confirms that this activation parameter provides a criterion for concertedness in sigmatropic shifts...". However, a negative $\Delta V^{\neq}$ demonstrates only that the system is more compact in the transition state than in the reactant,[10] and does not distinguish the between the proposed intramolecular sigmatropic rearrangement and a bimolecular nucleophilic displacement mechanism. The latter reaction is also known to exhibit a strongly negative $\Delta V^{\neq}$.[10]

The [1s,4s] sigmatropic rearrangement mechanism can be regarded as a special case of an intramolecular S_N2 displacement reaction.[11]



1 **2**

However, there is extensive theoretical evidence[11,12] that the barrier for retention of configuration in S_N2 reactions is at least 20 kcal/mol higher than the barrier of an unconstrained inversion process. This means that an intramolecular retention mechanism would never be able to compete kinetically with an intermolecular inversion process. It seemed desirable to reexamine the mechanism of the rearrangement **1** $\rightarrow$ **2.**

Chapter 2

Results and Discussion

2-1 The [1s, 4s] Sigmatropic Rearrangement Mechanism

The results of 3-21G calculations[13] carried out by Dr. C.-K.Kim, Dr. K. Yang and Dr. Z. Shi on the intramolecular rearrangement of **1** for R = CH_3 and R = CH_2Ph are summarized in Table 1. As expected from the previous work,[11,12] in both cases, the barriers are at least 20 kcal/mol higher than the experimental barrier. The calculated secondary CH_3/CD_3 kinetic isotope effect[14] in the intramolecular rearrangement of **1** (R = CH_3) is 1.35, and is consistent with previous calculations for other intramolecular methyl transfer reactions with retention of configuration.[11]

Table 1 : Intramolecular mechanism of the rearrangement of **1** to **2**.

R	Species	Relative energy (kcal/mol)
CH_3	reactant	0.00
	product	-17.97
	TS	48.78
CH_2Ph	reactant	0.00
	product	-16.69
	TS	42.94

The above findings do not support the notion that the Tieckelmann reaction is a [1s, 4s] sigmatropic rearrangement. In fact, a closer examination of Figure 2 reveals that such a process cannot occur. The Figure shows a phase relationship at the termini of the 1,4 system that permits suprafacial migration of a methyl group, but as seen in the double-headed arrows, this migration is inhibited by the out-of-phase relationship of the migrating group with the internal 2,3-orbitals.

Figure 3 shows the HOMO of **1** (R = CH_3), and clearly indicates that a 1,4-migration of the methyl group would have to overcome the repulsive wall at the 2,3-positions. This repulsion forces the methyl group towards the nodal plane of the π-system, with concomitant loss of pericyclic stablization of the transition state.[11]

Figure 4 shows side views of the two intramolecular transition structures. At the 3-21G level, the methyl and benzyl groups are not perpendicular to the plane of the pyridine ring, but only 18 and 25 degrees, respectively, out of the plane of the ring.

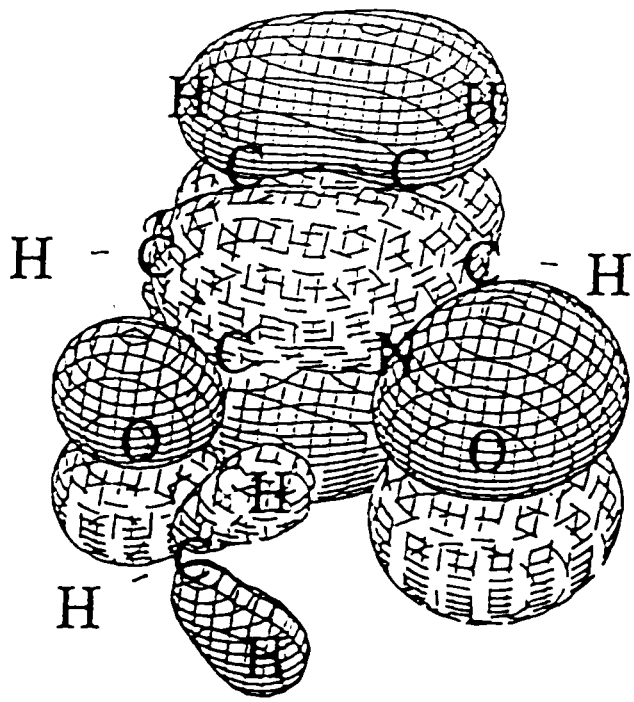
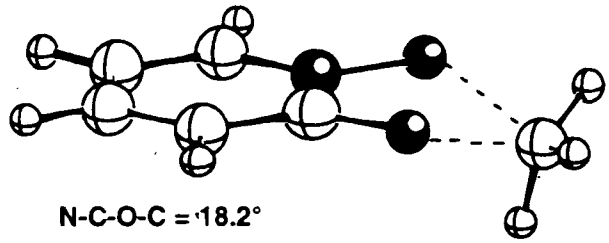
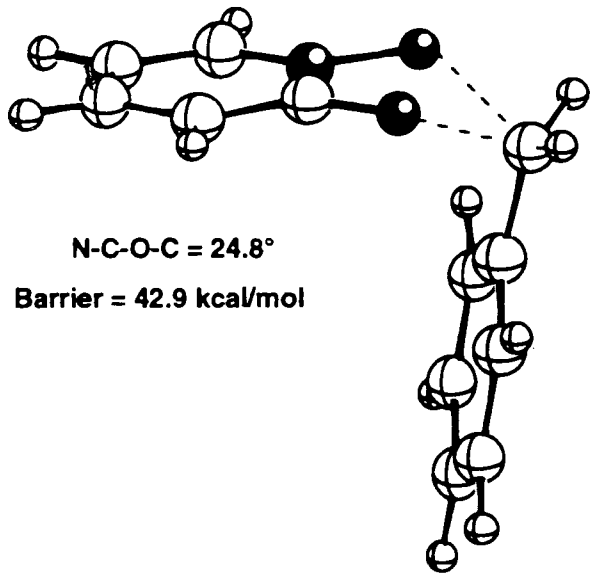


Figure 3 : Calculated HOMO of 2-methoxypyridine-1-oxide



N-C-O-C = 18.2°

Barrier = 48.8 kcal/mol



N-C-O-C = 24.8°

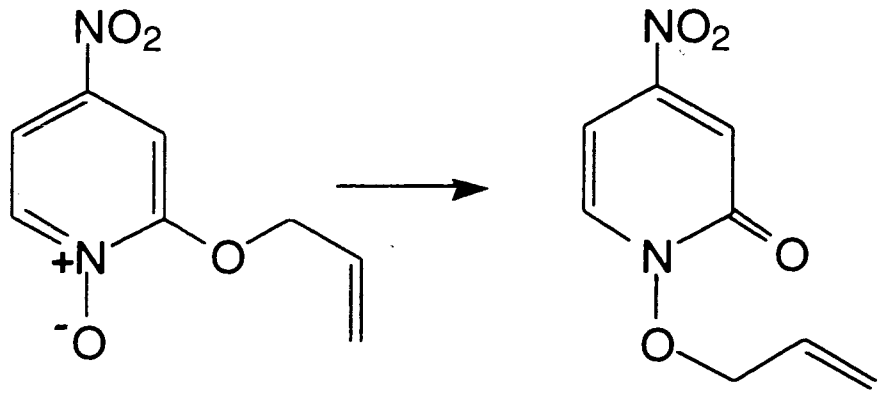
Barrier = 42.9 kcal/mol

Figure 4 : Side views of the 3-21G transition structures for intramolecular rearrangement of **1** (R = methyl and benzyl)

2-2 A Bimolecular Mechanism

2-2-1 Initial calculations.

Ollis and coworkers[4] have made the interesting observation that **11** is transformed quantitatively into **12** in the solid state during 13 months at -15 ^{0}C.



11 **12**

Although the crystal structure of **1** (R = CH_3),[15] a portion of which is shown in Figure 5 shows an intermolecular O•••O distance of 4.45 Å, and an O•• CH_3 ••O angle of 150.3 deg, intermolecular methyl transfer between two ether oxygens is unlikely to be productive. It is noteworthy that **1** (R = CH_3) shows no evidence of rearrangement in the solid state.

The structure of Figure 5 is not a minimum at the 3-21G level but, if the methyl groups are allowed to rotate from the *anti*-orientations, the dimeric structure **13** (Figure 6), with an intermolecular O•••O distance of 4.32 Å, and an O•• CH_3 ••O angle of 174.2 deg is obtained.

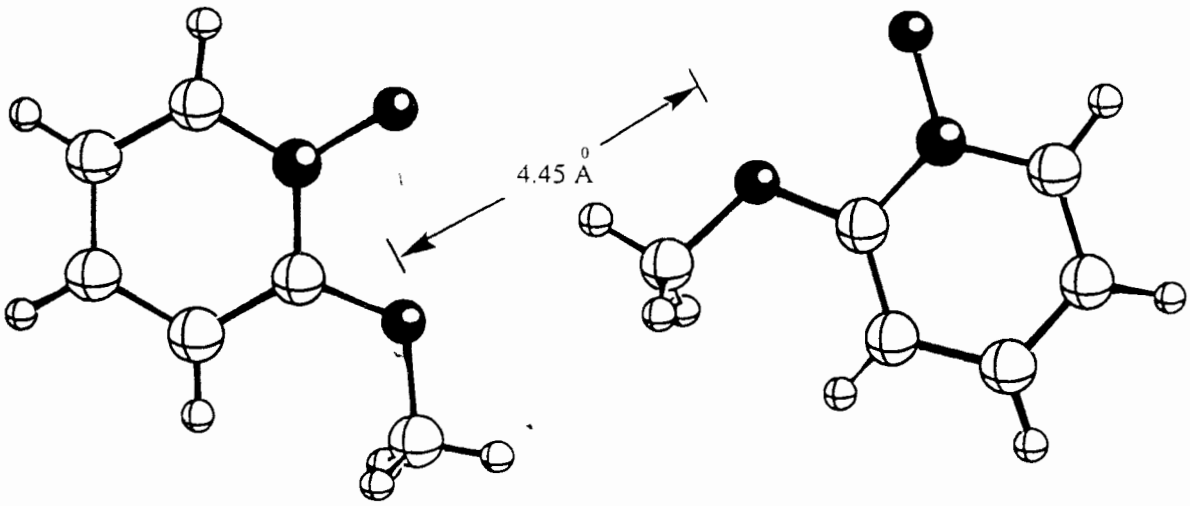


Figure 5 : A portion of the crystal structure of 2-methoxypyridine-1-oxide (water molecules deleted).

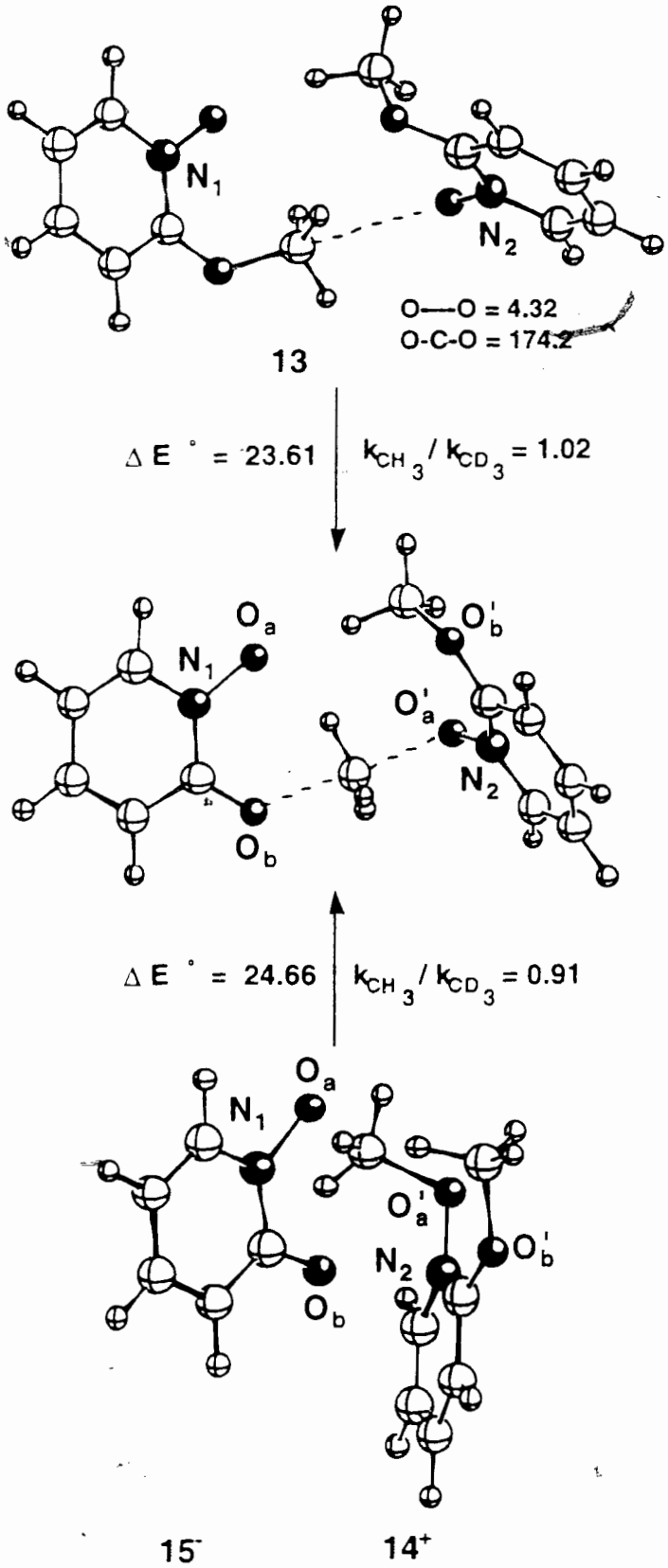
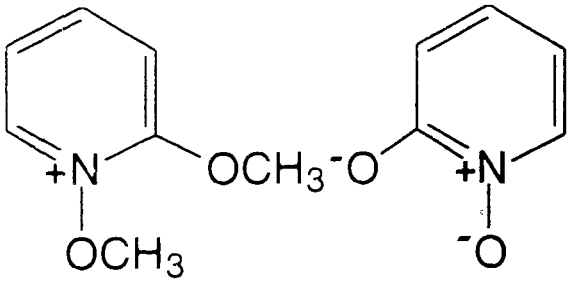


Figure 6 : Calculated dimeric structure of 2-methoxypyridine-1-oxide (**13**), and the transition state structure for methyl transfer with inversion of configuration to give $\mathbf{14}^{+}\mathbf{15}^{-}$.

Figure 6 also shows the calculated transition structure for intermolecular methyl transfer in **13**. The 3-21G barrier is 23.6 kcal/mol, within the range observed experimentally for the Tieckelmann reaction,[8] and the calculated secondary CH_3/CD_3 kinetic isotope effect is 1.02. The product of the methyl transfer is the complex $\mathbf{14^+15^-}$.

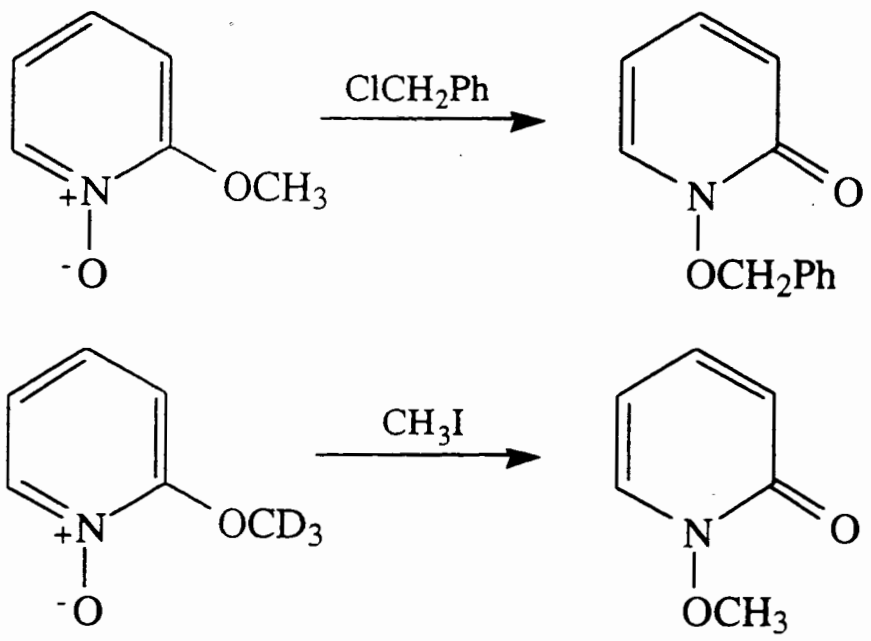


$\mathbf{14^+}$ $\mathbf{15^-}$

2-2-2 Syntheses of 14^+ and 15^- and their reaction to form 2 (R = CH_3)

The reaction of **1** (R = CH_3) with methyl triflate yielded the crystalline triflate salt $\mathbf{14^+}OTf^-$. Refluxing of **1** (R = CH_3) with hydrochloric acid gave 1-hydroxy-2-pyridone, which was converted with butyllithium to the lithium salt $\mathbf{Li^+15^-}$. On standing overnight at room temperature, a solution of the two salts in dimethylformamide afforded **2** (R = CH_3) quantitatively, In water solvent, a solution of $\mathbf{14^+}OTf^-$ and $\mathbf{Na^+15^-}$ yielded a 55 : 45 mixture of **2** (R = CH_3) and *methanol*, together with unreacted 1-hydroxy-2-pyridone.

In subsequent experiments, refluxing of a chloroform solution of **1** (R = CH_3) and benzyl chloride gave **2** (R = benzyl). Under the same conditions, **1** (R = CD_3) and CH_3I gave **2** (R = CH_3) quantitatively.



The results of these initial experiments are compatible with the novel postulate that the thermal rearrangement of **1** to **2** proceed via two consecutive bimolecular nucleophilic displacement reactions.

2-2-3 Which alkyl group is transferred in the second step? Crossover and Stereochemical consequences.

After the formation of $\mathbf{14^{+}15^{-}}$, the reaction can continue along four different channels, and only modest vibrations of the two rings will position either methyl group of $\mathbf{14^{+}}$ for transfer, in a second inversion step, to either of the oxygens of $\mathbf{15^{-}}$. Figure 7 shows the barriers and secondary kinetic CH_3/CD_3 isotope effects calculated in our laboratory for the four reactions. The primary data of this Figure are collected in Table 2.

Table 2 : Energy barriers and isotope effects for different channels.

Channel	Barrier (kcal/mol)	CH_3/CD_3 isotope effect
A	24.66	0.91
B	19.73	0.89
C	18.48	1.02
D	15.69	0.87

Channel A is the reverse of the initial step; it returns the methyl group to the oxygen atom from which it originated. The barrier is 24.66 kcal/mol, and the CH_3/CD_3 isotope effects is 0.91. Channel B returns the methyl group to the molecule from which it originated, but to a different oxygen atom within this molecule. The barrier is 19.73 kcal/mol, and the isotope effect is 0.89. In Channel C, the methyl group attached to O_B', which did not move in the first step, is transferred to O_B, the site of the original methyl group. The barrier is 18.48 kcal/mol, and the isotope effect is 1.02. In Channel D, the methyl group attached to O_B', is transferred to O_A, the N-oxide. The barrier is 15.69 kcal/mol, and the isotope effect is 0.87.

The consequences of reaction via each of these Channels are summarized in Figure 8. Since Channel A leads only to **1** and Channel D leads only to the much more stable **2**, it is not surprising that the latter has a significantly lower barrier.[16] Channels B and C lead to a 1 : 1 mixture of **1** and **2**, and the barriers of these reaction channels are intermediate between those of channels A and D.

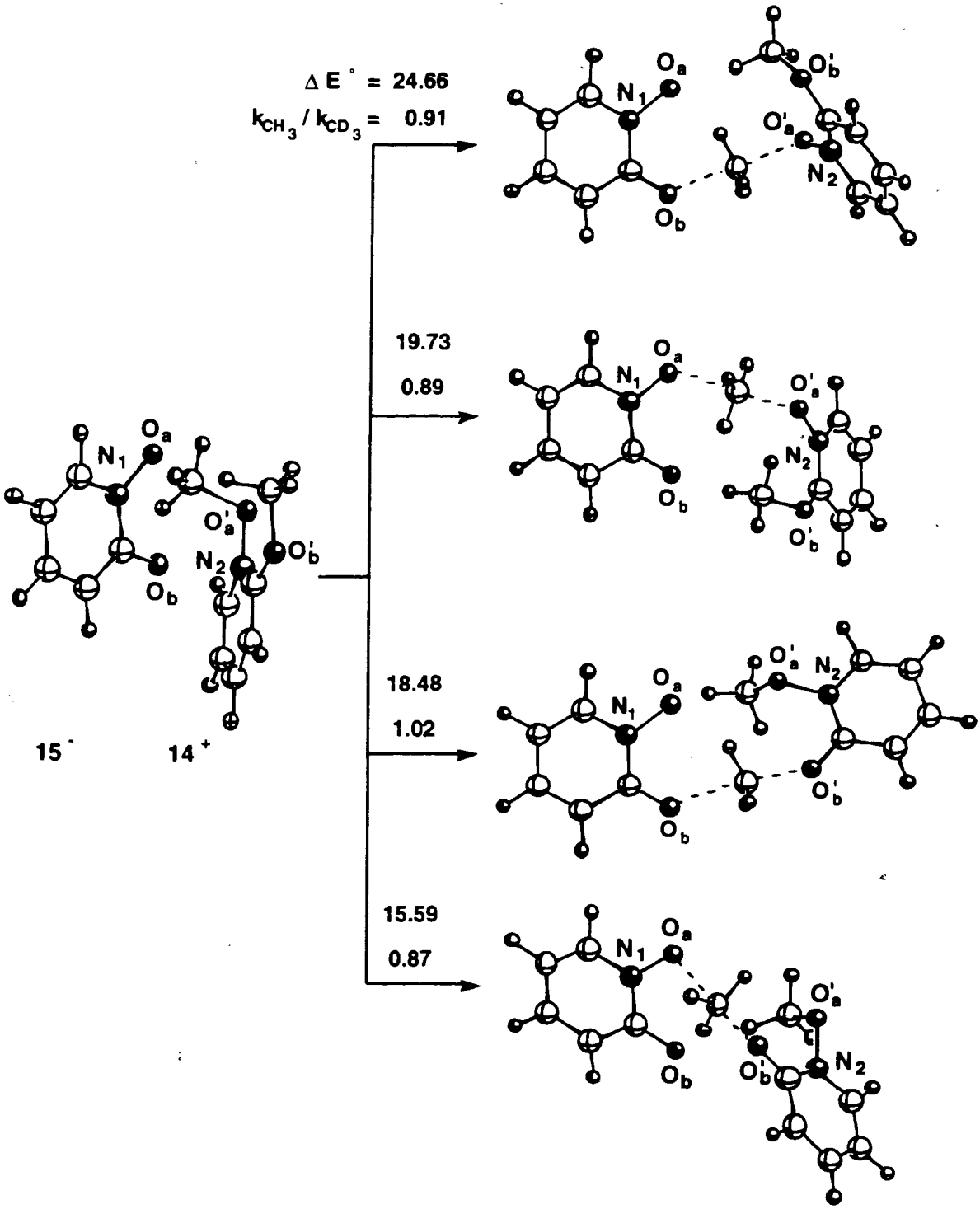


Figure 7 : Calculated transition structures and isotope effects for methyl transfer in $14^{+}15^{-}$ via, in descending order, Channels **A**, **B**, **C** and **D**.

The following conclusions can be reached by careful analysis of each of the reaction Channels. Channel A does not lead to a product and the recovered reactant has the same stereochemistry as the starting material. In Channel B, the product **2** is formed by a double inversion pathway with retention of configuration. There is no change in the stereochemistry of **1**, which acts as a catalyst. Neither Channel A nor Channel B leads to crossover into reactant or product. In Channel C, both the product and the recovered reactant arise from the exchange of a methyl group between two initial reactants, one from O_B to O_A' and the other from O_B' to O_B. In both cases, the methyl groups undergo a single inversion. In Channel D, the situation is the same as Channel C except that both methyl groups transfer once to form the product, one from O_B to O_A' and the other from O_B' to O_A. The overall effect of the methyl transfer is net inversion. Because exchange of methyl groups occurs in Channels C and D, there is crossover into reactants and products.

The calculations predict that D will be the principal channel for the second methyl transfer, so that **2** must form with inversion of configuration and crossover of the methyl group. These predictions can be tested from the results of competition experiments using R = CH_3 and R= CD_3, if it is assumed that the rearrangement is kinetically first order and that the kinetic CH_3/CD_3 isotope effects of retention (calculated 1.35 for the sigmatropic rearrangement) and inversion (calculated 1.02) methyl transfer mechanisms are not the same.[17] If there is crossover, the mass spectrum of the product of the rearrangement of a mixture of undeuterated **1** (R = CH_3, *m/z* 125) and tetradeuterated **1** (R = CD_3, monodeuterated in the pyridine ring, *m/z* 129) will contain two products 2 (R = CH_3 or CD_3) with peaks at *m/z* 126 and *m/z* 128 respectively.

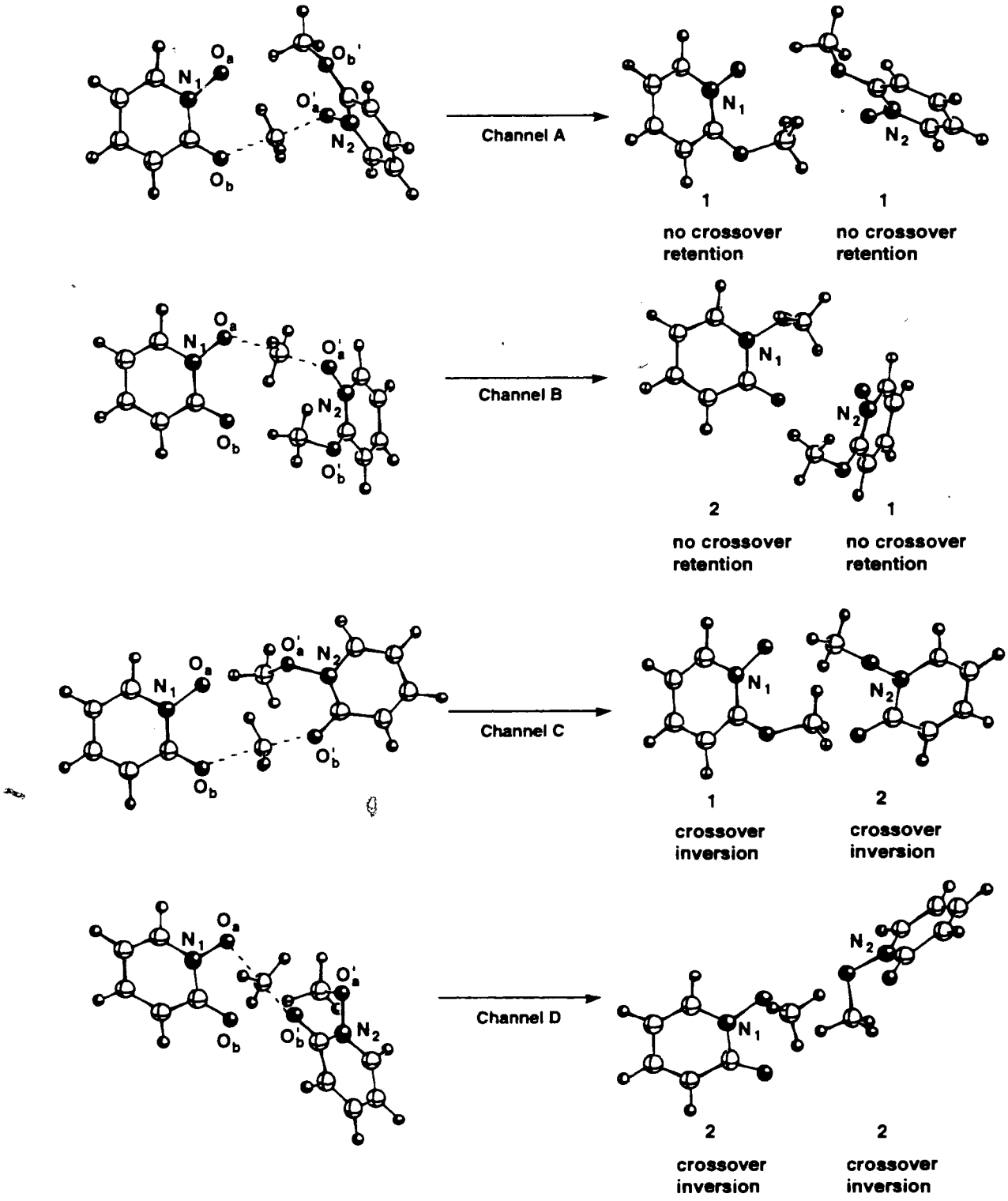


Figure 8 : Stereochemical and crossover consequences of product formation via Channels **A**, **B**, **C** and **D**.

2-2-4 Crossover experiments with R = Methyl and R = Benzyl.

Chart 1 summarizes the syntheses of the substrates required for crossover and isotope effect experiments. Following previous workers,[2,4,5,18] refluxing of 2-chloropyridine-1-oxide for 1 h with sodium methoxide in methanol or in methanol-d_4 gave **1** (R = CH_3), *m/z* = 125, or **1** (R = CD_3), *m/z* = 128, respectively. Extension of the refluxing period in methanol-d_4 led to hydrogen exchange at C6 and formation of 6-deuterio-**1** (R = CD_3), *m/z* = 129. As described later, a mixture of the *m/z* 125 and *m/z* 128 isotopomers was used to determine the secondary CH_3/CD_3 isotope effect. A mixture of the *m/z* 125 and *m/z* 129 isotopomers was used in the crossover experiments.

For crossover experiments in the benzyl series, 2-chloropyridine-1-oxide was reacted with sodium benzyloxide in tetrahydrofuran to give **1** (R = CH_2Ph), *m/z* = 201. The trideuterio compound 6-deuterio-**1** (R = CD_2Ph), *m/z* = 204, was prepared from 6-deuterio-**1** (R = CD_3) by reaction with sodium benzyl-α,α-d_2-oxide in tetrahydrofuran.

Figures 9 and 10 summarize the mass spectral data obtained from crossover experiments performed in dimethylformamide at 140 ± 0.8 ^{0}C. In the methyl series (Figure 9), aliquots of a 0.45 M 1 : 1 mixture of the *m/z* 125 and *m/z* 129 isotopomers were heated in sealed tubes for the indicated times. The solvent was then removed under reduced pressure and the mixtures of **1** and **2** were separated by preparative layer chromatography. Figure 9 shows the electron impact mass spectra, in the region of the molecular ion, of the initial mixture and of the recovered reactant and product after 40 min and after 70 min. The mass spectrum of the mixture of **1** and **2** was identical to that calculated from the individual mass spectra. In addition, control experiments established that the composition and mass spectra of mixtures of isotopomers did not change during the isolation process.

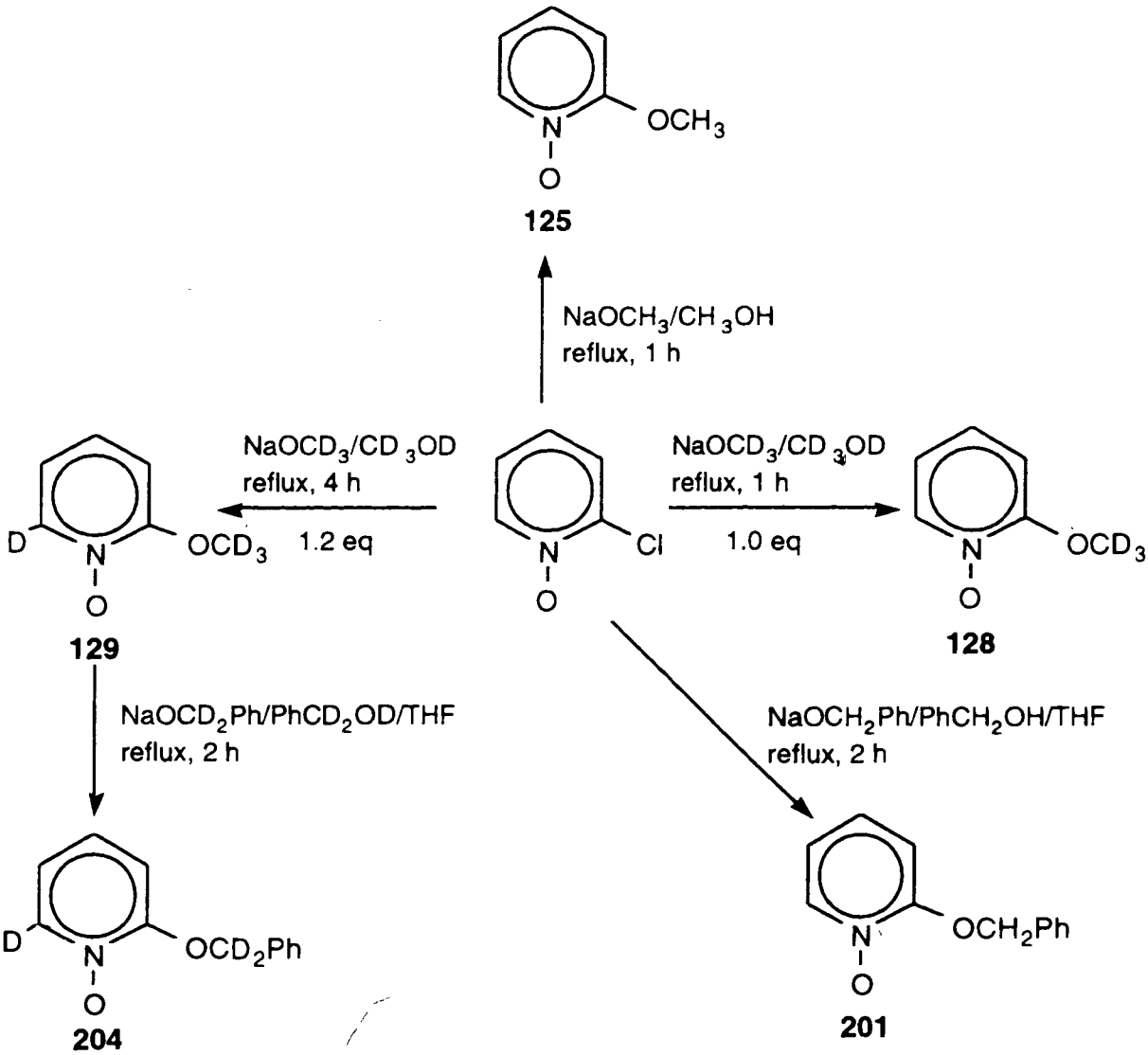
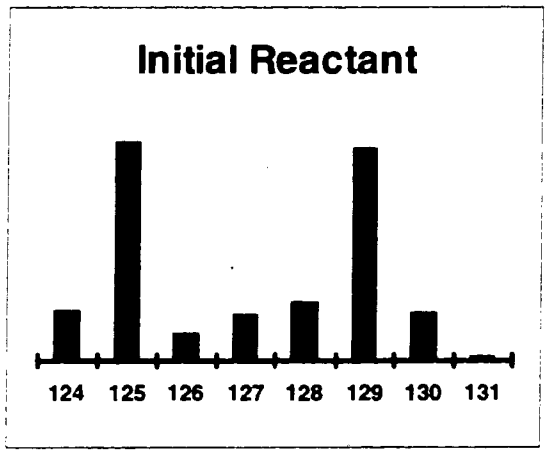
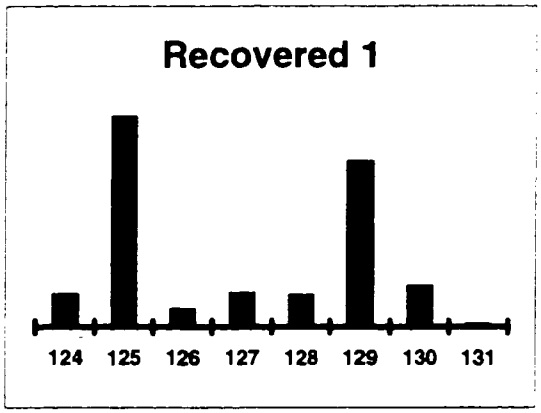
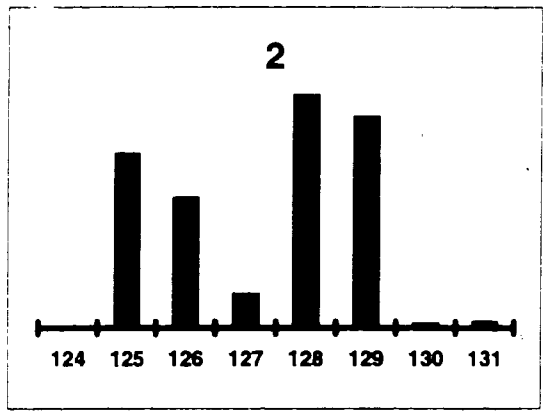


Chart 1 : Syntheses of substrates for crossover and isotope effect experiments.

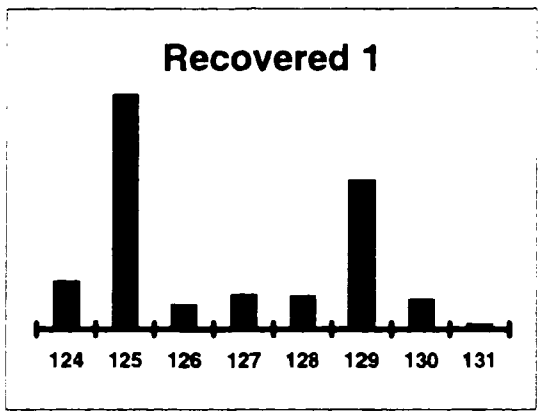


40 Min





70 Min



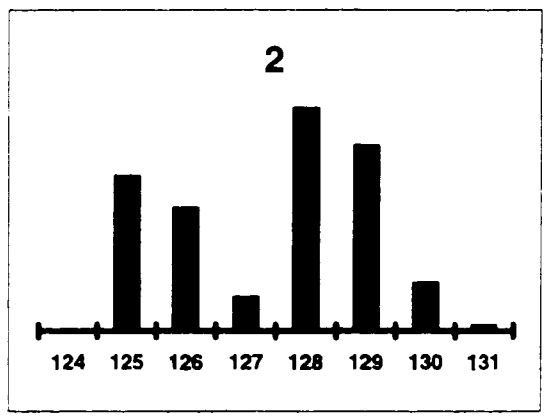


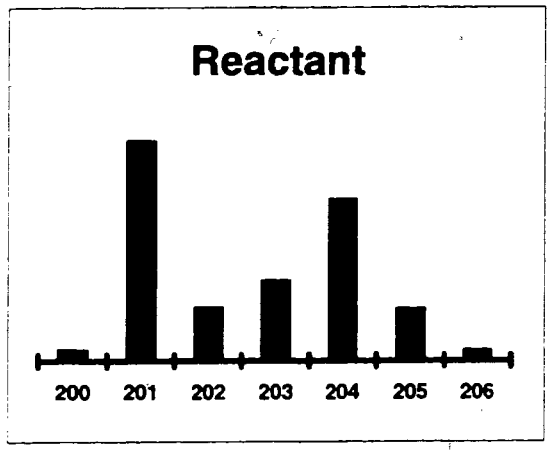
Figure 9 : Crossover experiment for the rearrangement of 2-methoxypyridine-1-oxide in dimethylformamide at 140 ^{0}C. The mass spectrum of the initial reactant is shown at the top; the mass spectra of the recovered reactants are shown on the left, and the mass spectra of the products are shown on the right.

The crossover study in the benzyl series (Figure 10) was performed in the same way, except that the concentration of the 1 : 1 mixture of the *m/z* 201 and *m/z* 204 isotopomers was 0.22 M. Figure 10 shows the mass spectrum calculated for the 1 : 1 mixture from the mass spectra of the individual isotopomers (see below) and the mass spectrum of the product isolated after 20 min and after 40 min.

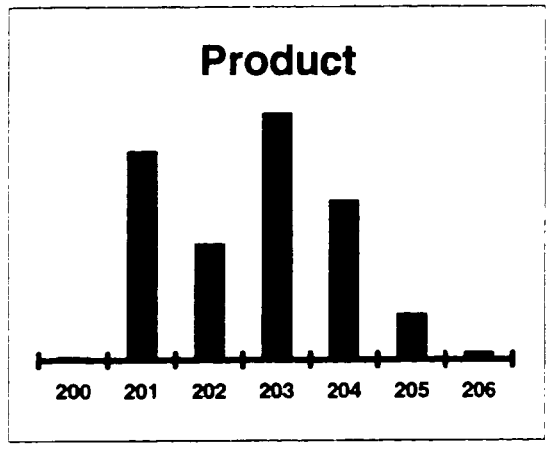
In the case of the methyl compound, the recovered reactant shows no evidence of crossover, but there is an increase in the 125/129 ratio. This indicates that the reaction has an inverse CH_3/CD_3 kinetic isotope effect. The formation of crossover products unambiguously establishes that the rearrangement follows an *inter*molecular pathway, and the data of Table 3 show that the crossover is complete. This Table gives the experimental result of Figure 9, and also the mass spectrum calculated from the mass spectra of the *m/z* 125 and *m/z* 129 isotopomers and the 125/129 mixture, assuming 100 percent crossover in the product.[19]

Table 3 : Relative intensities of the *m/z* 124-129 peaks in the electron impact mass spectrum of the product of the rearrangement of a mixture of undeuterated and tetradeuterated **1** (R = methyl).

	Relative intensity		
mass	**initial**	**calculated for 100% crossover**	**found**
124	0.08	0.04	0.00
125	0.33	0.24	0.22
126	0.04	0.17	0.17
127	0.07	0.04	0.04
128	0.09	0.27	0.29
129	0.32	0.21	0.27



20 Min



40 Min

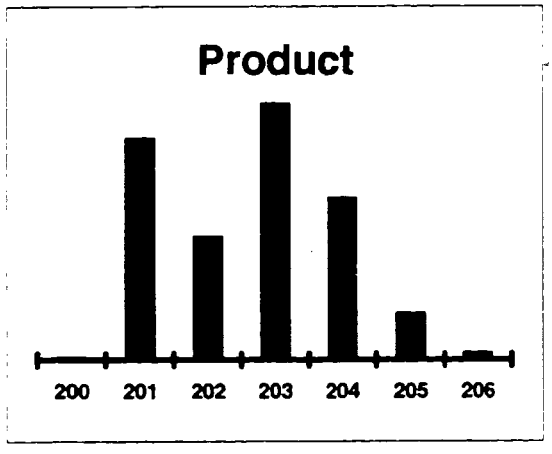


Figure 10 : Crossover experiment for the rearrangement of 2-benzyloxypyridine-1-oxide in dimethylformamide at 140 ^{0}C. Upper: Calculated mass spectrum of the initial reactant. Lower: mass spectra of the products isolated after different times.

Referring to Figure 8, the results of the crossover experiments imply that the rearrangement product is formed exclusively via Channel D. Because of the correlation between stereochemistry and crossover, it follows that 2-methoxypyridine-1-oxide rearranges, with *inversion* of configuration of the methyl group, according to Scheme 1.

Scheme 1.

$$\mathbf{1} + \mathbf{1} \xrightarrow{k_1} P^+ P^- \xrightarrow{k_2} \mathbf{2} + \mathbf{2}$$

The benzyl compound exhibited different behaviour, whose analysis was complicated by the finding that rearrangement, with crossover, occurred in the mass spectrometer.

In the initial experiments, the mass spectra were recorded at 160 ^{0}C. Subsequent experiments revealed that the mass spectra of **1** (R = benzyl) and **2** (R = benzyl) were identical, and that simply heating the N-oxide for 1 min at 160 ^{0}C led to complete rearrangement to **2**. Since extensive crossover of the isotopic label of **1** was observed even when the mass spectra were taken at 80 ^{0}C, the composition of the initial 1 : 1 mixture of isotopomers was calculated from the mass spectra of the individual compounds (Table 4). This is a reasonable strategy, in view of the crossover experiments with **1** (R = methyl), which does not rearrange in the mass spectrometer, and for which the calculated and observed mass spectra of the 1 : 1 mixture of isotopomers are the same. As an additional check, the mass spectrum of a 1 : 1 mixture of the isotopomers of **2** (R = benzyl) was examined; no crossover was observed.

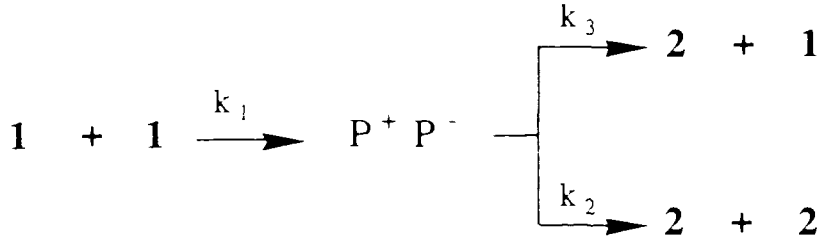
Table 4 : Calculated relative intensities of the *m/z* 201-205 peaks in the mass spectrum of the reactant, calculated relative intensities of the product, assuming 100%, 90%, 80%, 70% crossover, and the relative intensities found in the product of the rearrangement of a mixture of undeuterated and trideuterated **1** (R = benzyl).

		Calculated for product assuming (%) crossover				found
mass	**Calculated for reactant**	**100%**	**90 %**	**80 %**	**70 %**	**20 min**
201	0.391	0.255	0.268	0.282	0.295	0.273
202	0.095	0.206	0.195	0.185	0.174	0.152
203	0.140	0.294	0.277	0.260	0.243	0.313
204	0.284	0.206	0.217	0.228	0.239	0.202
205	0.090	0.039	0.042	0.046	0.049	0.060
		(0.0612)	(0.0592)	(0.0683)	(0.0852)[a]	

a, Numbers in parentheses are the rms deviation between calculated and experimental relative intensities. See Appendix A-1 for details.

Table 4, which is analogous to Table 3, shows that there is less than 100 percent crossover into the products.[19] The result is consistent with an intermolecular mechanism to which Channels B and D (Figure 8, benzyl in place of methyl) contribute, with D predominating. The mechanism is summarised in Scheme 2, with $k_2 > k_3$.

Scheme 2

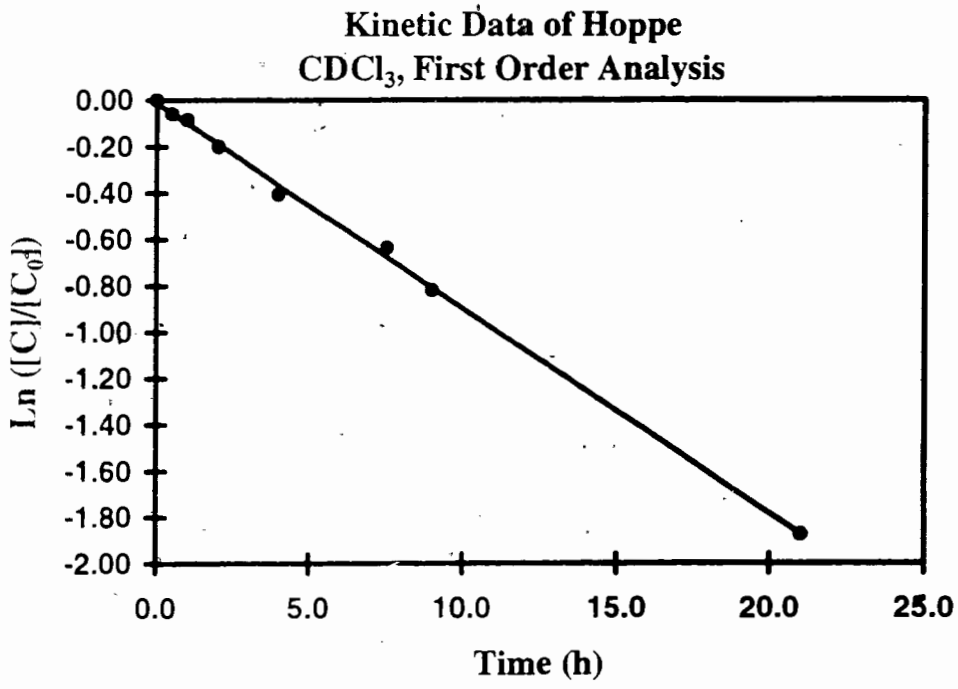


Obviously neither Scheme 1 nor Scheme 2 is compatible with the previously reported[5,8] first order kinetic behaviour. Further, if the stereochemistry and crossover are correlated, a contribution from Channel B requires that optically active **1** (R = CHDPh) retain its stereochemical integrity as the reaction proceeds, but the product **2** (R = CHDPh) will be formed with predominant inversion of configuration. Since Hoppe reported retention of configuration,[5] it became necessary at this stage to reexamine the stereochemistry and the kinetics of the Tieckelmann reaction.

2-2-5 Kinetic Studies.

The primary kinetic results of Hoppe's study of the rearrangement of **1** (R = methyl) are available in Ref 5. Figure 11 shows first order and second order plots of those data, obtained by integration of the methyl peaks in the nmr spectra of mixtures of **1** and **2**. The experiment was performed in sealed nmr tubes at 140 ± 0.2 ^{0}C using a 0.45 M deuteriochloroform solution of **1**. The first order plot is linear; the second order plot is not. Data for other concentrations of **1** (R = methyl) are not reported. There are no primary data for the rearrangement of **1** (R = benzyl), but a 0.2 M deuteriochloroform solution is reported to rearrange with a first order rate constant of 6.63 x 10 $^{-5}$ s^{-1} at 140 ^{0}C.

In the present work, experiments were performed at 140 ± 0.8 ^{0}C, using several concentrations of **1** (R = methyl), in sealed nmr tubes in deuteriochloroform solvent, and also in sealed tubes in dimethylformamide solvent. In the latter case, as described earlier, the solvent was evaporated under reduced pressure, and the composition of mixtures was determined by nmr integration in deuteriochloroform.



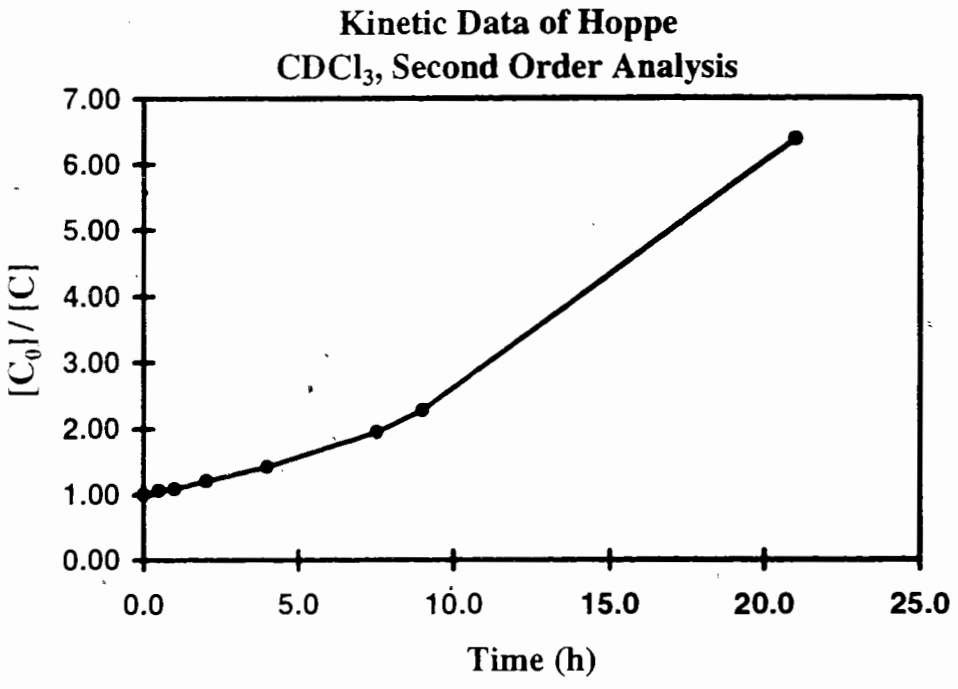


Figure 11. Kinetic data of Hoppe for the rearrangement of 2-methoxypyridine-1-oxide in chloroform at 140 ^{0}C. Upper : first order plot. Lower : second order plot.

The previously reported use of the methyl signals was not possible, even at 400 MHz. Although the methyl chemical shifts of pure **1** and pure **2** differ by 0.02 ppm, mixtures of **1** and **2** exhibited the same methyl chemical shift. Integration was, therefore, performed on the 8.28 ppm peak of **1** and the 6.13 ppm peak of **2**.

For kinetic studies with **1** (R = benzyl), most of the experiments were performed in sealed tubes in dimethylformamide at 140 ± 0.8 ^{0}C. After evaporation of the solvent, integration of deuteriochloroform solutions was performed using the methylene peaks of **1** and **2** at 5.44 and 5.29 ppm, respectively.

Figure 12 shows first order and second order plots of the chloroform data for R = methyl. Figure 13 shows first order and second order plots of the dimethylformamide data for R = methyl. Figure 14 shows first order and second order plots of the data for R = benzyl.

In agreement with Hoppe,[5] the plot of Figure 12 for the rearrangement of a 0.45 M solution of **1** (R = methyl) in chloroform appears to be linear. All of the other plots of Figures 12-14 are nonlinear.

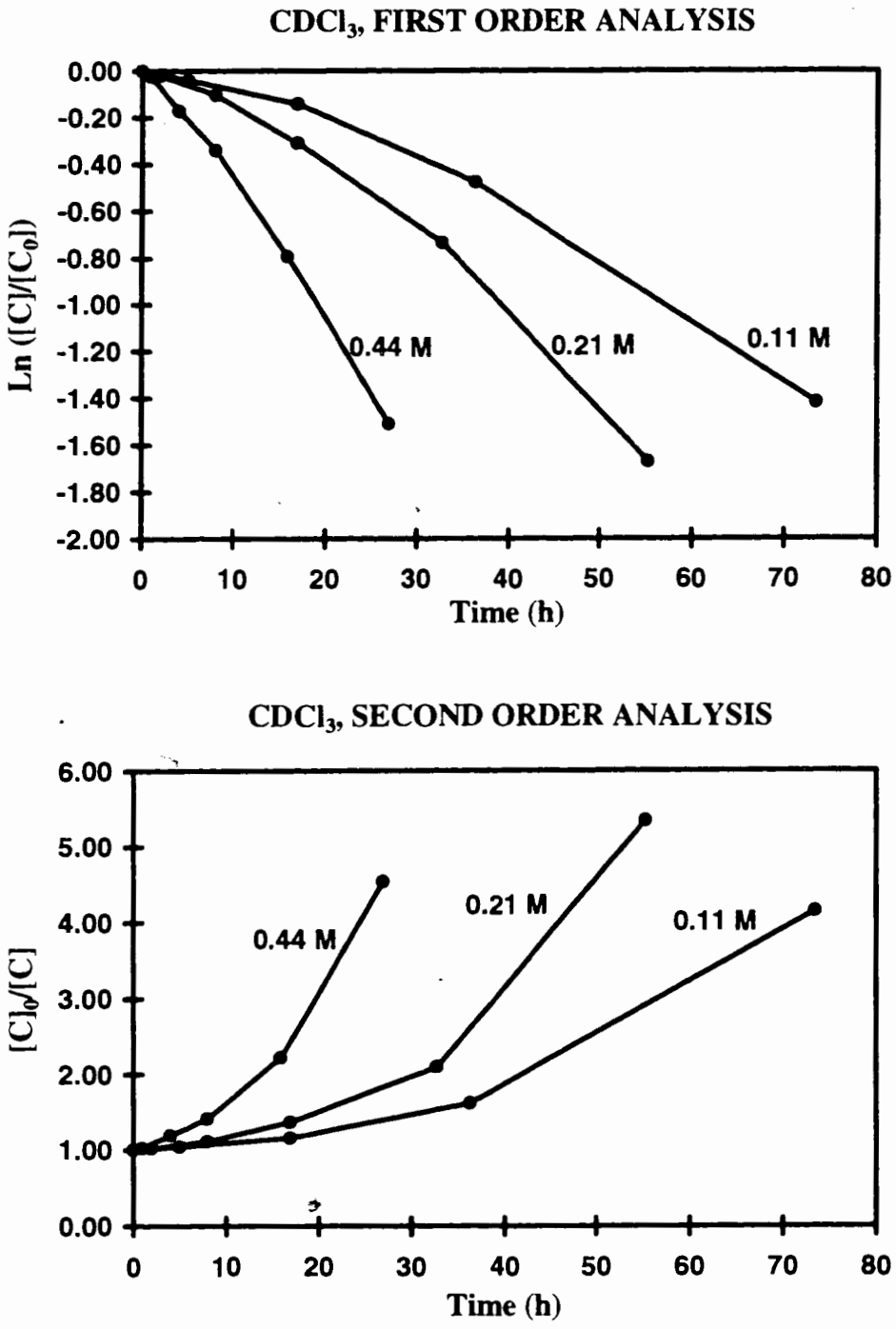
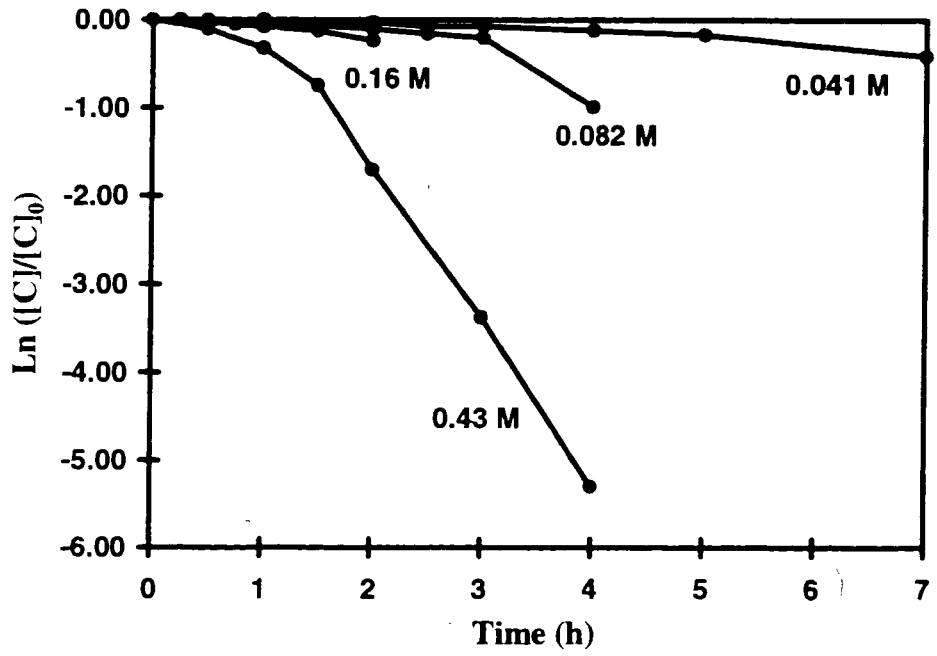


Figure 12. Concentration dependence of the rearrangement of 2-methoxypyridine-1-oxide in chloroform at 140 ^{0}C. Upper : first order plots. Lower : second order plots.

METHYL

DMF, FIRST ORDER ANALYSIS



DMF, SECOND ORDER ANALYSIS

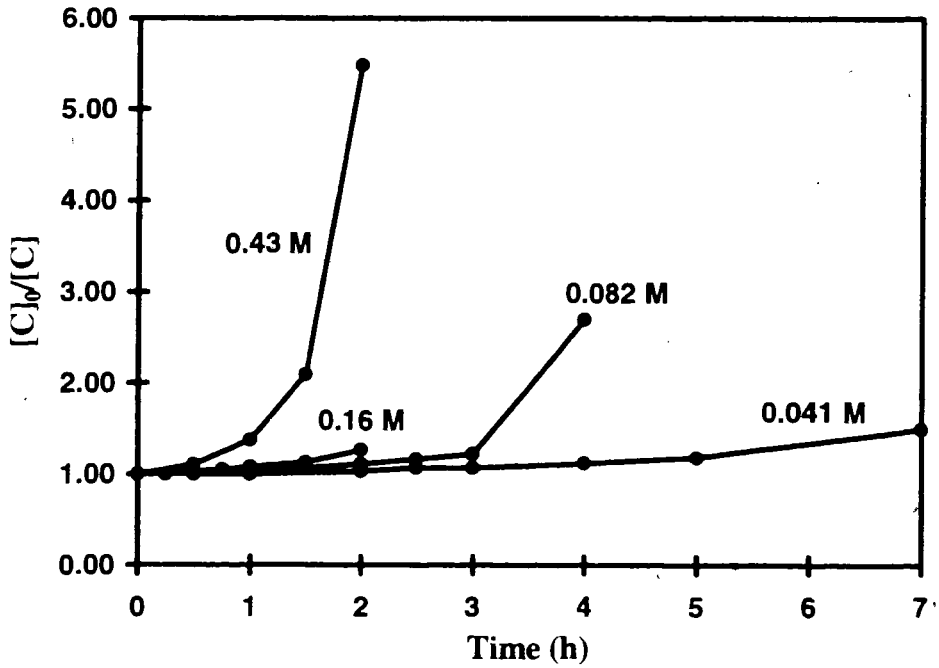


Figure 13. Concentration dependence of the rearrangement of 2-methoxypyridine-1-oxide in dimethylformamide at 140 ^{0}C. Upper : first order plots. Lower : second order plots.

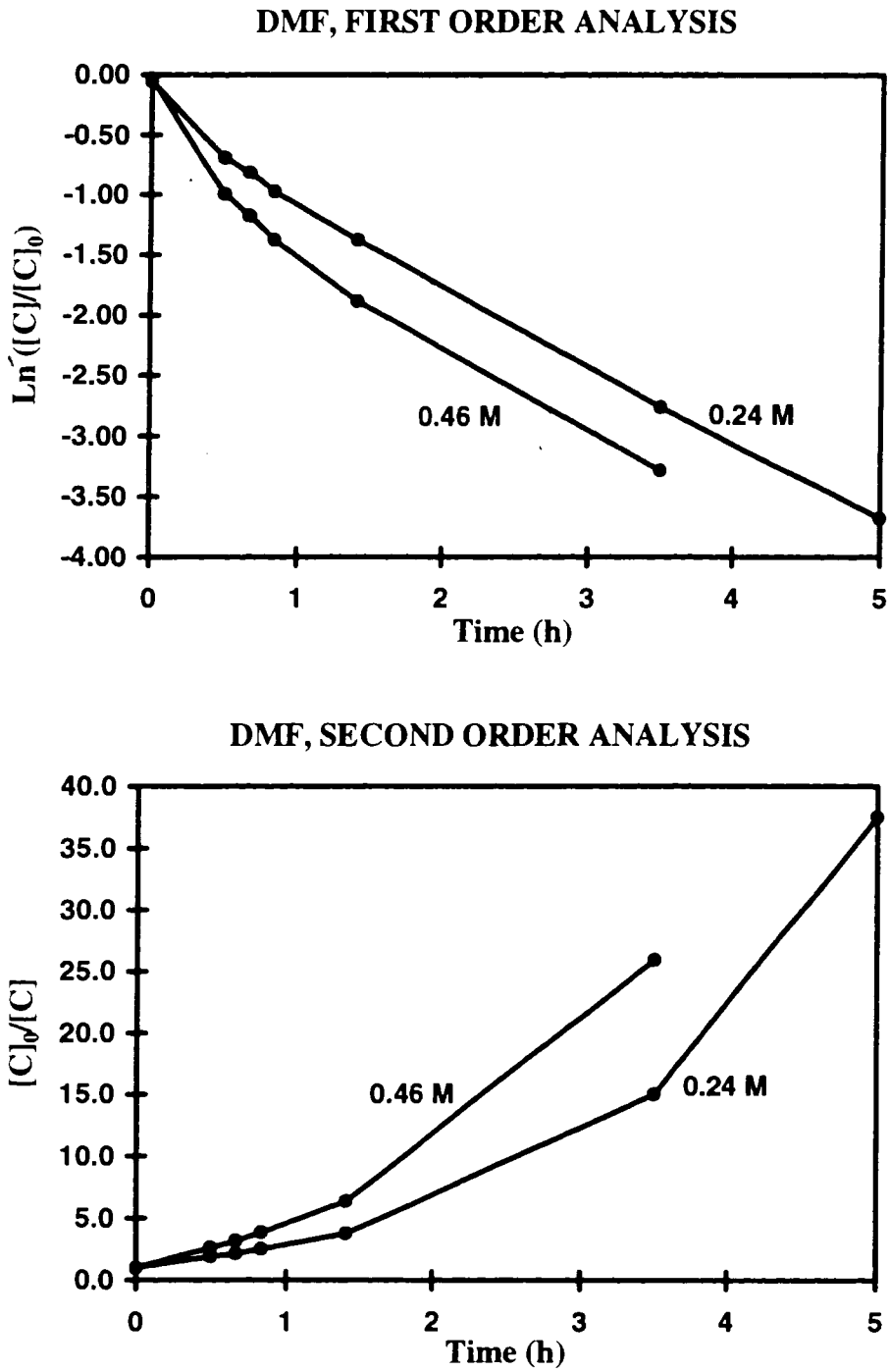


Figure 14. Concentration dependence of the rearrangement of 2-benzyloxypyridine-1-oxide in dimethylformamide at 140 ^{0}C. Upper : first order plots. Lower : second order plots.

Figures 15 and 16 are concentration-time plots of the kinetic data for the rearrangement of **1** (R = methyl) in chloroform and in dimethylformamide, respectively. The theoretical curves shown in these Figures have been generated *using Scheme 1*,[20] with the following rate constants: in chloroform, $k_1 = 3 \times 10^{-5}\ M^{-1}s^{-1}$; $k_2 = 4 \times 10^{-5}\ s^{-1}$. In dimethylformamide, $k_1 = 3 \times 10^{-4}\ M^{-1}s^{-1}$; $k_2 = 1.5 \times 10^{-4}\ s^{-1}$. Figure 17 shows the concentration-time plots of the kinetic data for the rearrangement of **1** (R = benzyl). The theoretical curves have been generated *using Scheme 2*,[20] with $k_1 = 1.5 \times 10^{-3}\ M^{-1}s^{-1}$; $k_2 = 2.5 \times 10^{-3}\ s^{-1}$, $k_3 = 8 \times 10^{-4}\ s^{-1}$.

The kinetic results are consistent with the results of the crossover experiments: in chloroform and in dimethylformamide, 2-methoxypyridine-1-oxide rearranges via Channel D, with a single inversion of the alkyl group. Each of the two consecutive alkyl transfers is faster in the more polar solvent. In dimethylformamide, 2-benzyloxypyridine-1-oxide rearranges via both Channel B, which leads to a double inversion of the alkyl group, and Channel D, which leads to a single inversion of the alkyl group. The single inversion pathway is preferred.

METHYL

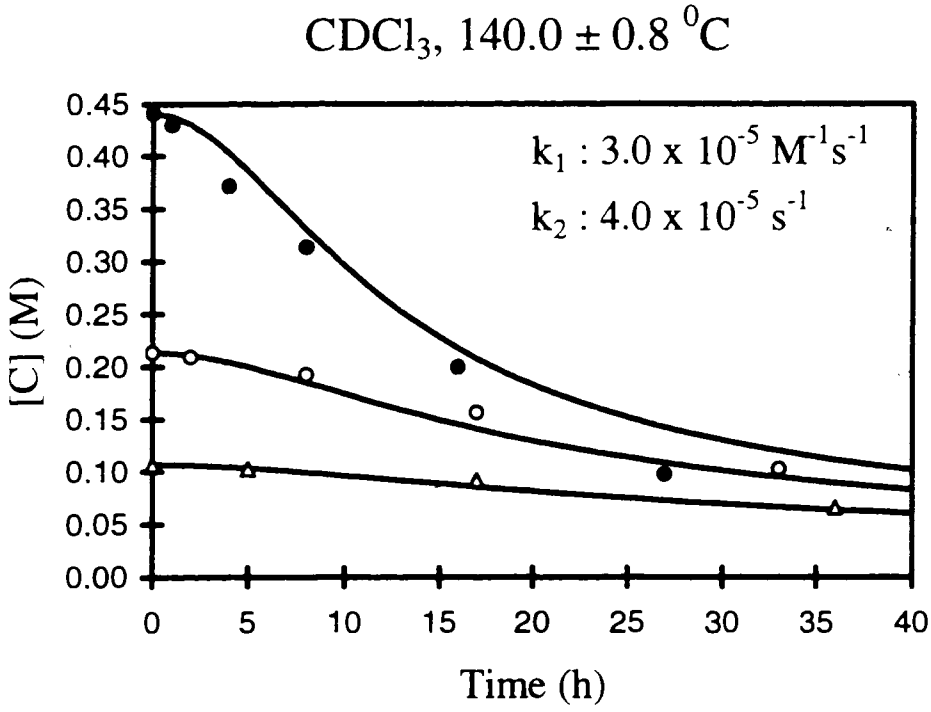


Figure 15. Concentration-time plots of the rearrangement of 2-methoxypyridine-1-oxide in chloroform at 140 °C. The theoretical curves are based on Scheme 1, which assumes that Channel D is the principal reaction path.

METHYL

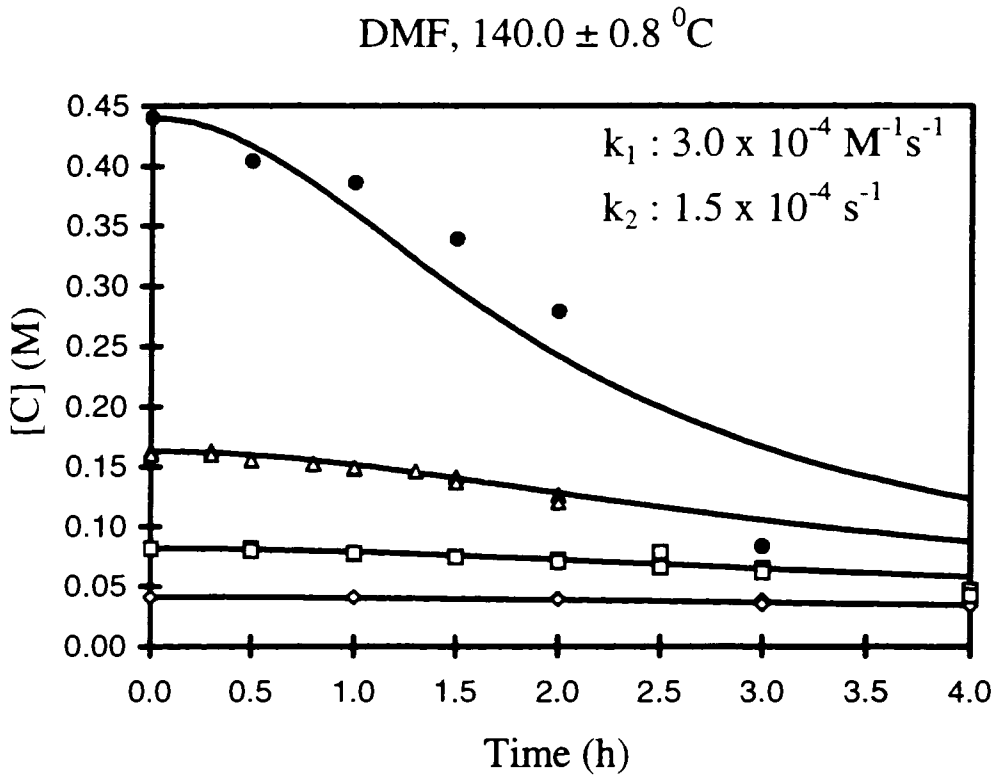


Figure 16. Concentration-time plots of the rearrangement of 2-methoxypyridine-1-oxide in dimethylformamide at 140 °C. The theoretical curves are based on Scheme 1, which assumes that Channel D is the principal reaction path.

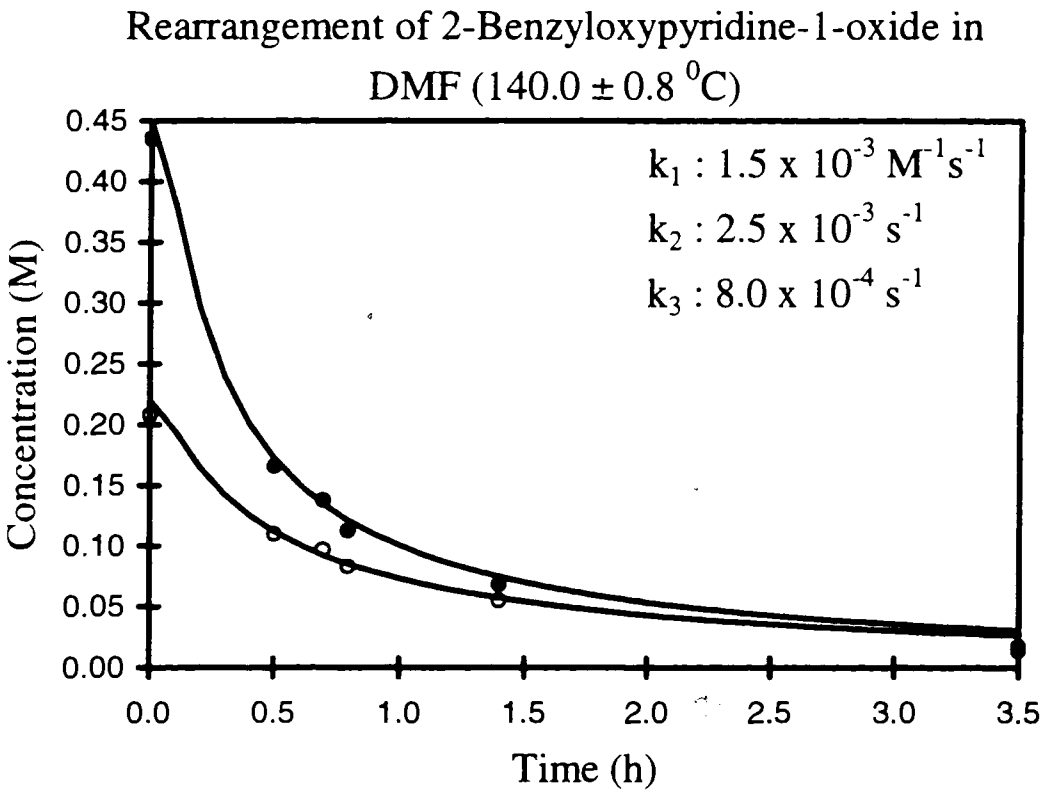
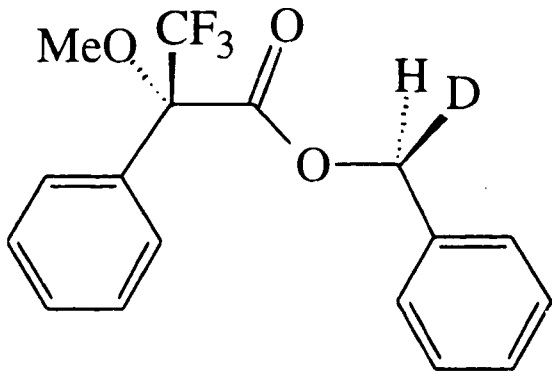


Figure 17. Concentration-time plots of the rearrangement of 2-benzyloxypyridine-1-oxide in dimethylformamide at 140 ^{0}C. The theoretical curves are based on Scheme 2, which assumes competition between Channels B and D.

2-2-6 Stereochemical Studies.

The benzyl ester of the (**S**)-(-) enantiomer of α-methoxy-α–(trifluoro-methyl)phenylacetic acid (MTPA) (**16**), Mosher's acid, was prepared by the method of Ward and Rhee.[21]



16

In chloroform-d, the diastereotopic benzylic protons of **16** are observed in the ^{1}Hmr as an AB-quartet at 5.35 and 5.31 ppm (Figure 18a). The deuterium-decoupled ^{1}Hmr spectrum of the MTPA ester prepared from racemic benzyl-α-d-alcohol (Figure 18b) shows two singlets, with an isotope shift of 0.02 ppm for both hydrogens. These observations allowed nmr to be used in place of polarimetry to determine the stereochemical course of the rearrangement of **1** (R = CHDPh).[22]

Following Keck and coworkers,[23] chiral benzyl-α-alcohol was prepared by reduction of benzaldehyde with tributyl tin deuteride in the presence of (S)-binaphthol and titanium (IV) isopropoxide. The deuterium-decoupled spectrum of the benzylic region of the MTPA ester of this alcohol is shown in Figure 18c. As summarized in Chart 2, the chiral alcohol was then converted to **1** (R = CHDPh), the latter was heated in DMF at 140 ^{0}C until the rearrangement was 67 percent complete (3 h), and the unreacted **1** and the product **2** (R = CHDPh) were isolated.

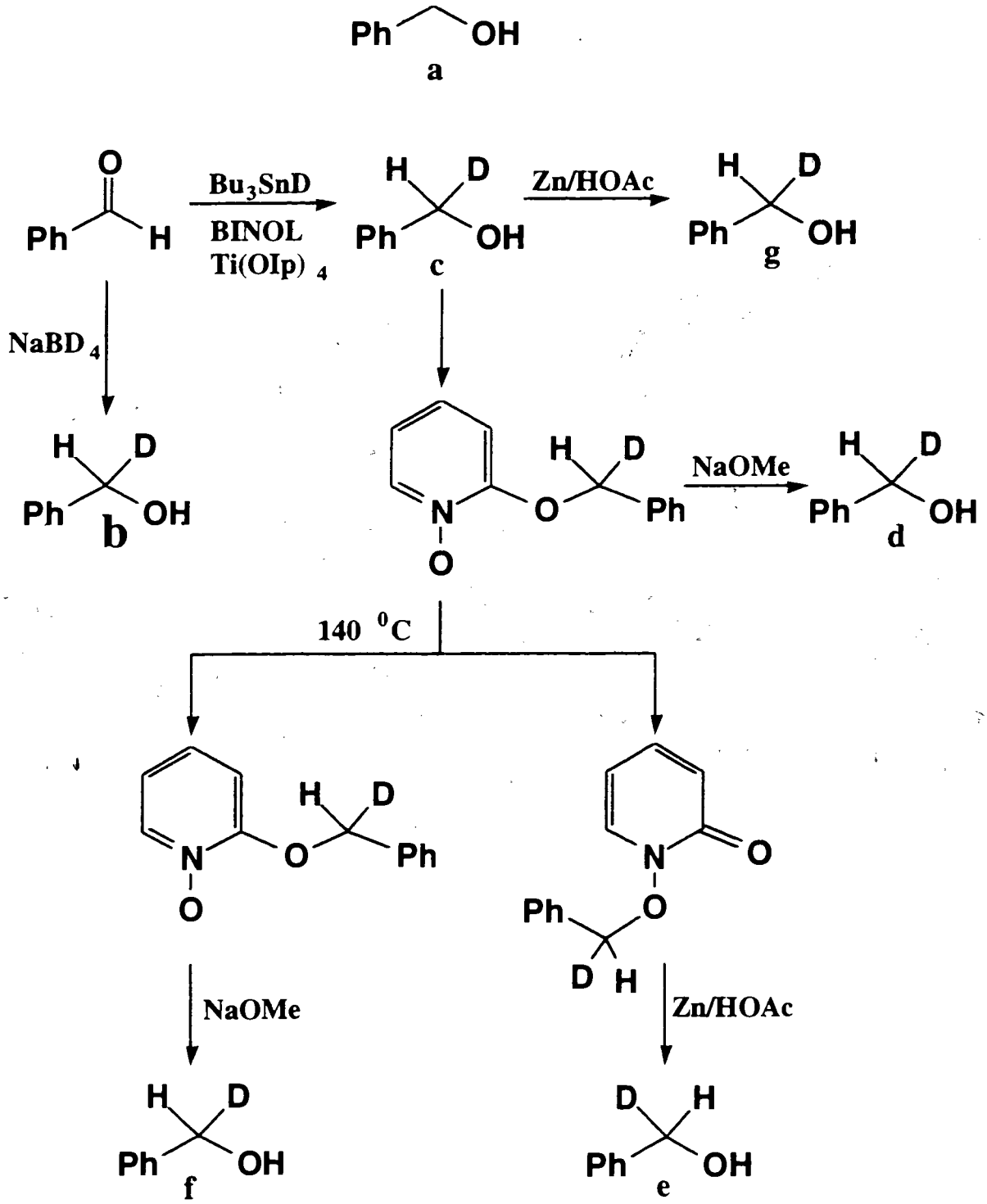


Chart 2. Chiral syntheses

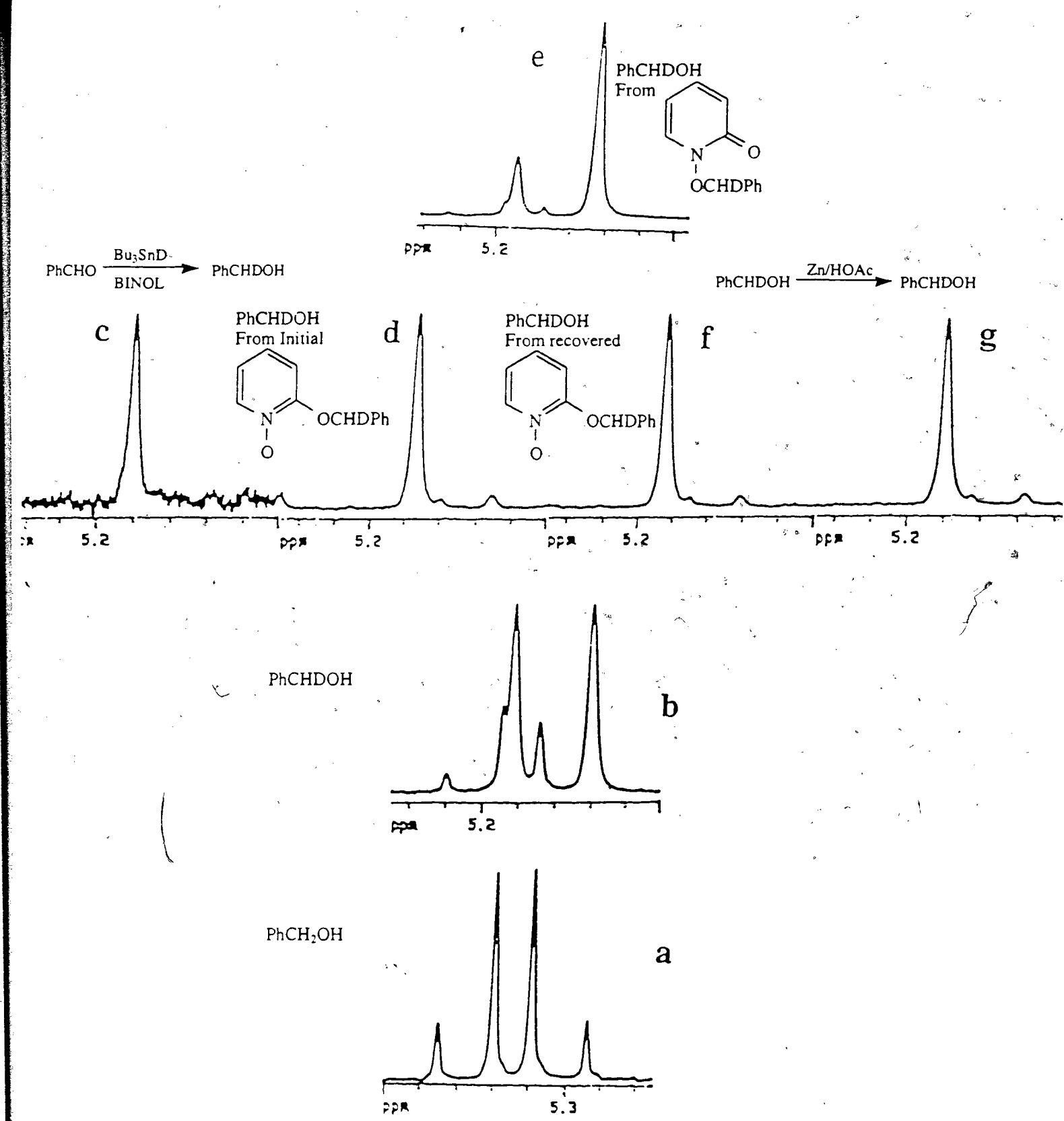


Figure 18 Benzylic region in the ^{1}Hmr spectra of the Mosher esters of (**a**) benzyl alcohol; (**b**) racemic benzyl-α-d-alcohol; (**c**) chiral benzyl-α-d-alcohol; (**d**) the benzyl alcohol recovered from freshly prepared **1** (R = benzyl-α-d) following treatment with NaOMe; (**e**) the benzyl-α-d-alcohol obtained by partial conversion of **1** (R = benzyl-α-d) (from d) to **2** (R = benzyl-α-d) and treatment of **2** with Zn/HOAc; (**f**) the benzyl alcohol obtained upon treatment of **1** (R = benzyl-α-d) (recovered from e) with NaOMe; (**g**) the benzyl alcohol obtained upon treatment of the alcohol (from c) with Zn/HOAc. The spectra of (b)-(g) have been deuterium decoupled.

Benzyl alcohol was recovered from the product by reduction with zinc and acetic acid,[5] and from the reactant by treatment with NaOMe/MeOH. Figures 18e and 18f are the benzylic regions of the MTPA esters of the alcohol from **2** and the alcohol from **1**, respectively. Figures 18d and 18g refer to control samples obtained, respectively, following NaOMe/MeOH treatment of the initial sample of **1** and Zn/HOAc treatment of the original sample of benzyl-α-d-alcohol. There is no significant racemization of the starting material during the course of the rearrangement or during the recovery of benzyl-α-d-alcohol. Any racemization in the benzyl alcohol recovered from the product must, therefore, have occurred during the rearrangement.

The key results are those of Figures 18c and 18e, which show that in dimethylformamide solvent the product forms with a 3 : 1 ratio of inversion to retention. This is the result expected from the crossover and kinetic experiments already described, but it does not agree with the stereochemical observation of Schöllkopf and Hoppe,[5] using polarimetry. The rearrangement of chiral **1** (R = CHDPh) was, therefore, also examined under their experimental conditions (chloroform, 0.3 M, 140 ^{0}C).

2-2-7 Kinetics and stereochemistry of the rearrangement of 1 (R = benzyl) in chloroform solvent.

Figure 19 shows the deuterium decoupled benzylic protons in the ^{1}Hmr spectra of the MTPA esters of the benzyl alcohol recovered from **1** after 60 percent of reaction, and, in a second experiment, the benzyl alcohol recovered from **2** after rearrangement was complete. There is no significant racemization of the reactant, but the product is formed with apparent racemization.

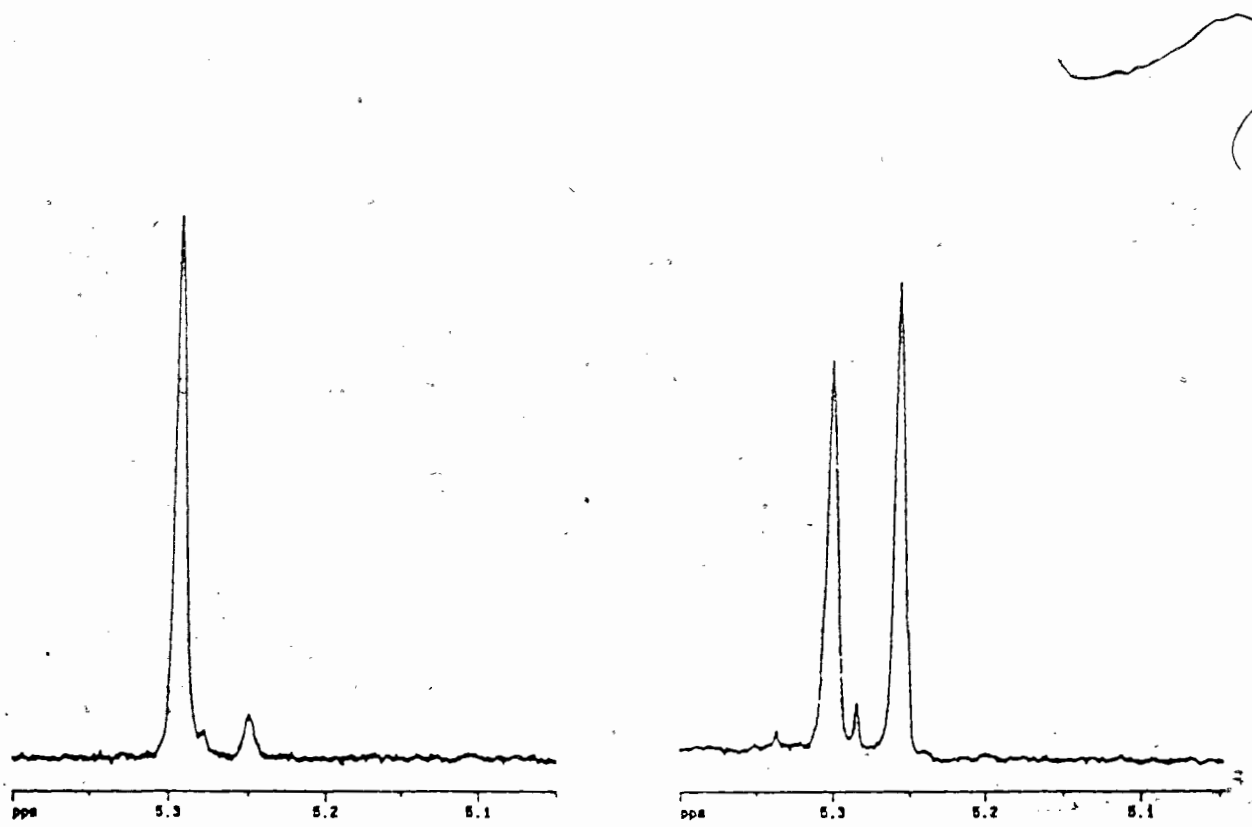


Figure 19 Deuterium-decoupled ^{1}Hmr spectra of, Left : the Mosher ester of the benzyl-α-d-alcohol recovered from chiral **1** (R = benzyl-α-d) after 60% rearrangement of a 0.3 M chloroform solution at 140 ^{0}C. Right : the Mosher ester of the benzyl-α-d-alcohol recovered from chiral **2** (R = benzyl-α-d) after complete rearrangement of a 0.3 M chloroform solution of **1** (R = benzyl-α-d) at 140 ^{0}C.

The usual interpretation of racemization, i.e., that an achiral intermediate must have been produced, would be incorrect in this case. In fact, *two* reactions have occurred. One, via Channel B, has given the product with net retention of configuration; the other, via Channel D, has afforded the product with net inversion of configuration. Under the specific reaction conditions employed (0.3 M, chloroform), the two rate constants are almost the same.

The results of a kinetic study, performed under the same conditions, are consistent with this interpretation. Figure 20 is a first order plot of the rearrangement of 2-benzyloxypyridine-1-oxide at 140 ^{0}C. The plot is curved; if the curvature is ignored, the apparent first order rate constant is 4.9 x 10^{-5} s^{-1}, in reasonable agreement with the first order rate constant reported by Hoppe,[5] 6.64 x 10^{-5} s^{-1}. Figure 21 is a concentration-time plot of the rearrangement of 2-benzyloxypyridine-1-oxide at 140 ^{0}C. The theoretical plot has been generated *using Scheme 2*, with the following rate constants: k_1 = 1.5 x 10^{-4} $M^{-1}s^{-1}$; k_2 = 8 x 10^{-4} s^{-1}; k_3 = 8 x 10^{-4} s^{-1}.

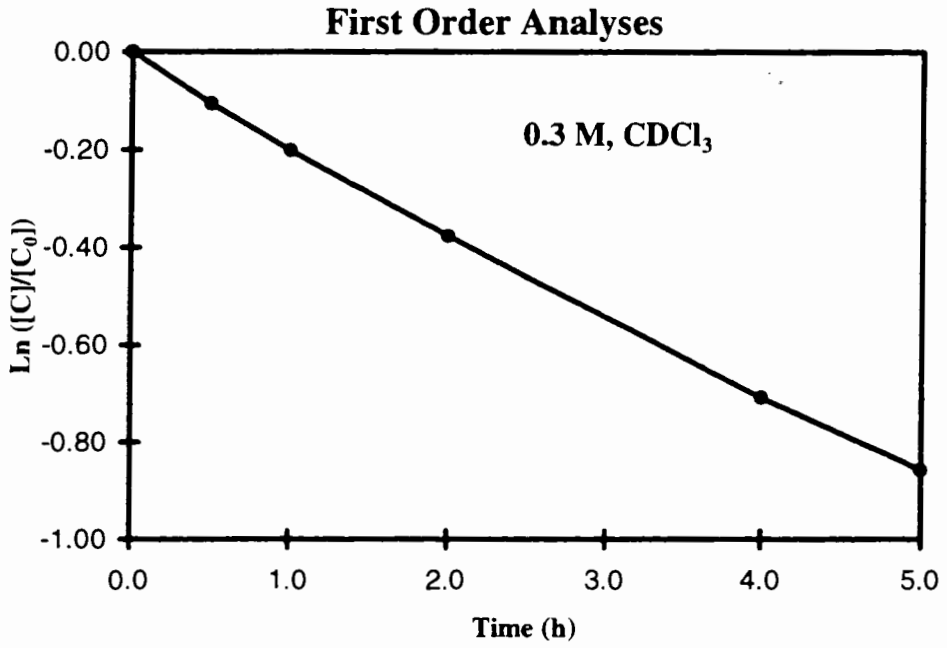


Figure 20 First order plot of the kinetic data for the rearrangement of a 0.3 M chloroform solution of 2-benzyloxypyridine-1-oxide at 140 ^{0}C.

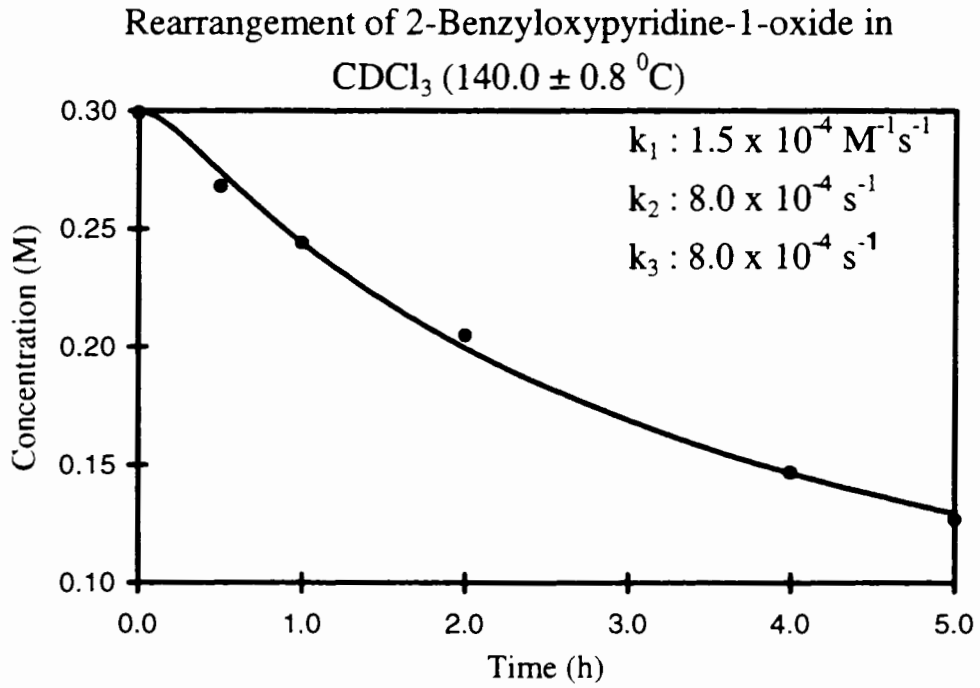


Figure 21 Concentration-time plot of the rearrangement of 2-benzyloxypyridine-1-oxide in chloroform at 140 ^{0}C. The theoretical curve has been calculated using Scheme 2, with Channels B and D contributing equally to the formation of the product.

2-2-8 Secondary kinetic isotope effect in the rearrangement of 1 (R = Me).

The kinetic, stereochemical and crossover experiments in the benzyl series all lead to the conclusion that the rearrangement of **1** (R = benzyl) to **2** (R = benzyl) proceeds via two channels, one of which involves a single inversion of configuration and the other a double inversion. For R = methyl, the kinetic and crossover experiments are consistent with a single inversion process. We did not attempt to confirm this point by stereochemical studies based on the use of a chiral methyl group.[24] Instead, since the CH_3/CD_3 kinetic isotope effects calculated for the retention and inversion mechanisms are not the same (1.35 and 1.02, respectively), and calculated secondary H/D isotope effects agree well with experiment,[25] we attempted to determine this isotope effect. In view of the complex kinetics already discussed, the direct measurement of k_H/k_D was problematical, and an indirect determination based on competition experiments was considered. For this approach to be readily applicable, the reaction should exhibit a unit order (e.g. 1 or 2), and this was the case only under the special conditions reported by Hoppe[5] and confirmed in the present work: 0.45 M in chloroform solvent.

Therefore, an approximately 1 : 1 mixture of **1** (R = CH_3) and **1** (R = CD_3) was prepared, recrystallized from ethyl acetate, and the EI-MS was measured (*a*). Two determinations were made. In one, a 0.45 M solution of the mixture in chloroform was heated for 8.0 h at 140 ^{0}C, at which time the mole fraction of unreacted **1** (*c*), determined as already described, was 0.768. In the second experiment, the 0.45 M solution was heated for 16.0 h, and the mole fraction of unreacted **1** (*c*) was 0.508. The unreacted **1** from each of these experiments was then recovered and the EI-MS was measured (*b*).

The results are summarized in Table 5, and the secondary isotope effects were calculated using equation 1,[26] where *a*, *b*, *c* are as defined above. The average isotope effect is 0.99.

Table 5 : Competition experiments to determine the secondary CH_3/CD_3 kinetic isotope effect in the rearrangement of **1** (R = CH_3) in chloroform.

Time (h)	125/128 ratio	mole fraction of **1**	k_H/k_D[a]
0.0	1.206	1.000	
8.0	1.194	0.768	1.03
16.0	1.253	0.508	0.94

a : Calculated using equation 1.

$$\frac{k_H}{k_D} = \frac{\ln \dfrac{b}{a} \cdot \dfrac{c(1+a)}{(1+b)}}{\ln \dfrac{c(1+a)}{(1+b)}} \qquad \textbf{(1)}$$

This result is significantly lower than the value (1.35) computed for the intramolecular (retention) mechanism. On the other hand, the theoretical isotope effects are 1.02 and 0.87, respectively, for the first and second steps of the intermolecular (inversion) mechanism of Scheme 1. These values lead to a calculated pseudo-first-order isotope effect for this mechanism of 0.95-0.98, in much better agreement with the experimental result. We suggest that the isotope effect criterion employed here may be useful to distinguish genuine retention from double inversion mechanisms in other methyl transfer reactions that have been found to proceed with retention of configuration.[4a,27]

2-2-10 Solvent effects.

The evidence presented so far has shown that the rearrangement of **1** (R = CH_3) and **1** (R = benzyl) are two-step processes. In the case of the methyl compound, Channel D is the major contributor to the second step. In the case of the benzyl compound, Channels B and D contribute to the second step. With both substrates, a change in solvent, from chloroform to dimethylformamide, leads to a change in the rate constants of the individual steps, but does not alter the mechanism.

Ballesteros et al[8] had reported that no rearrangement of the methyl compound was observed after refluxing for 20 h in toluene, and concluded that an ionic mechanism was inhibited in the non-polar solvent. The present work suggests an alternative interpretation of this solvent effect, namely, that dimeric complexes of type **13** are present only in low concentrations in aromatic solvents because of preferential complexation of a 2-alkoxypyridine-1-oxide with the solvent.

Accordingly, **1** (R = CH_3) was heated at 140 ^{0}C in toluene, in anisole, and in nitrobenzene. Although at this temperature the rearrangement of **1** is 70 percent complete in 4 h in dimethylformamide, there was no significant reaction in 24 h in toluene or in 4 h in the polar aromatic solvents.

Chapter 3

Conclusion

The central thesis of this work has been confirmed. Retention of configuration in nucleophilic displacement at carbon should be regarded as evidence of a complex reaction mechanism that includes an even number of inversion steps. In the case of the Tieckelmann reaction, two inversions at the same carbon, leading to net retention of configuration, compete kinetically with single inversion at two different carbons, leading to net inversion of configuration.

All previous studies of this rearrangement are consistent with this mechanism. These include the crossover studies of Lister and Tieckelmann,[2] and of Ballesteros et al,[8] the rearrangement of **6** to **7**,[4] the p-substituent effect in the rearrangement of 2-benzyloxypyridine-1-oxides,[5] the negative volume of activation,[9] and the skeletal isomerization in the rearrangement of the cyclopropylcarbinyl substituent.[2a, 5, 28]

Although the Woodward-Hoffmann rules[7] can allow us to make a prediction of the reaction mechanism, it is not necessary that the reaction itself will follow the predicted behaviour. As noted by Ollis and coworkers,[4c] there are several structurally similar [1,4] anionic rearrangements (Figure 22). In all cases, because of the inherent problems associated with a six-electron [1s,4s] pericyclic rearrangement, they can be considered as candidates for a more complex bimolecular mechanism. Whether these reactions will exhibit the same behaviour as 2-alkoxypyridine-1-oxides remains to be determined.

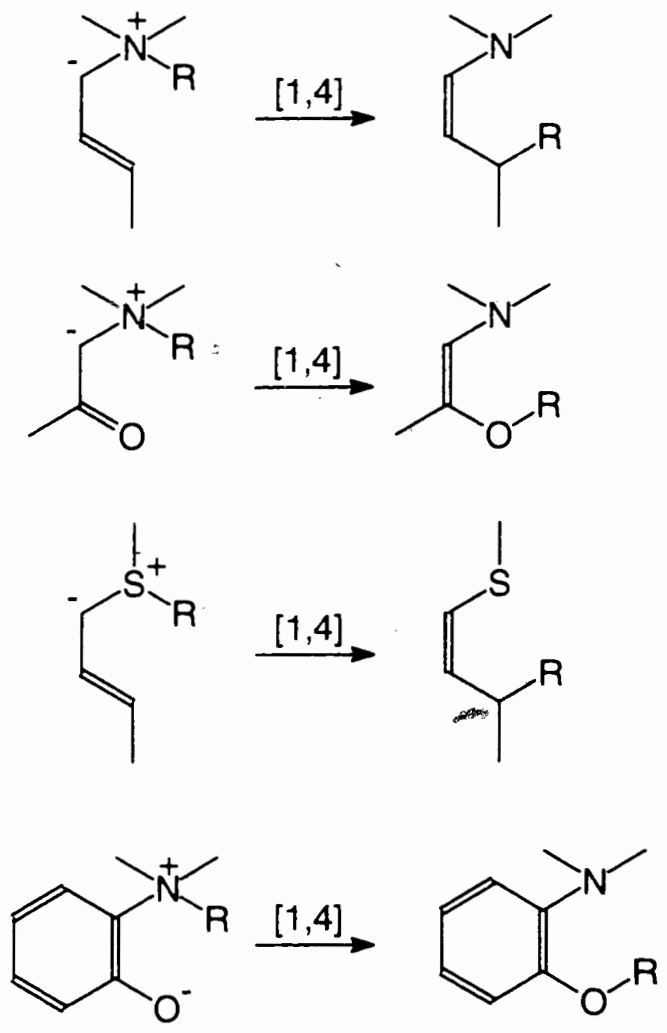


Figure 22 : Potential candidates for a complex bimolecular mechanism.

Chapter 4

Experimental Section

Solvents were dried by standard procedures and distilled prior to use. ^{1}Hmr and ^{13}Cmr spectra were obtained on either a Bruker model SY-100 or AMX 400 spectrometer. Chemical shifts are recorded in ppm downfield from tetramethylsilane. Infrared spectra were obtained on a Perkin-Elmer 599B spectrophotometer (1% KBr pellet or 1% solution). Mass spectra were obtained, at Simon Fraser University, by Mr. G. Owen on a Hewlett-Packard 5985 GC/MS/IS system operating at 70 eV and, at the University of British Columbia, by Dr. G. Eigendorf on a Kratos MS 50 system. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Microanalyses were carried out at Simon Fraser University by M. K. Yang on a Carlos Erba model 1106 elemental analyser. Analytical thin layer chromatography was performed on precoated Merck silica gel 60 F-24 plates with aluminium backing. Spots were observed under ultraviolet light or were visualized with 1% ceric sulfate. Column chromatography was carried out using 230-400 mesh silica gel (Merck). Kinetic studies were performed in sealed tubes in a Fisher high temperature oil bath (silicone oil) fitted with a Thermotronic Devices, Inc. Model 51 proportional temperature controller. Solutions for kinetic studies were degassed by several freeze-pump-thaw cycles.

1. 2-Chloropyridine-1-oxide.

To a 250 mL three-necked flask fitted with magnetic stirrer, condenser and dropping funnel were added chloroform (70 mL) and m-chloroperbenzoic acid (14.6 g, 85 mmol). The mixture was stirred for 1 min and a solution of 2-chloropyridine (6.7 mL, 8.0 g, 70.5 mmol) in chloroform (30 mL) was added dropwise during 20 min. When the addition was complete, the mixture was warmed to 65-70 °C, stirred for 24 h, and then cooled to room

temperature and poured, with stirring, into ice-cold 3N sodium hydroxide (100 mL). This mixture was stirred vigorously for 10 min and the layers were then separated. The aqueous layer was extracted with chloroform (3 x 150 mL). The combined organic extracts were dried and evaporated under reduced pressure. The product was purified by chromatography on silica gel (ethyl acetate) and crystallized from dichloromethane-ether-hexane (1 : 2 : 10) to give 5.5 g (60 %) of white shiny plates m.p. 63-65 °C. (lit.[2], m.p. 69-71 °C, evacuated capillary)

^{1}Hmr ($CDCl_3$): 8.34-8.36 (1H, m, *H6*), 7.49-7.51 (1H, m, *H* 4), 7.18-7.23 (2H, m, *H3, H5*).

^{13}Cmr ($CDCl_3$): 140.8 (*C2*), 127.2 (*C3, C5*) 125.6 (*C6*), 123.9 (*C4*).

MS (EI, m/z) : 131, 129 (ratio ≈ 25 : 75).

Anal : Calculated for C_5H_4NOCl : C, 46.36; H, 3.11; N, 10.81. Found : C, 46.45; H, 3.14; N 10.74.

2. 2-Methoxypyridine-1-oxide :

To a round-bottomed flask fitted with magnetic stirrer and condenser were added distilled methanol (15 mL) and sodium metal (390 mg, 17.0 mg-atom). When the sodium had reacted, a solution of 2-chloropyridine-1-oxide (2 g, 15.4 mmol) in methanol (10 mL) was added dropwise during 10 min. The solution was refluxed for 1 h after the addition was complete, cooled, and the solvent was removed under reduced pressure. The crude mixture was dissolved in water (30 mL) and extracted with chloroform (4 x 100 mL). The combined organic extracts were dried and evaporated to afford a light yellow solid which was purified by chromatography (silica gel; methanol : ethyl acetate, 1 : 1). Crystallization from ethyl acetate afforded white needles. 0.97 g (50 %). m.p. 73-76 °C.

(lit.[18] m.p. 78-79 ^{0}C, hydrate, 66.5-67.5 ^{0}C). The sample submitted for x-ray crystallographic determination was obtained by recrystallization from boiling toluene.

^{1}Hmr ($CDCl_3$): 8.27-8.29 (1H, ddd, 6.4Hz, 1.6Hz, 0.5 Hz, *H6*), 7.28-7.32 (1H, dd, 7.7 Hz, 1.6 Hz, *H4*), 6.89-6.95 (2H, m, *H3*, *H5*), 4.08 (3H, s, OCH_3).

IR : 1606, 1522, 1348 cm^{-1}.

^{13}Cmr ($CDCl_3$): 158.87, 140.18, 127.72, 117.63, 108.34, 57.25.

MS (EI, m/z) : 125.

Anal. : Calculated for $C_6H_7NO_2 \bullet 1.0H_2O$: C, 50.35; H, 6.33; N, 9.79. Found : C, 50.46; H, 6.22; N, 9.84.

3. 2-d3-Methoxypyridine-1-oxide

Repetition of the above reaction with d4-methanol (10 mL), sodium metal (177 mg, 7.7 mg-atom) and 2-chloropyridine-1-oxide (1 g, 7.7 mmol). gave 0.42 g (43 %) of product, m.p. 73-76 ^{0}C.

^{1}Hmr : 8.27-8.29 (1H, *H* 6, d, 6.4 Hz), 7.28-7.32 (1H, *H* 4, dd, 7.8, 8.2 Hz), 6.89-6.95 (2H, *H* 3, *H* 5, m).

^{13}Cmr : 158.87, 140.18, 127.72, 117.63, 108.34.

MS (EI, m/z) : 128.

4. 2-d3-Methoxy-6-d-pyridine-1-oxide

The above reaction was repeated using d4-methanol (10 mL), sodium metal (210 mg, 9.2 mg-atom) and 2-chloropyridine-1-oxide (1 g, 7.7 mmol). When the addition was complete, the reaction was refluxed for 12 h. Isolation gave 0.36 g (36 %), m.p. 73-76 ^{0}C.

^{1}Hmr ($CDCl_3$): 8.25-8.27 (0.2 H, dd, 6.4 Hz, 1.6 Hz, *H6*), 7.26-7.30 (1H, m, *H4*), 6.88-6.93 (2H, m, *H3, H5*).

^{13}Cmr ($CDCl_3$): 158.87, 140.18, 127.72, 117.63, 108.34.

MS (EI, m/z) : 129, 128 (ratio, 4 : 1).

5. 1-Methoxy-2-Pyridone

A solution of 2-methoxypyridine-1-oxide (200 mg, 1.6 mmol) in dimethylformamide (4 mL) was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (ethyl acetate : methanol, 1 : 1) to give a yellow oil, 144 mg (72%).

^{1}Hmr ($CDCl_3$): 7.50-7.52 (1 H, dd, 6.4 Hz, 1.6 Hz, *H6*), 7.28-7.32 (1H, dt), 6.65-6.67 (1H, dd), 6.11-6.15 (1H, dt), 4.06 (3H, s).

^{1}Hmr (DMF-d_7): 7.95-7.97 (1 H, dd), 7.40-7.46 (1H, dt), 6.51-6.53 (1H, dd), 6.21-6.24 (1H, m), 4.00 (3H, s).

^{13}Cmr ($CDCl_3$): 158.1, 138.4, 135.1, 122.5, 105.0, 64.3.

MS (EI, m/z) : 125.

Anal. : Calculated for $C_6H_7NO_2 \bullet 0.75H_2O$: C, 52.00; H, 6.14, N, 10.11. Found : C, 52.23, H, 6.20, N, 11.22.

6. Kinetic Studies of the rearrangement of 2-Methoxypyridine-1-oxide, General procedure :

A. In Dimethylformamide :

A solution of 2-methoxypyridine-1-oxide (142.6 mg, 1.14 mmol) in dimethylformamide (7 mL, 0.16 M) was divided into seven portions and sealed in glass tubes. These tubes were then heated for different times at 140 ± 0.8 ^{0}C. The solvent was removed and the residue was dissolved in chloroform-d to obtain the ^{1}Hmr spectrum. The peaks at 8.28 ppm and 6.13 ppm were used to determine the ratio of reactants and products, respectively.

B. In Dimethylformamide-d_7 :

A solution of 2-methoxypyridine-1-oxide (50.3 mg, 0.4 mmol) in dimethylformamide-d_7 (2.5 mL, 0.16 M) was divided into five portions, degassed and sealed in nmr tubes. The tubes were heated for different times at 140 ± 0.8 ^{0}C. ^{1}Hmr spectra were obtained directly. The peaks at 8.25 and 6.23 ppm were used to determine the ratio of reactants and products, respectively.

C. In Chloroform-d :

The procedure of part B was repeated with chloroform-d as solvent. The ^{1}Hmr peaks at 8.28 and 6.13 ppm were used to determine the ratio of reactants and products, respectively.

D. Results :

In Dimethylformamide :

Concentration (0.041 M) :

Time (hr)	P / R	R (M)
0.00	0.000	0.041
1.00	0.000	0.041
2.00	0.049	0.039
3.00	0.167	0.035
4.00	0.214	0.034
5.00	0.277	0.032
7.00	0.788	0.023

Concentration (0.082 M) :

Time (hr)	P / R	R (M)
0.50	0.000	0.082
1.00	0.038	0.079
1.50	0.076	0.076
2.00	0.133	0.072
2.50	0.216	0.067
3.00	0.294	0.063
4.00	0.891	0.043

Concentration (0.160 M) :

Time (hr)	P / R	R (M)
0.25	0.000	0.160
0.50	0.028	0.156
0.75	0.052	0.152
1.00	0.072	0.149
1.25	0.096	0.146
1.50	0.167	0.137
2.00	0.336	0.120

Concentration (0.164 M) :

Time (hr)	P / R	R (M)
0.00	0.000	0.164
0.50	0.029	0.159
1.00	0.106	0.148
1.50	0.222	0.134
2.00	0.261	0.130
3.00	1.262	0.072

Concentration (0.162 M) :

Time (hr)	P / R	R (M)
0.00	0.000	0.162
0.50	0.012	0.160
1.00	0.043	0.155
1.50	0.051	0.154
2.00	0.103	0.146
3.00	0.533	0.105
4.50	2.905	0.041
5.00	5.963	0.023

Concentration (0.163 M) :

Time (hr)	P / R	R (M)
0.00	0.000	0.163
0.50	0.040	0.156
1.00	0.139	0.143
1.50	0.203	0.135
2.00	0.228	0.132
3.00	2.217	0.051
4.00	4.178	0.031

Concentration (0.161 M) :

Time (hr)	P / R	R (M)
0.50	0.000	0.161
1.00	0.047	0.154
1.50	0.132	0.142
2.00	0.202	0.134
2.50	0.505	0.107
3.00	3.191	0.038

Concentration (0.43 M) :

Time (hr)	P / R	R (M)
0.00	0.000	0.432
0.50	0.106	0.390
1.00	0.379	0.313
1.50	1.096	0.206
2.00	4.480	0.079

In Dimethylformamide-d_7 :

Concentration (0.161 M) :

Time (h)	P / R	R (M)
0.00	0.000	0.161
0.33	0.020	0.158
0.67	0.025	0.157
1.00	0.110	0.145
1.33	0.211	0.133
1.67	0.290	0.125
2.00	0.487	0.108

Concentration (0.16M) :

Time (h)	P / R	R
0.00	0.000	0.160
1.00	0.039	0.154
2.00	0.182	0.135
4.00	2.414	0.047
4.67	4.932	0.027

R : 2-methoxypyridine-1-oxide
P : 1-methoxy-2-pyridone

In Chloroform-d :

Concentration (0.44M) :

Time (hr)	P / R	R (M)
0	0.000	0.441
1	0.026	0.430
4	0.188	0.371
8	0.407	0.313
16	1.214	0.199
27	3.533	0.097

Concentration (0.21M) :

Time (hr)	P / R	R (M)
0.00	0.000	0.213
2.00	0.022	0.209
8.00	0.111	0.192
17.00	0.365	0.156
32.75	1.090	0.102
55.30	4.333	0.040

Concentration (0.11M) :

Time (hr)	P / R	R (M)
0.0	0.000	0.107
5.0	0.041	0.103
17.0	0.155	0.092
36.0	0.613	0.066
73.5	3.151	0.026
117.0	8.969	0.011

R : 2-methoxypyridine-1-oxide
P : 1-methoxy-2-pyridone

7. Kinetic Isotope Effect Studies :

A mixture of 2-methoxypyridine-1-oxide (71.2 mg) and 2-d_3-methoxypyridine-1-oxide (70.1 mg) in chloroform (20 mL) was evaporated and dried in vacuo. The mixture was designated as A and the mass spectrum was determined.

A solution of mixture A (113.9 mg, 0.9 mmol) in chloroform-d (2.0 mL, 0.45 M) was divided into two portions and sealed into degassed tubes The tubes were heated for different times at 140 ± 0.8 ^{0}C. After the ^{1}Hmr spectrum was recorded, the solvent was removed and the residue was separated by column chromatography (ethyl acetate : methanol, 1 : 1) to recover the reactant. The ratio of 2-methoxypyridine-1-oxide to 2-d3-methoxypyridine-1-oxide of the recovered reactant was determined from the EI-MS operated at 100 ^{0}C. The degree of reaction was determined from the ratio of the peaks at 8.25 and 6.23 ppm.

Results :

	Degree of Reaction	Ratio	
		H	D
Starting Materials		1.206	1.00
Recovered St. M after 8h	0.232	1.194	1.00
Recovered St. M after 16h	0.492	1.253	1.00

H : 2-Methoxypyridine-1-oxide
D : 2-d3-Methoxypyridine-1-oxide

8. Solvent Effect :

1. Toluene :

2-Methoxypyridine-1-oxide (2.5 mg, 0.02 mmol) was dissolved in toluene (0.2 mL, 0.1 M), sealed in a tube and heated at 140 ^{0}C for 24 h. The solvent was removed and the ^{1}HMR spectrum ($CDCl_3$) found to be identical to that of 2-methoxypyridine-1-oxide.

2. Anisole :

2-Methoxypyridine-1-oxide (20.5 mg, 0.16 mmol) was dissolved in anisole (0.5 mL, 0.32 M) and heated at 140 ^{0}C for 4 h. The solvent was removed and the ^{1}HMR spectrum ($CDCl_3$) was again identical to that of 2-methoxypyridine-1-oxide.

3. Nitrobenzene :

2-Methoxypyridine-1-oxide (20.0 mg, 0.16 mmol) was dissolved in nitrobenzene (0.5 mL, 0.32 M) and heated at 140 ^{0}C for 4 h. The infrared spectrum showed peaks at 1522 and 1348 cm^{-1} with minor peaks at 1666 and 1499 cm^{-1}.

The infrared spectrum of 2-methoxypyridine-1-oxide (1 mg, 0.008 mmol) in nitrobenzene (1 mL) showed peaks at 1522 and 1348 cm^{-1}.

The infrared spectrum of 1-methoxy-2-pyridone (1 mg, 0.008 mmol) in nitrobenzene (1 mL) showed peaks at 1668 and 1499 cm^{-1}.

The infrared spectrum of the reaction mixture was similar to that of a 95 : 5 mixture of 2-methoxypyridine-1-oxide and 1-methoxy-2-pyridone.

9. 2-Benzyloxypyridine-1-oxide

To a round-bottomed flask fitted with a magnetic stirrer and a condenser were added tetrahydrofuran (10 mL), sodium metal (60.5 mg, 2.6 mg-atom) and benzyl alcohol (2.1 g, 19 mmol). The mixture was stirred until all of the sodium had dissolved, and 2-chloropyridine-1-oxide (308 mg, 2.4 mmol) was added in one portion. The mixture was

heated to reflux and stirred for 3 h, then cooled to room temperature and water (10 mL) was added. Extraction with chloroform (4 x 50 mL), drying and evaporation gave a white solid which was purified by column chromatography (silica gel; ethyl acetate followed by methanol : ethyl acetate, 1 : 2). Crystallization from ethyl acetate-hexane gave 0.34 g (73 %), m.p., 108-109 ^{0}C. (lit.[29], m.p. 103-106 ^{0}C)

^{1}Hmr ($CDCl_3$): 8.26-8.28 (1H, dd, 6.5 Hz, 1.6 Hz, *H6*), 7.43-7.46 (2H, m, Ph*H*), 7.33-7.40 (3H, m, Ph*H*), 7.13-7.17 (1H, dd, 7.7 Hz, 1.6 Hz, *H4*), 6.88-6.92 (1H, m, *H5*), 6.83-6.85 (1H, dd, 8.3 Hz, 1.7 Hz, *H3*), 5.44 (2H, s, CH_2).

^{13}Cmr ($CDCl_3$): 157.95, 140.45, 135.03, 128.78, 128.65, 127.72, 126.98, 118.48, 112.58, 72.51.

MS (EI, m/z) : 201.

Anal. : Calculated for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96, Found : C, 71.73; H, 5.64; N, 6.79.

11. 1-Benzyloxy-2-pyridone

A solution of 2-benzyloxypyridine-1-oxide (100 mg, 0.5 mmol) in dimethylformamide (4 mL) was refluxed for 12 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (ethyl acetate : hexane, 1 : 1). The product was crystallized from hexane to give a white solid, 87 mg (87%), m.p. 82-84 ^{0}C (Lit.[18] 85-86 ^{0}C).

^{1}Hmr ($CDCl_3$): 7.36-7.40 (5H, m, Ar), 7.24-7.28 (1H, dt), 7.09-7.11 (1H, ddd), 6.68-6.70 (1H, ddd), 5.90-5.94 (1H, dt), 5.29 (2H, s).

^{13}Cmr ($CDCl_3$): 158.9, 138.5, 136.7, 133.9, 130.0, 129.3, 128.7, 122.9, 104.3, 78.4.

MS (EI, m/z) : 201.

Anal. : Calculated for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96, Found : C, 71.48; H, 5.35; N, 7.03.

11. Kinetic Studies of 2-Benzyloxypyridine-1-oxide, General Procedures :

A. In Dimethylformamide-d_7 :

A solution of 2-benzyloxypyridine-1-oxide (225.3 mg, 1.12 mmol) in dimethyl-formamide-d_7 (2.5 mL, 0.45 M) was divided into five portions, degassed and sealed in nmr tubes. These tubes were heated for different times at 140 ± 0.8 ^{0}C. The ratio of reactants and products was determined from the ^{1}Hmr peaks at 8.25 and 6.23 ppm.

B. In Chloroform-d :

A solution of 2-methoxypyridine-1-oxide (150.0 mg, 0.75 mmol) in chloroform-d (2.5 mL, 0.30 M) was divided into five portions, degassed and sealed in nmr tubes. These tubes were heated for different times at 140 ± 0.8 ^{0}C. The ratio of reactants and products was determined from the ^{1}Hmr peaks at 8.28 and 6.13 ppm.

C. Results :

In Dimethylformamide-d_7 :

Concentration (0.22 M) : **Concentration (0.45 M) :**

Time (h)	P / R	R (M)	Time (h)	P / R	R (M)
0.00	0.058	0.222	0.00	0.034	0.446
0.50	0.999	0.117	0.50	1.712	0.170
0.67	1.266	0.104	0.67	2.251	0.142
0.83	1.652	0.089	0.83	2.970	0.116
1.42	2.971	0.059	1.42	5.600	0.070
3.50	14.860	0.015			

In Chloroform-d :

Concentration (0.45 M) :

Time (h)	P / R	R
0.00	0.000	0.448
0.50	0.432	0.313
1.00	0.921	0.233
2.00	2.262	0.137
2.75	3.819	0.093
3.75	6.385	0.061

Concentration (0.30 M) :

Time (h)	P / R	R (M)
0.00	0.000	0.299
0.50	0.112	0.268
1.00	0.224	0.244
2.00	0.457	0.205
4.00	1.032	0.147
5.00	1.358	0.127

R : 2-methoxypyridine-1-oxide concentration
P : 1-methoxy-2-pyridone

12. 2-Benzyl-a,a-d_2-oxy-6-d-pyridine-1-oxide

To a round-bottomed flask fitted with magnetic stirrer and dropping funnel were added distilled tetrahydrofuran (10 mL) and lithium aluminium deuteride (0.8 g, 19 mmol). A solution of freshly recrystallized benzoic acid (3 g, 24.6 mmol) in tetrahydrofuran (15 mL) was added dropwise during 5 min. Stirring was continued for 1 h, and saturated sodium sulfate (10 mL) was then added dropwise, followed by solid anhydrous sodium sulfate. The supernatant was decanted and concentrated under reduced pressure. The residue was dissolved in water (20 mL) and extracted with chloroform (3 x 100 mL). The organic extract was dried and evaporated and the product was purified by column chromatography (hexane : ethyl acetate, 5 : 1) to give 1.7 g (62 %) of benzyl-α,α-d_2 alcohol.

^{1}Hmr ($CDCl_3$): 7.32-7.39 (5H, m, Ph*H*), 2.57 (1H, O*H*, s).

MS (EI, m/z) : 110.

In the next step, tetrahydrofuran (15 mL), sodium metal (37.6 mg, 1.6 mg-atom) and benzyl-α,α-d_2-alcohol (1.05 g, 9.5 mmol) were stirred until the sodium had dissolved, and 2-d_3-methoxy-6-*d*-pyridine-1-oxide (135 mg, 1.0 mmol) was added in one portion. The mixture was refluxed for 4.5 h, cooled and treated with water (20 mL). The product was isolated by chromatography, as described above, to give 0.139 g (65 %) of the product, m.p., 108-109 ^{0}C

^{1}Hmr ($CDCl_3$): 8.26-8.28 (0.3 H, d, 6.5 Hz, *H6*), 7.44-7.46 (2H, m, Ph*H*), 7.32-7.39 (3H, m Ph*H*), 7.13-7.17 (1H, m, *H4*), 6.88-6.89 (1H, m, *H5*), 6.82-6.85 (1H, dd, 8.3 Hz, 1.6 Hz, *H3*).

MS (EI, m/z) : 204, 203 (ratio, 4.5 : 1)

13. Crossover experiments of 2-methoxypyridine-1-oxide and 2-d3-methoxy-6-d-pyridine-1-oxide in dimethylformamide, General procedures :

A mixture of 2-methoxypyridine-1-oxide (designated as H, 190.4 mg) and 2-d_3-methoxy-6-d-pyridine-1-oxide (designated as D, 250.7 mg) in chloroform (20.0 mL) was evaporated and maintained under reduced pressure until the residue solidified. The mass spectrum was obtained (initial reactants).

The above mixture (287.5 mg), in freshly distilled dimethylformamide (5.0 mL, 0.45M), was degassed, divided into five portions and sealed in glass tubes. These were heated for different times at 140 ± 0.8 ^{0}C. The solvent was then removed under reduced pressure and the residue was separated into reactant and product by preparative layer chromatography (methanol : ethyl acetate, 1 : 1). The mass spectra were recorded.

Results :

Experiment 1 :

Initial reactants

		Area	Ratio
	124	12540000	0.075
	125	54595000	0.327
	126	6667000	0.040
	127	11625000	0.070
	128	14862000	0.089
	129	53100000	0.318
	130	12225000	0.073
	131	1140000	0.007
Sum		166757000	

40 Min., Degree of Reaction : 19%

Recovered Reactants				**Products :**			
		Area	**Ratio**			**Area**	**Ratio**
	124	414000	0.061		124	72000	0.001
	125	2658000	0.393		125	11811000	0.219
	126	221000	0.033		126	8856000	0.165
	127	427000	0.063		127	2307000	0.043
	128	401000	0.059		128	15769000	0.293
	129	2088000	0.309		129	14315000	0.266
	130	516000	0.076		130	293000	0.005
	131	33000	0.005		131	410000	0.008
Sum	:	6758000		Sum	:	53833000	

70 Min., Degree of Reaction : 53%

Recovered Reactants			Products		
	Area	Ratio		Area	Ratio
124	399000	0.085	124	3000	0.000
125	1980000	0.423	125	65785000	0.200
126	199000	0.043	126	52379000	0.159
127	286000	0.061	127	14357000	0.044
128	274000	0.059	128	94533000	0.288
129	1254000	0.268	129	78738000	0.240
130	246000	0.053	130	20331000	0.062
131	36000	0.008	131	2403000	0.007
Sum :	4672000		Sum :	3.29E+08	

Experiment 2 :

Initial Reactants :			30 Min., Recovered Reactants :		
	Area	Ratio		Area	Ratio
124	129000	0.093	124	116000	0.094
125	494000	0.353	125	444000	0.359
126	62000	0.045	126	55000	0.045
127	103000	0.074	127	90000	0.073
128	118000	0.084	128	104000	0.085
129	385000	0.275	129	333000	0.270
130	95000	0.069	130	82000	0.067
131	9000	0.007	131	8000	0.007
Sum :	1395000		Sum :	1232000	

10 Min., Recovered Reactants :

		Area	Ratio
	124	80000	0.095
	125	300000	0.354
	126	34000	0.040
	127	62000	0.074
	128	73000	0.086
	129	234000	0.276
	130	58000	0.068
	131	6000	0.007
Sum	:	847000	

40 Min., Recovered Reactants :

		Area	Ratio
	124	194000	0.092
	125	724000	0.344
	126	96000	0.046
	127	160000	0.076
	128	181000	0.086
	129	586000	0.279
	130	146000	0.069
	131	15000	0.007
Sum	:	2102000	

20 Min., Recovered Reactants :

		Area	Ratio
	124	115000	0.093
	125	438000	0.355
	126	56000	0.045
	127	91000	0.074
	128	105000	0.085
	129	336000	0.272
	130	84000	0.068
	131	9000	0.007
Sum	:	1234000	

50 Min., Recovered Reactants :

		Area	Ratio
	124	179000	0.095
	125	664000	0.354
	126	85000	0.045
	127	138000	0.074
	128	159000	0.085
	129	511000	0.272
	130	128000	0.068
	131	13000	0.007
Sum	:	1877000	

14. Cross-over experiment of 2-benzyloxypyridine-1-oxide and 2-(benzyloxy-α,α–d_2)-6-d-pyridine-1-oxide in dimethylformamide :

A mixture of 2-benzyloxypyridine-1-oxide (H, 61.2mg, 30.4 mmol) and 2-(benzyloxy-α,α–d_2)-6-d-pyridine-1-oxide (D, 64.5 mg, 31.7 mmol) was used.

Results :

2-(Benzyloxy-α,α-d_2)-6-d-pyridine-1-oxide :			**2-Benzyloxypyridine-N-oxide:**		
	Area	**Ratio**		**Area**	**Ratio**
201	591	0.003	200	941	0.038
202	4202	0.023	201	18789	0.764
203	43528	0.240	202	3976	0.162
204	95270	0.526	203	630	0.026
205	31055	0.171	204	255	0.010
206	6496	0.036			
Sum :	181142		Sum :	24591	

Reactants		
	Relative intensities[a]	**Ratio**
200	0.0117	0.019
201	0.2337	0.376
202	0.0566	0.091
203	0.0840	0.135
204	0.1699	0.273
205	0.0543	0.087
206	0.0114	0.018
Sum :	0.6214	

a. Calculated from the mole percentages of H and D.

20 Min., Degree of Reaction : 12 %

	Product		
		Area	Ratio
	200	650	0.003
	201	55892	0.266
	202	31061	0.148
	203	66162	0.314
	204	42701	0.203
	205	12116	0.058
	206	1792	0.009
Sum	:	210374	

40 Min., Degree of Reaction : 22 %

	Product		
		Area	Ratio
	200	1610	0.003
	201	154014	0.271
	202	85177	0.150
	203	177719	0.313
	204	112354	0.198
	205	32015	0.056
	206	4860	0.009
Sum	:	567749	

60 Min., Degree of Reaction : 28 %

	Product		
		Area	Ratio
	200	1402	0.003
	201	132958	0.275
	202	72123	0.149
	203	150927	0.312
	204	95713	0.198
	205	26453	0.055
	206	3625	0.008
Sum	:	483201	

90 Min., Degree of Reaction : 39 %

	Product		
		Area	Ratio
	200	1294	0.003
	202	63629	0.149
	201	119087	0.279
	203	132202	0.310
	204	83521	0.196
	205	23217	0.054
	206	3449	0.008
Sum	:	426399	

120 Min., Degree of Reaction : 48 %

	Product	
	Area	**Ratio**
200	1408	0.003
201	144406	0.278
202	76935	0.148
203	162304	0.313
204	101796	0.196
205	28412	0.055
206	3837	0.007
Sum :	519098	

15. Reaction of Methyl Iodide with 2-d_3-Methoxypyridine-1-oxide :

A solution of 2-d_3-methoxypyridine-1-oxide (50.8 mg, 0.4 mmol) and methyl iodide (75 μL, 0.7 mmol) in chloroform-d (3 mL) was refluxed for 27 h and evaporated. The ^{1}Hmr spectrum of the residue was identical to that of 1-methoxy-2-pyridone.

16. Reaction of Benzyl Chloride with 2-Methoxypyridine-1-oxide :

A solution of 2-methoxypyridine-1-oxide (50.2 mg, 0.4 mmol) and benzyl chloride (50 μL, 0.4 mmol) in chloroform-d (2 mL) was refluxed for 20 h and then evaporated. A 1 : 4 mixture of 1-methoxy-2-pyridone and 1-benzyloxy-2-pyridone was seen in the ^{1}Hmr spectrum.

17. Chiral Benzyl-α-d-alcohol[23]

A suspension of (S)-(-)-1,1'-bi-2-naphthol (0.70 g, 2.4 mmol), titanium(IV) isopropoxide (1.23 mL of 1 M in dichloromethane, 1.2 mmol), trifluoroacetic acid (0.5 M

in dichloromethane, 70 μL) and 4 Å molecular sieves (5 g, heated at 110 °C and then powdered), in ether (50 mL), was refluxed for 1 h, cooled to room temperature, and benzaldehyde (1.25 mL, 1.30 g, 12.3 mmol) was added dropwise, with stirring. The reaction mixture was cooled to -78 °C by a dry-ice/acetone bath and a solution of tributyltin deuteride (3.60 mL, 13.5 mmol) in ether (15 mL) was added dropwise. After the addition was complete, the mixture was stirred for 10 min at -78 °C and then maintained at -20 °C for 20 h. The reaction was quenched by addition of saturated sodium bicarbonate solution (20 mL), with stirring. Stirring was continued for 1 h and the mixture was then filtered through a pad of Celite. The filtrate was extracted with ethyl acetate (3 x 100 mL) and the organic layer was dried and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate : hexane, 1 : 9 followed by ethyl acetate : hexane, 2 : 9) to give 1.12 g (84 %) of the product.

^{1}Hmr : 7.34 (5H, m, Ph*H*), 4.62 (1H, s, CD*H*), 2.57 (1H, s, O*H*).

MS (EI, m/z) : 109.

18. Conversion of Benzyl Alcohol to the Mosher Ester, General procedure :[21]

Oxalyl chloride (5 μL, 7.27 mg, 0.057 mmol) was added to a solution of (S)-(-)-α-methoxy-α-trifluoromethylphenylacetic acid (2.8 mg, 0.012 mmol) and dimethylformamide (1 μL, 0.94 mg, 0.012 mmol) in hexane (0.5 mL). A white precipitate formed immediately. The mixture was filtered after 1 h and the filtrate was concentrated under reduced pressure. The residue was treated with a solution of benzyl alcohol (1.1 μL, 1.15 mg, 0.01 mmol), triethylamine (4.0 μL, 2.9 mg, 0.03 mL) and 4-(*N*,*N*-dimethylamino)pyridine (one crystal) in chloroform-d (0.5 mL). The resulting solution was transferred to a nmr tube, shaken vigorously, and the ^{1}Hmr spectrum was recorded.

19. Chiral 2-Benzyl-α-d-oxypyridine-1-oxide

A mixture of tetrahydrofuran (20 mL), sodium hydride (0.44 g of a 60 % dispersion in mineral oil, 11.0 mmol) and chiral benzyl-α-d-alcohol (1.02 g, 9.2 mmol) was stirred for 10 min, and 2-chloropyridine-1-oxide (1.21 g, 9.2 mmol) was then added in one portion. The mixture was warmed to 55-65 ^{0}C, stirred for 4.5 h, cooled, and water (20 mL)was added. Extraction with chloroform (4 x 70 mL), followed by drying and evaporation, gave a white solid, which was purified by column chromatography (silica gel; ethyl acetate then methanol : ethyl acetate, 1 : 2). Crystallisation from ethyl acetate-hexane gave 1.06 g (57 %), m.p. 108-109 ^{0}C.

^{1}Hmr ($CDCl_3$): 8.26-8.28 (1H, d, 6.5 Hz, *H6*), 7.44-7.46 (2H, m, Ph*H*), 7.32-7.39 (3H, m, Ph*H*), 7.13-7.17 (1H, m, *H4*), 6.88-6.89 (1H, m, *H5*), 6.82-6.85 (1H, dd, 8.3 Hz, 1.6 Hz, *H3*), 5.46 (1H, s, CD*H*).

MS (EI, m/z) : 202

20. Stereochemical Studies.

A. 1–Benzyl-α-d-oxy-2-pyridone :

A solution of 2–benzyl-α-d-oxypyridine-1-oxide (0.8 g, 4.0 mmol) in dimethyl-formamide (9.0 mL) was heated at 140-150 ^{0}C for 3 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (ethyl acetate followed by ethyl acetate : methanol, 1 : 1) to give 1–benzyl-α-d-oxy-2-pyridone (0.43 g) and 2–benzyl-α-d-oxypyridine-1-oxide (0.18 g).

B. Recovered 2–Benzyl-α-d-oxypyridine-1-oxide :

2–Benzyl-α-d-oxypyridine-1-oxide (0.1 g, 0.5 mmol) was added to a solution of sodium hydride (48 mg, 1.2 mmol) in methanol (10 mL). This was refluxed, with stirring, for 7 h. The solvent was removed under reduced pressure and the residue was shaken with

water (5 mL) and ethyl acetate (3 x 50 mL). The organic layer was dried, concentrated and purified by preparative layer chromatography (ethyl acetate : hexane, 1 : 3) to give benzyl-α-d-alcohol 35 mg (65 %) which was converted to the Mosher ester.

C. Recovered 1–Benzyl-α-d-oxy-2-pyridone :

1–Benzyl-α-d-oxy-2-pyridone (0.3 g, 1.5 mmol) was added to a suspension of zinc (0.22 g, 3.3 mmol) in 30% acetic acid (10 mL). The suspension was refluxed, with stirring, for 5.5 h and then cooled to room temperature. Saturated sodium bicarbonate solution (30 mL) was slowly added and the mixture was extracted with ethyl acetate (3 x 100 mL). The organic layer was dried, concentrated and purified by column chromatography (ethyl acetate : hexane, 1 : 3) to give benzyl-α-d-alcohol 122 mg (75 %) which was converted to the Mosher ester.

21. 2-Hydroxypyridine-1-oxide

A solution of 2-methoxypyridine-1-oxide (0.1 g, 0.8 mmol) in concentrated hydrochloric acid (2 mL) was warmed to 90-100 ^{0}C, stirred for 16 h, and then cooled and evaporated under reduced pressure. Crystallization from chloroform-hexane (1 : 5) gave 48 mg of an off-white product (54 %). m.p. 148-149 ^{0}C (lit.[18] m.p. 148-149 ^{0}C).

^{1}Hmr (D_2O): 7.81-7.73 (1H, m), 7.46-7.50 (1H, m), 6.62-6.65 (1H, m), 6.45-6.48 (1H, m). :

MS (EI, m/z) : 111.

22. Lithium Salt of 2-Hydroxypyridine-1-oxide

n-Butyllithium (72 mL, 2.5 M in hexane, 0.18 mmol) was injected into an ice-cold solution of 2-hydroxypyridine-1-oxide (20.3 mg, 0.18 mmol) in tetrahydrofuran (10 mL). The mixture was stirred for 1 h., and the product was separated by centrifugation, washed with hexane, and dried to give 18.2 mg (85%) of an off-white solid.

^{1}Hmr (DMF-d7) : 7.93-7.94 (1H, br d), 7.29-7.33 (1H, br t), 6.45-6.48 (1H, br d), 6.21-6.24 (1H, br d).

^{13}Cmr : 164.9, 140.7, 136.9, 116.8, 111.6.

23. 1,2-Dimethoxypyridinium Trifluoromethanesulfonate

Methyl trifluoromethanesulfonate (0.4 mL, 3.5 mmol) was injected into a solution of 2-methoxypyridine-1-oxide (146.8 mg, 1.2 mmol) in chloroform-d (2.0 mL). The reaction mixture was stirred for 1.5 h, and the solvent was then removed under reduced pressure. Crystallization from dichloromethane-ether (1 : 5) gave 201 mg (56 %) of product. m.p. 126-127 ^{0}C.

^{1}Hmr ($CDCl_3$) : 8.55 (1H, dd, *H6*) 8.42 (1H, dt), 7.75 (1H, dd, *H3*), 7.54 (1H, dt), 4.36 (3H, s, OCH_3), 4.30 (3H, s, OCH_3).

^{13}Cmr ($CDCl_3$) : 205.5, 158.9, 147.4, 139.3, 119.7, 113.7, 68.8, 60.2.

MS (EI, m/z) : 214

Anal. : Calculated for $C_8H_{10}NO_5SF_3$: C, 33.22; H, 3.48; N, 4.84, Found : C, 33.19; H, 3.37; N, 4.75.

24. Reaction of the Lithium Salt with the Triflate Salt.

A. In DMF -d$_7$. To a solution of the lithium salt (2.2 mg, 0.018 mmol) in DMF-d7 (0.5 mL) was added 1,2-dimethoxypyridinium trifluoromethanesulfonate (5.1 mg, 0.018 mmol). The ^{1}Hmr spectrum, taken immediately after the addition, showed the peaks of the two reactants at 9.20 (d), 6.63 (t), 8.06 (d), 7.75 (t), 7.31 (br), 6.47 (d), 4.48 (s) and 4.40 (s), and approximately 50 % conversion to 1-methoxy-2-pyridone, with peaks at 7.96-7.98, 7.42-7.46, 6.51-6.54, 6.22-6.25 and 4.00 ppm. After 22 h, the conversion to 1-methoxy-2-pyridone was greater than 95%.

B. In D_2O. To a solution of 1-hydroxy-2-pyridone (20.2 mg, 0.18 mmol) in D_2O (0.5 mL) was added 1.43 N NaOD-D_2O (0.11 mL, 0.16 mmol). The resulting solution, designated solution A, exhibited nmr peaks at 7.75-7.77 (1H), 7.26-7.30 (1H), 6.53-6.56 (1H) and 6.40-6.43 (1H). A second solution, designated solution B, was prepared by dissolution of 1,2-dimethoxypyridinium trifluoromethanesulfonate (12.7 mg, 0.044 mmol) in D_2O (0.5 mL). This solution exhibited peaks at 8.66-8.68 (1H, d), 8.35-8.40 (1H, t), 7.65-7.67 (1H, d), 7.46-7.50 (1H, t), 4.32 (3H, s), 4.24 (3H, s). To begin the reaction, 0.16 mL (0.044 mmol) of solution A was injected into solution B. After 20 h at room temperature, the solution showed approximately 50 percent conversion to a 45 : 55 mixture of methanol (3.27 ppm) and 1-methoxy-2-pyridone. ^{1}Hmr : 7.83-7.85 (1H, d), 7.51-7.55 (1H, t), 6.61-6.65 (1H, d), 6.44-6.48 (1H, t), 3.95 (3H).

Appendix

A-1 Calculation of the degree of crossover in 1 (R = methyl or benzyl).

The mass spectra of **1** (R = methyl) and **1** (R = benzyl) exhibit two major peaks in each case, a higher intensity molecular ion, M, and a lower intensity satellite ion, M-1 for R = methyl and M+1 for R = benzyl. We assume that the mass spectra of deuterated and undeuterated products are characterized by the same structure, and introduce the parameter λ to describe the relative intensities of the molecular peak in the mass spectrum of an isotopically pure specimen. The intensity of a satellite peak is then $1-\lambda$. From the mass spectrum of the undeuterated compounds we find $\lambda = 0.85$ for R = methyl and $\lambda = 0.8$ for R = benzyl.

Deuterated reactants contain mixtures of fully deuterated and partially deuterated isotopomers. To describe the composition of such mixtures we introduce a parameter β, the mole fraction of the fully deuterated isotopomer. The mole fraction of the partially deuterated isotopomer is then $1-\beta$. We estimate β from the mass spectra of the *m/z* 129 and *m/z* 204 compounds (Chart 1): $\beta = 0.9$ for R = methyl and $\beta = 0.7$ for R = benzyl.

To describe the composition of a deuterated-undeuterated mixture we require the mole fraction of the undeuterated component, α. The mole fraction of the deuterated component, which includes both fully deuterated and partially deuterated isotopomers, is then $1-\alpha$.

The structure of the mass spectrum of a product depends on the degree of crossover, κ. This parameter can be found by interpolation between the two limiting cases, complete crossover ($\kappa = 100\%$), and no crossover ($\kappa = 0\%$). The relative intensities of the peaks for

these limiting cases can be predicted in terms of the parameters α, β and λ in the following way.

Case 1 : $\kappa = 0\%$. In this case we have the following contributions to the intensities of the peaks :

undeuterated :	molecular peak, $\lambda\alpha$
	satellite peak, $(1-\lambda)\alpha$
partially deuterated :	molecular peak, $\lambda(1-\alpha)(1-\beta)$
	satellite peak, $(1-\lambda)(1-\alpha)(1-\beta)$
fully deuterated :	molecular peak, $\lambda(1-\alpha)\beta$
	satellite peak, $(1-\lambda)(1-\alpha)\beta$

Case 2 : $\kappa = 100\%$. Here we use the following notations: R = deuterated migrating group (CD_3 or CD_2Ph), r = undeuterated migrating group, X = monodeuterated pyridine ring, x = undeuterated pyridine ring. With these definitions the composition of a reactant can be described as: XR = fully deuterated, xR = partially deuterated, and xr = undeuterated. The mole fraction of X is equal to the mole fraction of XR, $(1-\alpha)\beta$, and the mole fraction of r is equal to the mole fraction of xr, α. Analogously, the mole fraction of x is $1-(1-\alpha)\beta$ and the mole fraction of R is $1-\alpha$.

If we have 100% crossover, the composition of the mixture of products is purely statistical, and can be calculated from the mole fractions of X, x, R and r as

$$xr = \alpha[1-(1-\alpha)\beta]$$

$Xr = \alpha(1-\alpha)\beta$

$xR = (1-\alpha)[1-(1-\alpha)\beta]$

$XR = (1-\alpha)^2\beta$

The following are the contributions to the intensities of the peaks in the mass spectrum

xr :	molecular peak, $\lambda\alpha[1-(1-\alpha)\beta]$
	satellite peak, $(1-\lambda)\alpha[1-(1-\alpha)\beta]$
Xr :	molecular peak, $\lambda\alpha(1-\alpha)\beta$
	satellite peak, $(1-\lambda)\alpha(1-\alpha)\beta$
xR :	molecular peak, $\lambda(1-\alpha)[1-(1-\alpha)\beta]$
	satellite peak, $(1-\lambda)(1-\alpha)[1-(1-\alpha)\beta]$
XR	molecular peak, $\lambda(1-\alpha)^2\beta$
	satellite peak, $(1-\lambda)(1-\alpha)^2\beta$

A-2 Calculation of the secondary kinetic isotope effect.

Pseudo first order behaviour is observed for compound **1** (R = methyl) at 0.45 M in chloroform.

Under this special condition, the following kinetic scheme can be applied :

$$R_H \xrightarrow{k_H} P_H$$

$$R_D \xrightarrow{k_H} P_D$$

R_H and R_D refer to the undeuterated and deuterated reactants, respectively. P_H and P_D refer to the undeuterated and deuterated products, respectively. Under pseudo-first-order conditions, the following two equations can be found.

$(R_H)_t = (R_H)_0 \bullet \mathrm{Exp}\,(-k_H)_t$

$(R_D)_t = (R_D)_0 \bullet \mathrm{Exp}\,(-k_D)_t$

Therefore,

$$k_H = \frac{-1}{t} \ln \frac{(R_H)_t}{(R_H)_0}$$

$$k_D = \frac{-1}{t} \ln \frac{(R_D)_t}{(R_D)_0}$$

and

$$\frac{k_H}{k_D} = \frac{\ln \frac{R_{Ht}}{R_{H0}}}{\ln \frac{R_{Dt}}{R_{D0}}} = \frac{\ln\left(\frac{R_{Dt}}{R_{D0}} \cdot \frac{b}{a}\right)}{\ln \frac{R_{Dt}}{R_{D0}}}$$

where at t = 0, $R_{H0} = a\, R_{D0}$ and at t = t $R_{Ht} = b\, R_{Dt}$

Defining the mole fraction as X_R, we have

$$X_R = \frac{(R_H)t + (R_D)t}{R_{H0} + R_{D0}} = \frac{(1+b)R_{Dt}}{(1+a)R_{D0}} = C$$

a, b and c are as defined in the text.

This leads to

$$\frac{k_H}{k_D} = \frac{\ln \frac{b}{a} \cdot \frac{c\,(1+a)}{(1+b)}}{\ln \frac{c\,(1+a)}{(1+b)}}$$

A-3 Computer program for the theoretical curves of scheme 1 and 2.

```
c This program generates kinetics curves for the following reaction scheme
c A + A --> BC (k1)
c BC --> D + D (k2)
c BC --> A + D (k3)
c by Runge-Kutta numerical integration of the kinetic equations.
c
c Input (interactive, free format) :
c       rate constants k1 (in L/mol*h), k2, and k3 (in 1/h), initial concentration [A]o in
c       mol/L, time increment for the kinetic curve (tstep) in hours, final time (tmax)
c       h.
c Output (file OUT) :
c       Pairs of time (in h) and concentration (in mol/L) from time = 0 to time = tmax
c       with time increments = tstep
c Library routine used :
c D02PVF and D02PCF from NAG library

    implicit real*8 (a-h, o-z)
    character*1 task /'u'/
    logical err /.true./
    dimension ys(3), thr(3), work(10000)
    dimension y(3), yp(3), ym(3)
    dimension tt(0:2000)

    common /const/ rk(3), rk11, rk23, rk223

    external right

    open (7, file='OUT')

    lenw=10000
    tol=1.d-7
    ifail=0
    method=2

    n=3
    do 1 i=1, n
       thr(i)=1.d-4
1   continue

    ti=0.d0

    m=tmax/tstep
    tf=m*tstep
```

```
      rk11=-2.d0*rk(1)
      rk23=rk(2) + rk(3)
      rk223=rk(2) + rk23

      tt(0)=ti
      ys(1)=Ao
      ys(2)=0.d0
      ys(3)=0.d0

      write (7,100) 0.d0,Ao

      do 2 k=1,m
         tt(k)=k*tstep
2     continue

call D02PVF(n,ti,ys,tf,tol,thr,method,task,err,h,work,lenw,ifall)

      do 4 k=1,m
         t=tt(k)
         call D02PCF (right,t,tg,y,yp,ym,work,ifall)
         z1=Ao*y(1)/(y(1)+y(3))
         z3=Ao*y(3)/(y(1)+y(3))
         write (7,100) t,z1
4     continue

      stop
100   formate (2f15.5)
      end
c-----------------------------------------------------------------------
subroutine right (t,y,yp)
      implicit real*8 (a-h,o-z)
      dimension y(*), yp(*)
      common /const/ rk11, rk2, rk3, rk11, rk23, rk223

      A = y(1)
      BC = y(2)
      D = y(3)

      yp(1) = rk11*A**2 + rk2*BC
      yp(2) = rk1*A**2 - rk23*BC
      yp(3) = rk223*BC

      return
      end
```

From the output file (OUT), the data were graphed using MS-Excel.

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