Alkyl Transfer with Retention and Inversion of Configuration: Reexamination of a Putative [1s,4s] Sigmatropic Rearrangement**

Saul Wolfe,* Kiyull Yang, Noham Weinberg, Zheng Shi, Yih-Huang Hsieh, Rajendra Dev Sharma, Stephen Ro, and Chan-Kyung Kim

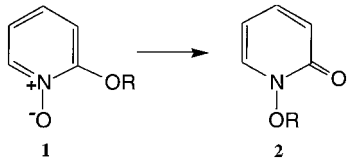
Abstract: The thermal rearrangement of 2-alkoxypyridine-1-oxides to 1-alkoxy-2-pyridones, which has been reported to proceed by an intramolecular [1s,4s] sigmatropic migration of the alkyl group with retention of configuration and first-order kinetics, has been reexamined. The intramolecular barriers have been computed to be at least 20 kcal mol^{-1} higher than the reported experimental barriers. An alternative bimolecular mechanism, discovered computationally, has been confirmed by a variety of experiments including crossover studies, determination of solvent effects and secondary H/D isotope effects, and 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 either without crossover, by a double inversion of one alkyl group, or with crossover by two single inversions of different alkyl groups. The proposed intermediates of this mechanism can be synthesized; they react to form a 1-alkoxy-2-pyridone at room temperature.

Keywords: ab initio calculations · configuration determination · crossover experiments · isotope effects · kinetics

Introduction

Background: Organic compounds do not undergo nucleophilic displacement reactions with retention of configuration. Even under favorable circumstances, for example an intramolecular reaction, transfer of a methyl group, and angular compression or pericyclic electronic stabilization of the transition state, recent work suggests[1] that the retention barrier is never less than 20 kcal mol^{-1} higher than that of a competing unconstrained intermolecular inversion process. Every nucleophilic substitution reaction that proceeds with retention of configuration at carbon[2] must, therefore, be presumed to be the result of a multistep process that is more complex, and more interesting,[3] than was previously supposed.

The present work is concerned with a theoretical and experimental reexamination of one of these reactions, the thermal rearrangement of 2-alkoxypyridine-1-oxides (**1**) to 1-alkoxy-2-pyridones (**2**) (Scheme 1). This reaction was first reported by Dinan and Tieckelmann in 1964.[4a] Heating **1** (R = methyl, ethyl, benzyl, allyl) neat at 100–140 °C led to complete rearrangement to **2** within 1.5–3.5 h. The reactions were not retarded by addition of the free radical scavenger *p*-benzoquinone. In a second study, conducted in diglyme at 83–84 °C,[4b] Litster and Tieckelmann found that substituted 2-alkenyloxypyridine-1-oxides (**1**, R = CHR^{1}CH=CHR^2; see



1 **2**

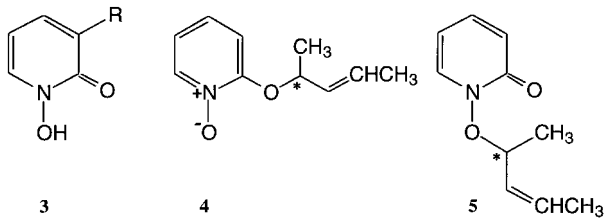
Scheme 1. The thermal rearrangement of 2-alkoxypyridine-1-oxides (**1**) to 1-alkoxy-2-pyridones (**2**).

[*] Prof. S. Wolfe, Prof. N. Weinberg, Dr. Z. Shi, Y.-H. Hsieh, S. Ro, Dr. R. D. Sharma
Department of Chemistry, Simon Fraser University
Burnaby, B.C. V5A 1S6 (Canada)
Fax: (+1) 604-291-5973
e-mail: swolfe@sfu.ca
Prof. K. Yang
Department of Chemical Education, Gyeongsang National University
Chinju 660-701 (Republic of Korea)
Fax: (+82) 591-751-5666
Prof. C.-K. Kim
Department of Chemistry, Inha University
Inchon 402-751 (Republic of Korea)
Fax: (+82) 32-867-5604

[**] Supporting information for this contribution is available on the WWW under http://www.wiley-vch.de/home/chemistry/

0947-6539/98/0405-0886 $ 17.50+.50/0

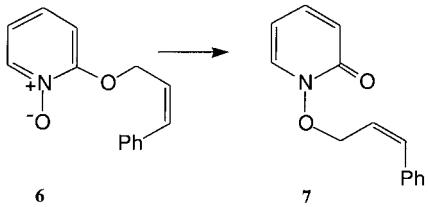
ref. [4b] for a definition of R^1 and R^2) rearranged to **2** (R = $CHR^1CH{=}CHR^2$), that is, without a concomitant 1,3-allylic double bond shift. Higher temperatures led to an *ortho*-Claisen rearrangement, to give **3** (R = $CHR_2CH{=}CHR_1$) as major products. The cyclopropylcarbinyloxy compound yielded, in addition to 96% of 1-cyclopropylcarbinyloxy-2-pyridone, about 4% of the skeletally rearranged 1-cyclobutyloxy-2-pyridone. Crossover products were seen in competition experiments with substituted and unsubstituted alkenyloxy compounds. In refluxing carbon tetrachloride, the optically active *N*-oxide **4**, $[\alpha]_{340}^{28}$ +35.0°, rearranged to **5**, $[\alpha]_{340}^{28}$ −169°.



3 **4** **5**

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 an intramolecular nucleophilic displacement would require a "rather unlikely"[4a] retention mechanism, intermolecular displacement or internal return through an ion pair were thought to be more probable.

Some of these results could not be confirmed. Schöllkopf and Hoppe[5] found no skeletal isomerization in the rearrangement of **1**, R = cyclopropylcarbinyl, and the α-methallyl compound (**1**, R = $CHCH_3$-CH=CH_2) gave only the Claisen rearrangement product, with skeletal isomerization of the alkenyl substituent, and not the reported **2**, R = $CHCH_3$-CH=CH_2. Ollis and co-workers[2, 6] have made similar observations concerning the competition between the O→O (Tieckelmann) and O→C (Claisen) rearrangement pathways. These workers also observed that heating the *cis*-cinnamyl ether **6** for 60 h at 53 °C yielded the *cis*-cinnamyl ether pyridone **7** exclusively.[6a]

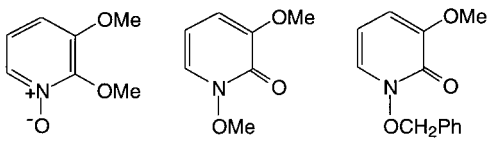


6 **7**

The latter result is not compatible with a radical-pair or ion-pair mechanism for this substrate. An ion-pair pathway had, in any event, already been ruled out by Schöllkopf and Hoppe for the rearrangement of substituted 2-benzyloxypyridine-1-oxides[5] on the basis of a Hammett ρ-value of −0.26.[7] On the other hand, the development of CIDNP signals during the course of the reaction indicated that the 2-benzhydryloxy compound rearranges by means of a radical mechanism. Using about 0.5 M solutions in $CDCl_3$, Hoppe observed first-order kinetics in the temperature range 130–150 °C for R = CH_3, C_2H_5, *i*-C_3H_7, and $CH_2CH_2OC_2H_5$.[8] For R = C_2H_5 and *i*-C_3H_7, 3-point Arrhenius plots yielded $\Delta H^{\neq}$ = 11–12 kcal mol^{-1} and $\Delta S^{\neq}$ = −52 to −56 cal mol^{-1} deg^{-1}. The reaction of 2-chloropyridine-1-oxide with α-deuteriobenzyl alcohol, $[\alpha]_{546}^{25}$ −0.556°, gave **1**, R = CHDPh, $[\alpha]_{546}^{25}$ −1.133°. This rearranged to **2**, $[\alpha]_{546}^{25}$ −0.899°, which upon refluxing with zinc and 30% acetic acid yielded α-deuteriobenzyl alcohol, $[\alpha]_{546}^{25}$ −0.423°. In a control experiment, the optically active alcohol underwent 18% racemization when refluxed with zinc and 30% acetic acid.

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 the conclusion[5, 8] "somit scheint für die 2-Alkoxypyridinoxide ein (symmetrie-erlaubt[10]) sigmatroper Umlagerungsverlauf als gesichert" (translation: *herewith it would appear that for the 2-alkoxypyridine a sigmatropic reaarangement mechanism (symmetry allowed[10]) is certain*; Figure 1). A concerted [1s,4s] sigmatropic rearrangement mechanism is also advocated by Ollis and co-workers[2, 6] and is consistent with the stereospecific rearrangement **6**→**7**.

Although the evidence in support of the proposed [1s,4s] sigmatropic rearrangement mechanism seems compelling, this mechanism does not account for the results of Tieckelmann's crossover experiments. Crossover has also been observed by Ballesteros et al.[11] Heating a mixture of **1** (R = benzyl) and **8** at 140 °C in the absence of solvent led to a mixture of **2** (R = CH_3), **2** (R = benzyl), **9**, and **10**. In [D_7]dimethylformamide



8 **9** **10**

(DMF) and [D_6]dimethyl sulfoxide (DMSO), 0.15 M solutions of **1** (R = CH_3) were reported to rearrange with first-order kinetics, and the following activation parameters: DMF, $\Delta H^{\neq}$ = 24.0 kcal mol^{-1}, $\Delta S^{\neq}$ = −17.7 cal mol^{-1} deg^{-1}; DMSO,

Abstract in Korean:

알킬기의 분자내 [1s,4s] 시그마 결합 자리옮김반응이 입체적 배치가 보존되며 일차반응으로 진행된다고 알려진 2-alkoxy-pyridine-1-oxide가 1-alkoxy-2-pyridone으로 재배열하는 반응을 다시 살펴보았다. 이론적으로 얻어진 분자내 재배열반응에 대한 활성화에너지는 실험적으로 알려진 것보다 최소한 20 kcal/mol 높게 나타났다. 교차반응, 용매효과, 이차 H/D 동위원소효과, 새로운 반응속도실험 및 입체화학적 연구를 사용하여 이론적으로 발견한 이분자 반응메카니즘이 존재함을 알 수 있었다. 새로운 반응메카니즘의 첫 번째 단계는 알킬기가 배치의 반전을 통한 분자간 반응에 의하여 N-oxide쪽으로 이동한다. 알킬기와 용매의 종류에 따라서 양이온 중간체 중 하나의 알킬기는 다시 두 번째 반전을 통하여 음이온 중간체중의 하나의 산소원자로 이동한다. 교차반응이 아닌 경우에는 하나의 알킬기가 두 번 반전을 하며, 교차반응인 경우에는 다른 알킬기가 각각 한번씩 반전을 하여 생성물을 만들게 된다. 이 메카니즘에서 제안된 중간체를 합성하였으며 실온에서 반응하여 1-alkoxy-2-pyridone을 형성함을 알 수 있었다.

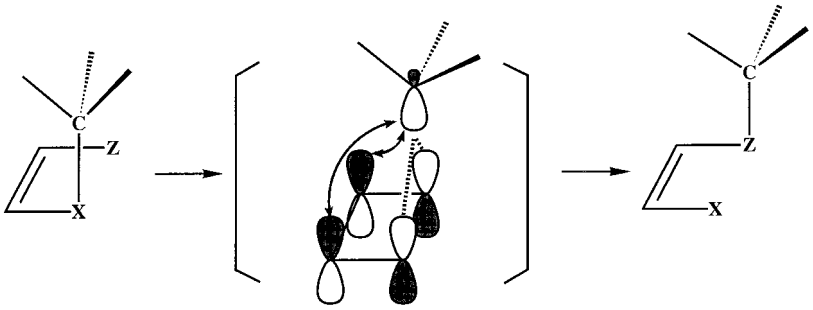


Figure 1. Schematic representation of a [1s,4s] sigmatropic rearrangement of an alkyl group, as proposed by Schöllkopf and Hoppe (double-headed arrows have been added).

$\Delta H^{\neq} = 23.6$ kcal mol^{-1}, $\Delta S^{\neq} = -17.4$ cal mol^{-1} deg^{-1}. The details of these kinetic studies were not provided by Ballesteros et al,[11] but the data for the rearrangement of **8** in DMF at 110 °C show an "induction-period" and an "acceleration of the reaction rate" as the concentration is increased from 0.128 M to 0.453 M. In refluxing [D_8]toluene, neither **1** (R = CH_3) nor **8** underwent significant rearrangement during 20 h. The Spanish workers concluded that the solvent effects and the results of the crossover experiments were consistent with an ionic mechanism and not a sigmatropic rearrangement.

The effect of pressure on the rearrangement of **1** (R = benzyl, benzhydryl) in diglyme solution at 100 °C has been investigated by le Noble and Daka.[12] The stepwise (radical) rearrangement of the benzhydryl compound exhibits $\Delta V^{\neq} = +10 \pm 2$ cm^3 mol^{-1}, and the rearrangement of the benzyl compound has $\Delta V^{\neq} = -30 \pm 5$ cm^3 mol^{-1}. These workers concluded that the sign of $\Delta V^{\neq}$ "confirm(s) that this activation parameter provides a criterion for concertedness *in sigmatropic shifts*". (italics added). It should be noted, however, that the removal of the italicized words will not change this conclusion. The negative value of $\Delta V^{\neq}$ demonstrates that the system is more compact in the transition state than in the reactant,[13] but this is not sufficient to distinguish between the proposed sigmatropic rearrangement and a bimolecular nucleophilic displacement mechanism. The latter reaction is also known to exhibit a strongly negative $\Delta V^{\neq}$.[13]

Present work: Using ab initio molecular orbital theory, we have studied the Tieckelmann rearrangements of **1** (R = methyl, ethyl, and benzyl). We have also performed new experiments suggested by the theoretical results. The principal findings are i) as is seen in all previous work,[1] the calculated intramolecular (retention) barrier is at least 20 kcal mol^{-1} higher than the experimental barrier; ii) a bimolecular inversion mechanism, discovered computationally, has a barrier in the range 20 – 30 kcal mol^{-1}, as is observed experimentally; iii) the intermediates suggested by these computations can be synthesized; they react to form a 1-alkoxy-2-pyridone at room temperature; iv) the kinetics are rarely first-order and are concentration and solvent dependent; v) there is extensive crossover; vi) the benzyl group rearranges with predominant *inversion* of configuration; vii) the stereochemistry of a rate-determining methyl-transfer reaction can be determined from the magnitude of the secondary CH_3/CD_3 isotope effect.

Results and Discussion

The [1s,4s] sigmatropic rearrangement mechanism: Table 1 summarizes the results of 3-21G calculations[14] on the intramolecular rearrangement of **1** for R = CH_3, C_2H_5, and CH_2Ph. In the case of the parent compound, R = CH_3, structures were also optimized at 3-21 + G and MP2/6-31 + G*. Although the 3-21G basis set considerably overestimates the energy difference between **1** and **2**, this basis set seems to be adequate for the calculation of the barriers, which are *at least 20 kcal mol^{-1} higher than the experimental barriers of refs. [8, 11]*. It is noteworthy that the trend in the retention barriers, methyl > ethyl > benzyl, is that expected for an ion-pair mechanism, but as seen earlier this mechanism is not operative in the Tieckelmann reaction. The secondary CH_3/CD_3 kinetic isotope effect[15] in the rearrangement of **1** (R = CH_3) is 1.35. This is in the range calculated previously for other intramolecular methyl transfer reactions with retention of configuration[1] and is also in the range encountered in solvolytic reactions that exhibit little or no nucleophilic assistance.[16]

Table 1. Intramolecular mechanism of the rearrangement of **1** to **2**.[a]

R	Species	Energy [au]	Relative energy [kcal mol^{-1}]
CH_3	reactant	– 432.93154	0.00
	product	– 432.96018	– 17.97
			– 9.64[b]
			– 8.38[c]
	TS	– 432.85380	48.78
			48.57[b]
			46.50[c]
C_2H_5	reactant	– 471.75911	0.00
	product	– 471.78510	– 16.31
	TS	– 471.68360	47.38
CH_2Ph	reactant	– 661.20206	0.00
	product	– 661.22866	– 16.69
	TS	– 661.13363	42.94

[a] Data refer to structures optimized at 3-21G, except where stated. [b] Structures optimized at 3-21 + G. [c] Structures optimized at MP2/6-31 + G*.

None of these findings supports the notion that the Tieckelmann reaction is a [1s,4s] sigmatropic rearrangement, and a closer examination of Figure 1 reveals that such a process cannot occur by movement of the alkyl group in the direction perpendicular to the plane of the aromatic ring. 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 by the double-headed arrows, this migration is inhibited by the out-of-phase relationship of the migrating group with the internal 2,3-orbitals. The HOMO of **1** (R = CH_3, Figure 2) shows this effect clearly: a 1,4-migration of the methyl group would have to

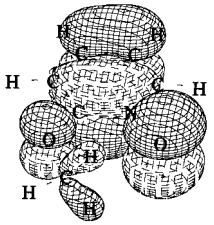


Figure 2. Calculated HOMO of 2-methoxypyridine-1-oxide.

0947-6539/98/0405-0888 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 5

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 stabilization of the transition state. This behavior has been discussed previously,[1] and it can be seen in Figure 3, which shows side views of the

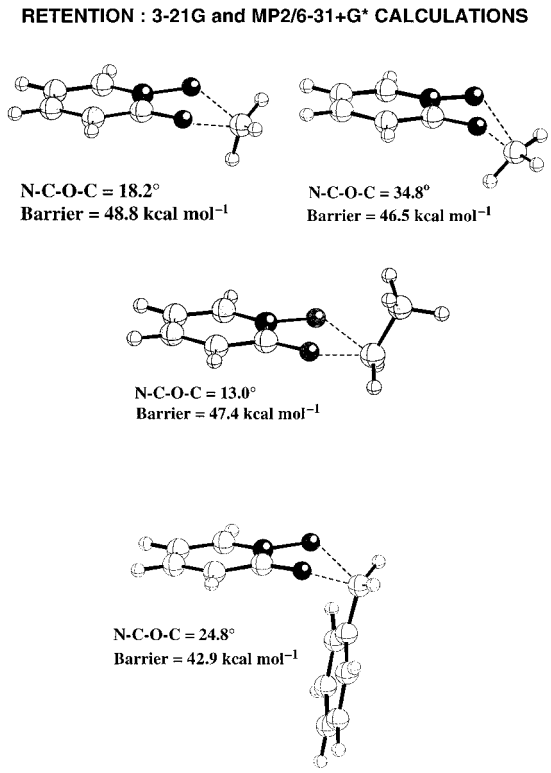


Figure 3. Side views of the 3-21G transition structures for intramolecular rearrangement of **1** (R = methyl, ethyl and benzyl). The MP2/6-31 + G* transition structure for R = methyl is shown at the upper right.

three transition structures calculated in the present work. At the 3-21G level the methyl, ethyl, and benzyl groups are not perpendicular to the plane of the pyridine ring, as projected in Figure 1, but are 18°, 13°, and 25°, respectively, out of the plane of this ring. Calculations at this level overestimate the effect of the orbital interaction discussed above, since in the higher level MP2/6-31 + G* calculations the methyl group is 34.8° degrees out of the plane of the ring (55° away from the perpendicular).

A bimolecular mechanism

A. Initial calculations: Ollis and co-workers[2a] have made the interesting observation that **11** is transformed quantitatively into **12** in the solid state over 13 months at −15 °C. The crystal structure of **11** has not yet been reported, but there are numerous examples, including determination of crystal structures, of intermolecular methyl transfer under topochemical control in the solid state.[17] In each case the reaction occurs exclusively, or is much faster in the solid state than in solution or in the melt, and in each case the crystal structure exhibits an intermolecular $X\cdots CH_3\cdots Y$ angle close to linearity, and an $X\cdots Y$ distance of 4–5 Å. There is no Tieckelmann rearrangement of **1** (R = CH_3) in the solid state. Although the crystal structure of **1** (R = CH_3), a portion of which is shown in Figure 4,[18] exhibits an intermolecular $O\cdots O$ distance of

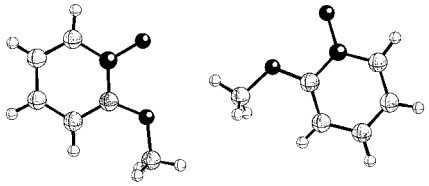
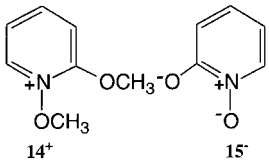
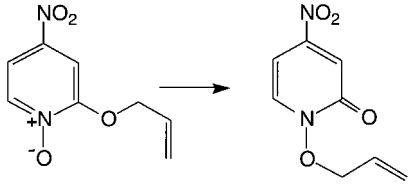


Figure 4. A portion of the crystal structure of 2-methoxypyridine-1-oxide (water molecules deleted).[18]

4.45 Å and an $O\cdots CH_3\cdots O$ angle of 150.3°, intermolecular methyl transfer between two ether oxygens is unlikely to be productive. The structure is not a minimum at the 3-21G level, and attempts to optimize the dimer while maintaining the methyl groups in the *anti* orientation did not yield a structure with an improved potential for intermolecular methyl transfer. However, when the methyl groups were allowed to rotate from the *anti* orientations of the crystal structure, the dimeric structure **13** (Figure 5), which has an intermolecular $O\cdots O$ distance of 4.32 Å, and an $O\cdots CH_3\cdots O$ angle of 174.2 deg, was discovered. Figure 5 also shows the calculated transition structure for intermolecular methyl transfer in **13**. The 3-21G barrier is 23.6 kcal mol^{-1}, within the range observed experimentally for the Tieckelmann reaction,[11] and the calculated secondary CH_3/CD_3 kinetic isotope effect is 1.02. The product of the methyl transfer is the complex **14**$^+$**15**$^-$.



*B. Synthesis of **14**$^+$ and **15**$^-$ and their reaction to form **2** (R = CH_3)*: Reaction of **1** (R = CH_3) with methyl triflate yielded the crystalline triflate salt **14**$^+$OTf$^-$. Compound **1** (R = CH_3) was refluxed with hydrochloric acid to give 1-hydroxy-2-pyridone, which was converted with butyllithium to the lithium salt Li$^+$**15**$^-$. A solution of the two salts in DMF left to stand overnight at room temperature afforded **2** (R = CH_3) quantitatively. In water, a solution of **14**$^+$OTf$^-$ and Na$^+$**15**$^-$ yielded a 55:45 mixture of **2** (R = CH_3) and methanol, together with unconverted 1-hydroxy-2-pyridone. In subsequent experiments, refluxing a solution of **1** (R = CH_3) and benzyl chloride in chloroform 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** proceeds by means of two consecutive bimolecular nucleophilic displacement reactions.



11 **12**

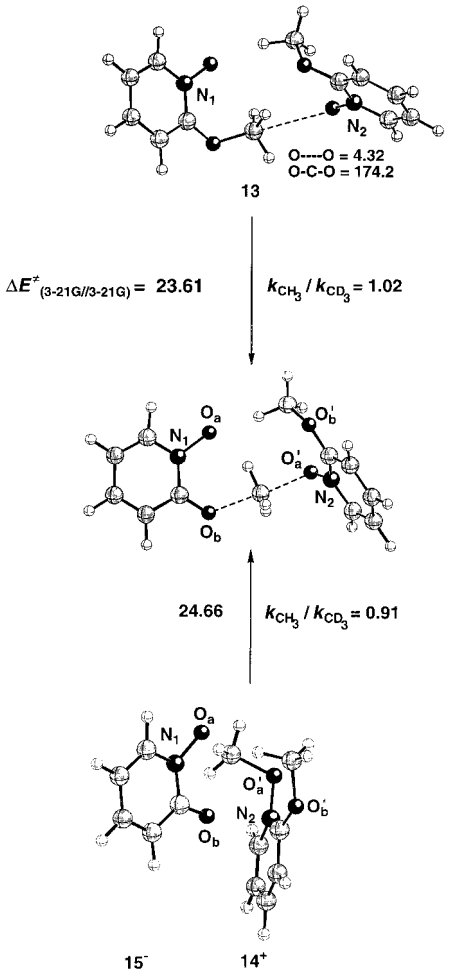


Figure 5. Calculated dimeric structure of 2-methoxypyridine-1-oxide (**13**), and the transition structure for methyl transfer with inversion of configuration to give $\mathbf{14}^{+}\mathbf{15}^{-}$.

C. Calculations of the initial alkyl transfer for R = ethyl and R = benzyl: The dimeric structures, analogous to **13** for R = ethyl and R = benzyl, led to the transition structures for alkyl transfer shown in Figure 6. For R = ethyl, the barrier is 26.08 kcal mol^{-1}. For R = benzyl, the barrier is 29.46 kcal mol^{-1}. The data of Figure 6 are summarized in Table 2.

The trend in the barriers of the three bimolecular initial steps is benzyl > ethyl > methyl. This is opposite to the trend seen earlier for the intramolecular reactions, as is expected for S_N2 reactions with inversion of configuration.

D. Which alkyl group is transferred in the second step? Crossover and stereochemical consequences: At the stage of $\mathbf{14}^{+}\mathbf{15}^{-}$, the reaction can continue along four different channels, and only modest librations 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 for the four reactions. The primary data of this figure are collected in Table 3.

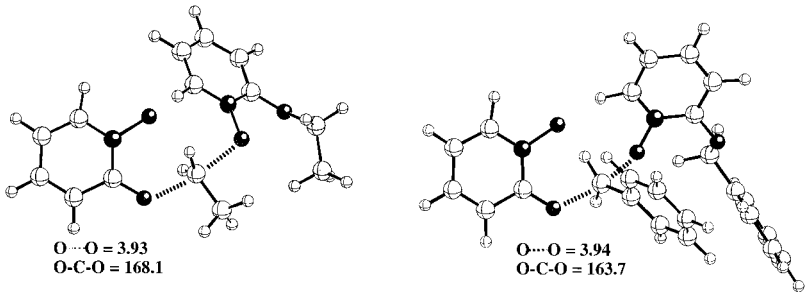


Figure 6. Calculated transition structures for ethyl transfer (left) and benzyl transfer (right) within dimeric complexes.

Table 2. Energetics of intermolecular methyl transfer in complexes of type **13**.[a]

R	Dimer	Transition structure	Product
methyl	– 865.88132	– 865.84369	– 865.88299
ethyl	– 943.54161	– 943.50005	–
benzyl	– 1322.43631	– 1322.38937	–

[a] Energies are in au; 1 au = 627.5 kcal mol^{-1}.

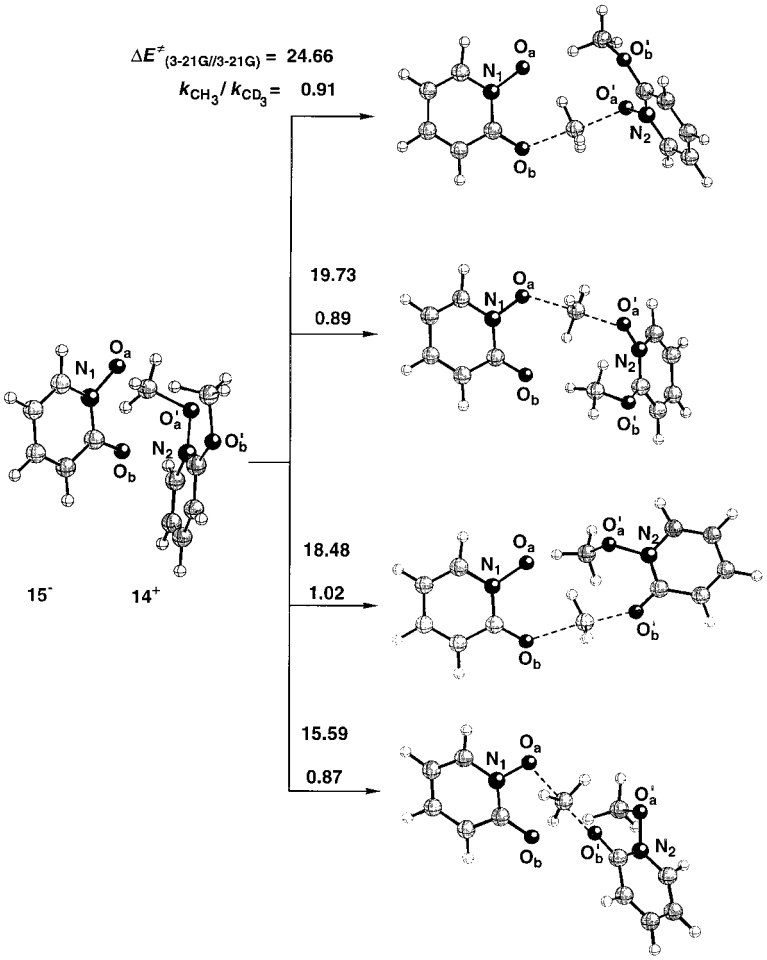


Figure 7. Calculated transition structures, barriers, and isotope effects for methyl transfer in $\mathbf{14}^{+}\mathbf{15}^{-}$ through, in descending order, channels A, B, C, and D.

0947-6539/98/0405-0890 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 5

Table 3. Energy barriers and isotope effects for different channels.

	Species	Energy [au]	Barrier [kcal mol^{-1}]	CH_3/CD_3 isotope effect
A	reactant	– 865.88299	–	–
	ts	– 865.84369	24.66	0.91
	product	– 865.88132	–	–
B	reactant	– 865.88299	–	–
	ts	– 865.85157	19.73	0.89
	product	– 865.90802	–	–
C	reactant	– 865.88299	–	–
	ts	– 865.85354	18.48	1.02
	product	– 865.90157	–	–
D	reactant	– 865.88299	–	–
	ts	– 865.85798	15.69	0.87
	product	– 865.93708	–	–

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^{-1}, and the CH_3/CD_3 kinetic isotope effect effect 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^{-1}, 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^{-1}, 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^{-1}, and the isotope effect is 0.87.

The consequences of reaction through 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.[19] 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.

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 experimentally. The stereochemical course of methyl transfer can be deduced from the results of competition experiments with $R = CH_3$ 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) and inversion (calculated 1.02) methyl transfer mechanisms are not the same.[20] If there is crossover, the mass spectrum of the product of the rearrangement of a mixture of undeuterated (*m/z*: 125) and tetradeuterated (*m/z*: 129) 2-methoxypyridine-1-oxides will contain peaks at *m/z*: 126 and *m/z*: 128.

E. Crossover experiments with R = methyl and R = benzyl: Scheme 2 summarizes the syntheses of the substrates required for crossover and isotope effect experiments. Following previous work,[2b, 4a, 5, 6, 8, 21] refluxing of 2-chloropyridine-1-oxide for 1 h with sodium methoxide in methanol or in [D_4]methanol gave **1** ($R = CH_3$), *m/z*: 125, or **1** ($R = CD_3$),

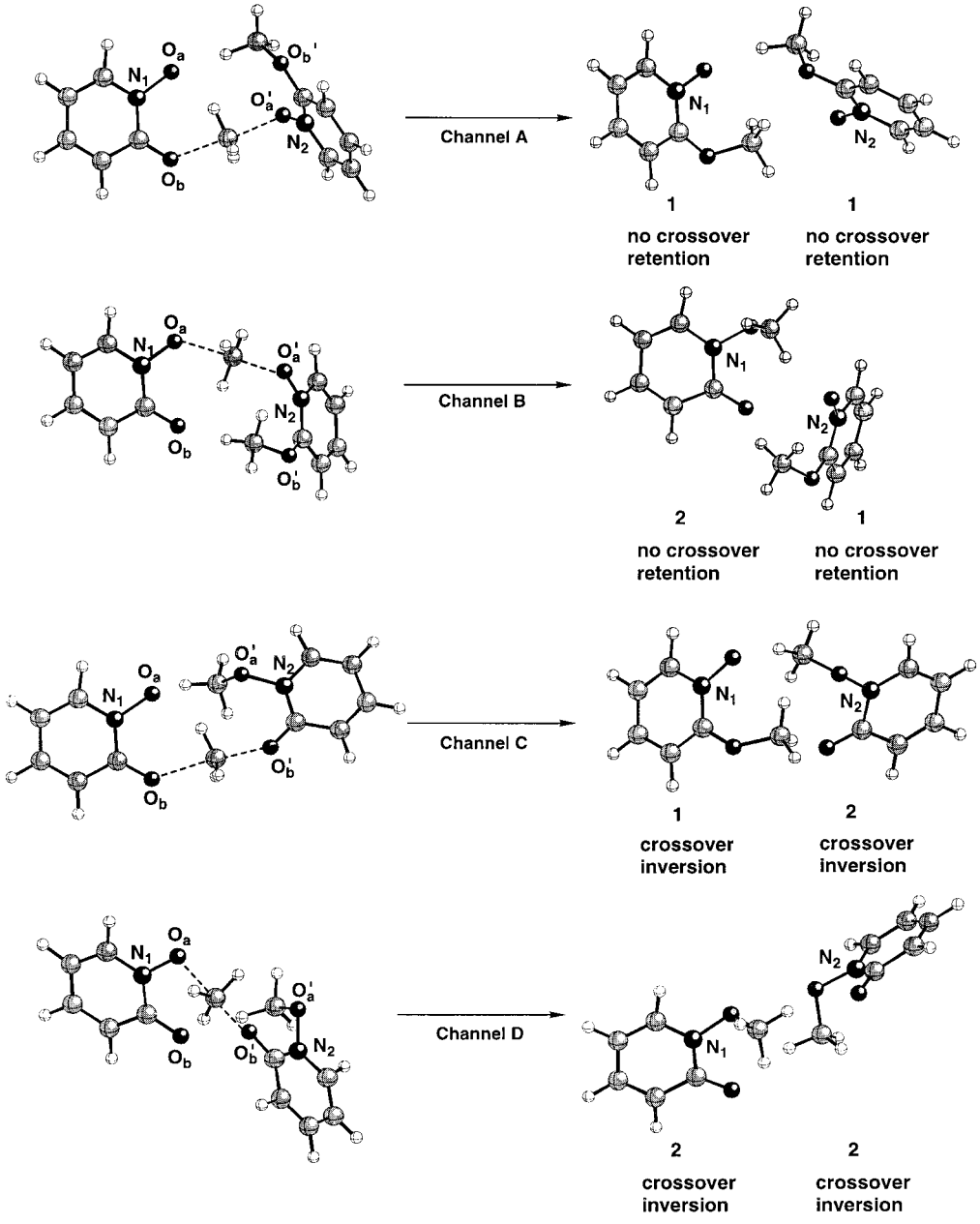
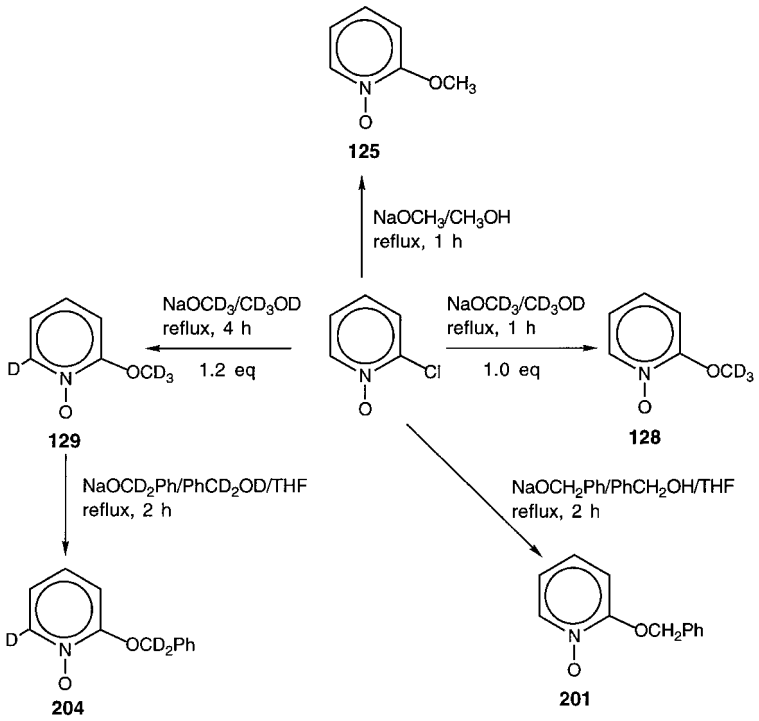


Figure 8. Stereochemical and crossover consequences of product formation by means of channels A, B, C, and D.



Scheme 2. Syntheses of substrates for isotope effect and crossover experiments.

m/z: 128, respectively. Extension of the refluxing period in [D_4]methanol to 12 h 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 treated 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 DMF at $140 \pm 0.8\,^{\circ}C$. 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 degassed 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. The figure 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.

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. The figure shows the mass spectrum calculated for the 1:1 mixture from the mass spectra of the individual isotopomers (vide infra) and the mass spectra of the product isolated after 20 min and after 40 min.

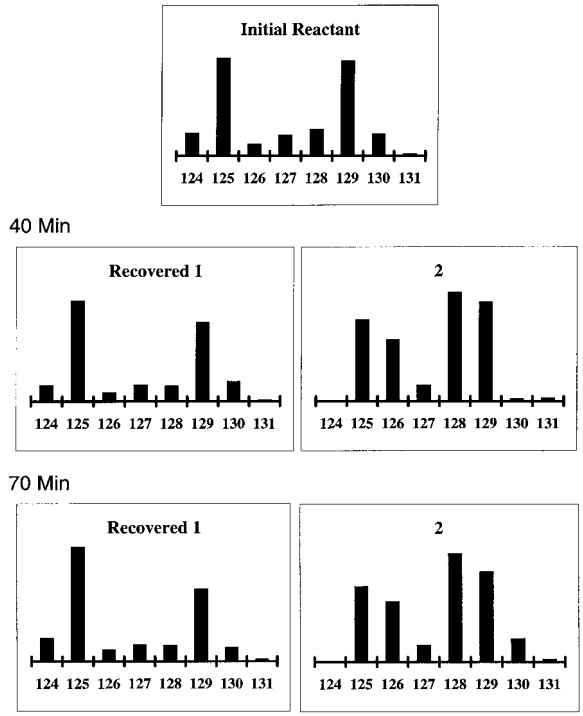


Figure 9. Crossover experiment for the rearrangement of 2-methoxypyridine-1-oxide in DMF at 140 °C. The mass spectrum of the initial reactant is shown at the top; the mass spectra of the recovered reactant are shown on the left, and the mass spectra of the product are shown on the right.

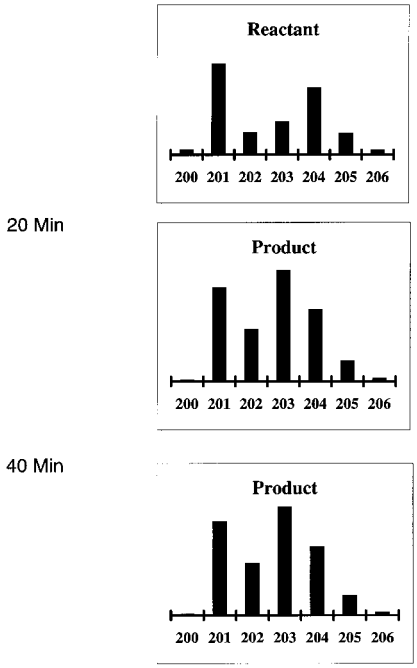


Figure 10. Crossover experiment for the rearrangement of 2-benzyloxypyridine-1-oxide in DMF at 140 °C. Upper: calculated mass spectrum of the initial reactant (see text). Lower: mass spectra of the product isolated after different times.

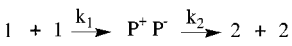
0947-6539/98/0405-0892 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 5

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 intermolecular pathway, and the data of Table 4 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.[22] The results of the crossover experiments imply that the rearrangement product is formed exclusively through channel D (see Figure 8). Because of the correlation between stereochemistry and crossover, it follows that 2-methoxypyridine-1-oxide rearranges, with inversion of configuration of the methyl group in accordance with Scheme 3.

Table 4. 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 = Me).[a]

Mass	Initial	Relative intensity Calculated for 100% crossover	Found[b]
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

[a] 0.45 M in dimethylformamide at 140 °C. [b] The same result is obtained after 40 min and after 70 min.

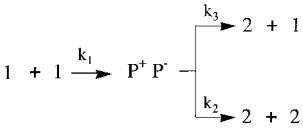


Scheme 3. Rearrangement of 2-methoxypyridine-1-oxide by means of channel D.

The benzyl compound exhibited different behavior, the analysis of which 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 °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 °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 °C, the composition of the initial 1:1 mixture of isotopomers was calculated from the mass spectra of the individual compounds (Table 5). 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 5, which is analogous to Table 4, shows that there is less than 100 percent crossover into the product. 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 summarized in Scheme 4, with $k_2 > k_3$.

Obviously neither Scheme 3 nor Scheme 4 is compatible with the previously reported first-order kinetic behavior.[5, 8, 11] Further, if 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,[8] it became necessary at this stage to reexamine the stereochemistry and the kinetics of the Tieckelmann reaction.



Scheme 4. Schematic representation of the intermolecular mechanism to which channels B and D contribute (see Figure 8) with $k_2 > k_3$.

F. Kinetic studies: The primary kinetic results of Hoppe's study of the rearrangement of **1** (R = methyl) are available in ref. [8]. 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 °C with 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 $6.64 \times 10^{-5}\ s^{-1}$ at 140 °C.

In the present work, experiments were performed on degassed solutions at 140 ± 0.8 °C with several concentrations of **1** (R = methyl) in sealed NMR tubes in deuteriochloroform and also in sealed tubes in DMF. In the latter case, as described earlier, the solvent was evaporated under reduced

Table 5. Calculated[a] relative intensities of the *m/z* 201–205 peaks in the mass spectra of the reactant, calculated relative intensities of the product, assuming 100%, 90%, 80% and 70% crossover,[a] and the relative intensities found in the product of the rearrangement of a mixture of undeuterated and tetradeuterated **1** (R = benzyl).

Mass	Calculated for reactant	Calculated for product assuming (%) crossover 100%	90%	80%	70%	Found 20 min	40 min
201	0.391	0.255	0.268	0.282	0.295	0.273	0.273
202	0.095	0.206	0.195	0.185	0.174	0.152	0.152
203	0.140	0.294	0.277	0.260	0.243	0.313	0.313
204	0.284	0.206	0.217	0.228	0.239	0.202	0.202
205	0.090	0.039	0.042	0.046	0.049	0.060	0.060
		(0.0612)	(0.0592)	(0.0683)	(0.0582)[b]		

[a] See text and ref. [22] for details. [b] Numbers in parentheses are the rms deviations between calculated and experimental relative intensities.

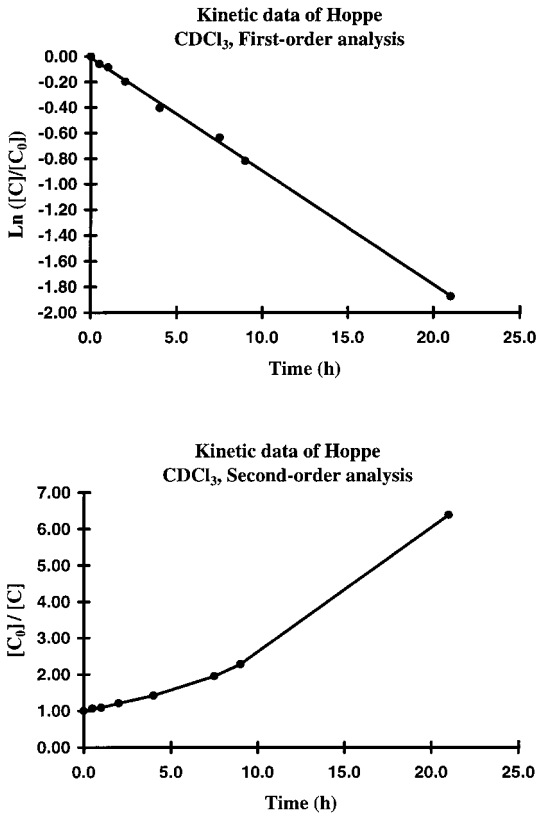


Figure 11. Kinetic data of Hoppe for the rearrangement of 2-methoxypyridine-1-oxide (0.45 M) in chloroform at 140 °C. Upper: first-order plot. Lower: second-order plot.

pressure, and the composition of mixtures was determined by NMR integration in deuteriochloroform. The previously reported use of the methyl signals was not possible.[8, 11] Although the chemical shifts of **1** and **2** differ by 0.02 ppm, mixtures exhibited the same chemical shift. Integration was, therefore, performed on the $\delta = 8.28$ peak of **1** and the $\delta =$ 6.13 ppm peak of **2**. The data are summarized in Tables 6 and 7. For kinetic studies with **1** (R = benzyl), most of the experiments were performed in sealed tubes in DMF at 140 ± 0.8 °C. After evaporation of the solvent, integration of deuteriochloroform solutions was performed with the methylene peaks of **1** and **2** at $\delta = 5.44$ and 5.29, respectively. The results are summarized in Table 8.

Table 6. Kinetic data for the rearrangement of 1 (R = methyl) at 140 °C in $CDCl_3$.

Time [h]	Concentration of **1** [M]		
0.0	0.441	0.213	0.107
1.0	0.430	–	–
2.0	–	0.209	–
4.0	0.371	–	–
5.0	–	–	0.103
8.0	0.313	0.192	–
16.0	0.199	–	–
17.0	0.097	0.156	0.092
27.0	–	–	–
32.8	–	0.102	–
36.0	–	–	0.066
55.3	–	0.040	–
73.5	–	–	0.026
117.0	–	–	0.011

Table 7. Kinetic data for the rearrangement of **1** (R = methyl) at 140 °C in DMF.

Time [h]	Concentration of **1** [M]			
0.00	0.432	0.163	0.082	0.041
0.25	–	0.163	–	–
0.50	0.390	0.159	0.082	–
0.75	–	0.155	–	–
1.00	0.313	0.152	0.079	0.041
1.25	–	0.149	–	–
1.50	0.206	0.140	0.076	–
2.00	0.079	0.122	0.072	0.039
2.50	–	–	0.067	–
3.00	0.015	–	0.063	0.035
4.00	0.002	–	0.043	0.034
5.00	–	–	–	0.032
7.00	–	–	–	0.023

Table 8. Kinetic data for the rearrangement of **1** (R = benzyl) at 140 °C in DMF solvent.

Time [h]	Concentration of **1** [M]	
0.00	0.446	0.222
0.50	0.170	0.117
0.67	0.142	0.104
0.83	0.116	0.089
1.42	0.070	0.059
3.50	0.017	0.015
5.00	–	0.006

Figures 12 – 14 show first-order plots of the chloroform data of Table 6, the DMF data of Table 7, and the data of Table 8, respectively. Second-order plots of the same data can be found as Figures 12 – 14 in the Supporting Information. In agreement with Hoppe,[8] the plot of Figure 12 for the rearrangement of a 0.44 M solution of **1** (R = methyl) in chloroform appears to be linear. All of the other plots of Figures 12 – 14 are nonlinear.

Figures 15 and 16 are concentration – time plots of the kinetic data for the rearrangement of **1** (R = methyl) in chloroform and in DMF, respectively. The theoretical curves shown in these figures have been generated from Scheme 3, with the following rate constants: in chloroform, $k_1 = 3 \times 10^{-5}\,\mathrm{M^{-1}s^{-1}}$, $k_2 = 4 \times 10^{-5}\,\mathrm{s^{-1}}$; in DMF, $k_1 = 3 \times 10^{-4}\,\mathrm{M^{-1}s^{-1}}$,

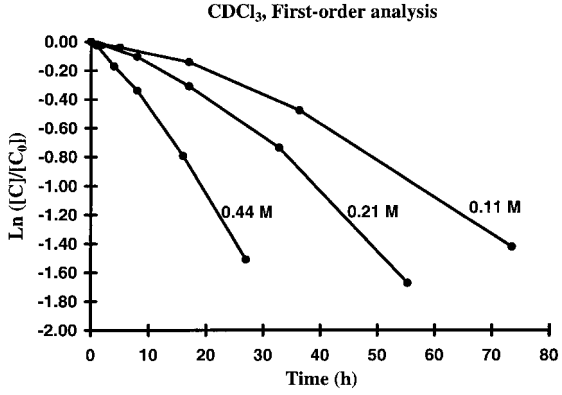


Figure 12. Concentration dependence of the rearrangement of 2-methoxypyridine-1-oxide in chloroform at 140 °C. The first-order plot is shown. A second-order plot can be found, labelled Figure 12, in the Supporting Information.

0947-6539/98/0405-0894 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 5

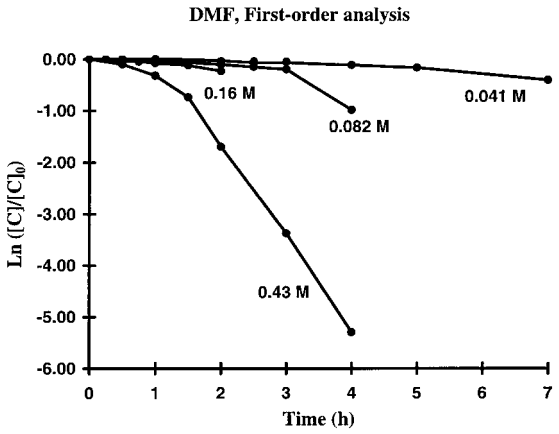


Figure 13. Concentration dependence of the rearrangement of 2-methoxypyridine-1-oxide in DMF at 140 °C. The first-order plot is shown. A second-order plot can be found, labelled Figure 13, in the Supporting Information.

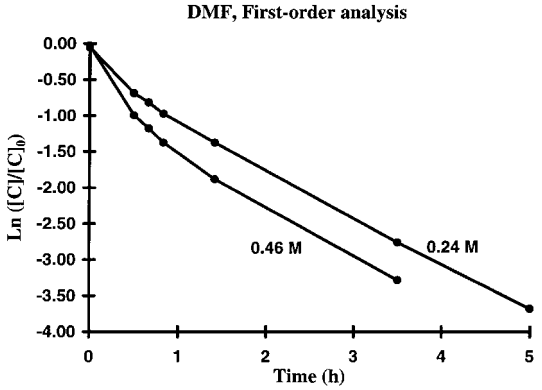


Figure 14. Concentration dependence of the rearrangement of 2-benzyloxypyridine-1-oxide in DMF at 140 °C. The first-order plot is shown. A second-order plot can be found, labelled Figure 14, in the Supporting Information.

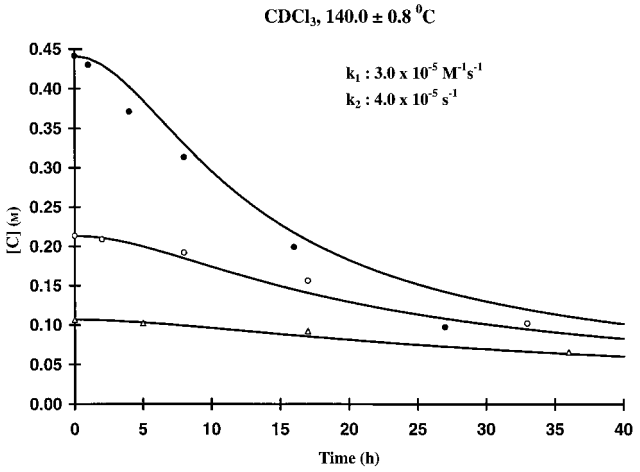


Figure 15. Concentration-time plots of the rearrangement of 2-methoxypyridine-1-oxide in chloroform at 140 °C. Theoretical curves are based on Scheme 3, which assumes that channel D is the principal reaction path.

$k_2 = 1.5 \times 10^{-4}\,s^{-1}$. Figure 17 shows the concentration–time plots of the kinetic data for the rearrangement of **1** (R = benzyl). The theoretical curves have been generated from Scheme 4, with $k_1 = 1.5 \times 10^{-3}\,M^{-1}s^{-1}$, $k_2 = 2.5 \times 10^{-3}\,s^{-1}$, and $k_3 = 8 \times 10^{-4}\,s^{-1}$.

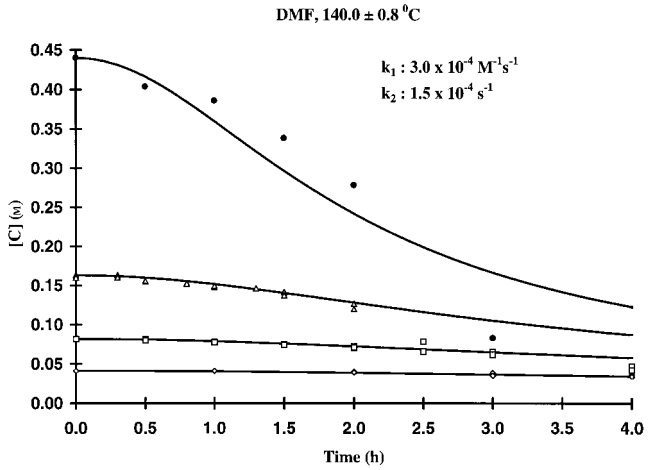


Figure 16. Concentration-time plots of the rearrangement of 2-methoxypyridine-1-oxide in DMF at 140 °C. The theoretical curves are based on Scheme 3, which assumes that channel D is the principal reaction path.

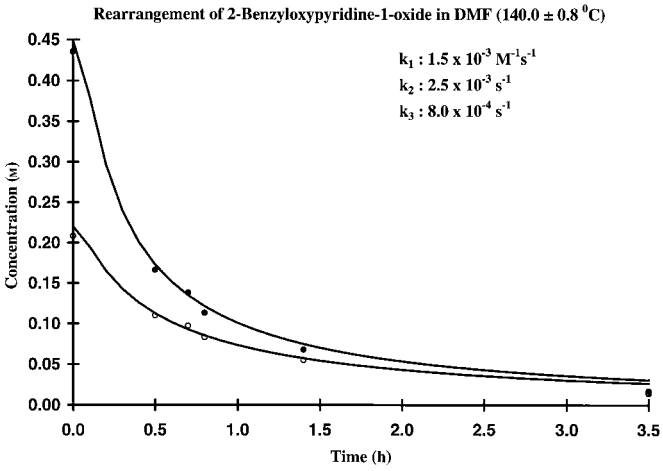
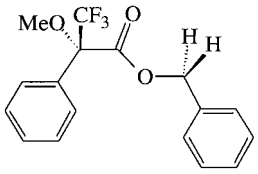


Figure 17. Concentration-time plots of the rearrangement of 2-benzyloxypyridine-1-oxide in DMF at 140 °C. The theoretical curves are based on Scheme 4, which assumes competition between channels B and D.

The fit of Scheme 3 to the experimental data of Figures 15 and 16 is somewhat poorer at the highest concentrations and the highest conversions. We found that the fit could be improved by allowing k_2 to decrease or by making Scheme 3 more complex. These variations are not shown here, as they do not alter the central conclusion that the Tieckelmann rearrangement is not a single-step first-order intramolecular process. With these caveats, we conclude that the kinetic results are consistent with the results of the crossover experiments: in chloroform and in DMF, 2-methoxypyridine-1-oxide rearranges by means of 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 DMF, 2-benzyloxypyridine-1-oxide rearranges by means of 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.

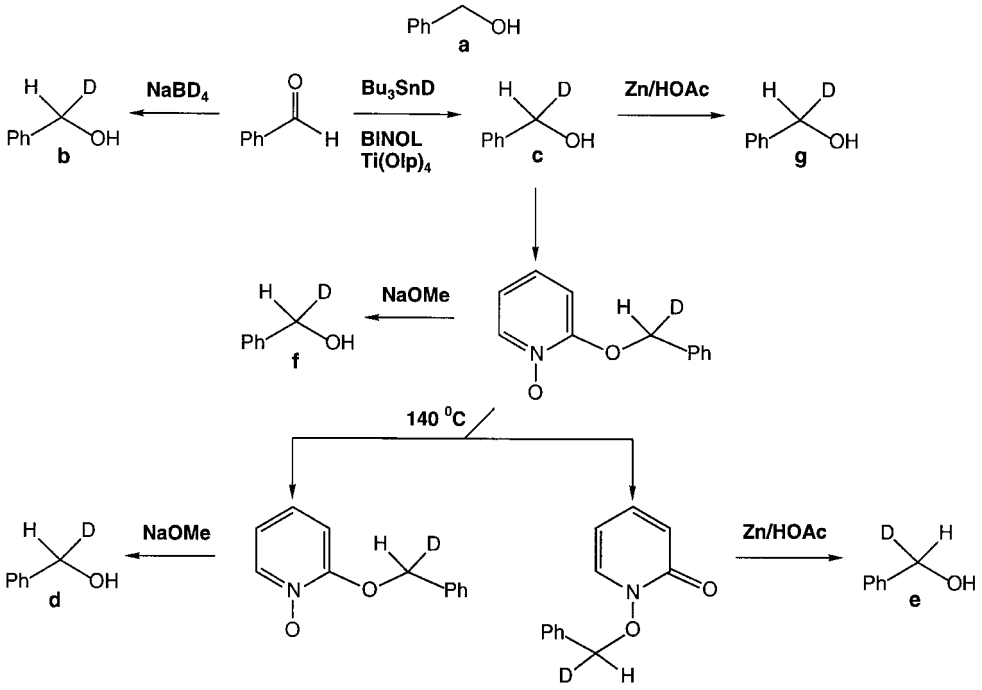
G. Stereochemical studies: The benzyl ester of the (S)-(−) enantiomer of Mosher's acid (α-methoxy-α-(trifluorome-

thyl)phenylacetic acid, MTPA, **16**) was prepared by the method of Ward and Rhee.[25] In [D]chloroform, the diastereo-



16

topic benzylic protons of **16** are observed in the ^{1}H NMR as an AB quartet at $\delta = 5.35$ and 5.31 (Figure 18a). The deuterium-decoupled ^{1}H NMR spectrum of the MTPA ester prepared from racemic benzyl-α-[D]alcohol (Figure 18b) exhibits 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 = α-deuteriobenzyl).[26]



Scheme 5. Synthesis, incorporation and recovery of chiral benzyl-α-[D]alcohol. See Figure 18 for details of **a**–**g**.

Following the procedure developed by Keck and co-workers,[28] we prepared chiral benzyl-α-[D]alcohol by reduction of benzaldehyde with tributyl tin deuteride in the presence of (S)-binaphthol and titanium tetraisopropoxide. The deuterium-decoupled spectrum of the benzylic region of the MTPA ester of this alcohol is shown in Figure 18c. As summarized in Scheme 5, the chiral alcohol was then converted to **1** (R = CHDPh), the latter was heated in DMF at 140 °C until the rearrangement was 67 percent complete (3 h), and the

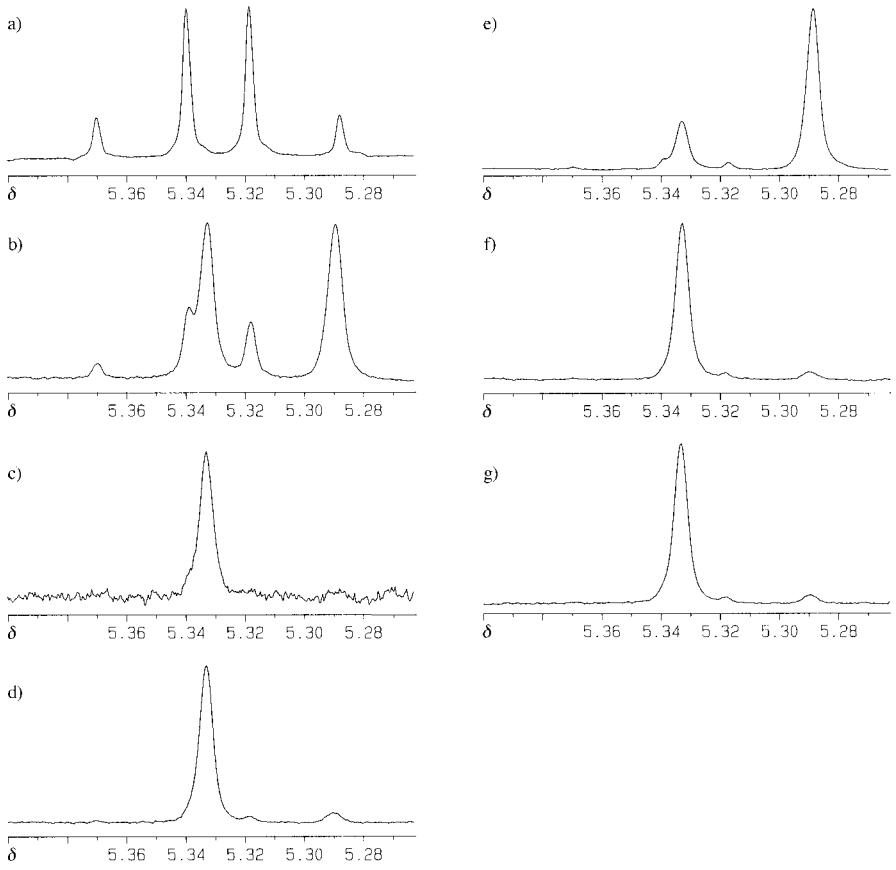


Figure 18. Benzylic region in the ^{1}H NMR spectra of the Mosher esters of a) benzyl alcohol ($PhCH_2OH$); b) racemic benzyl-α-[D]alcohol (PhCHDOH; contains some benzyl alcohol); c) chiral PhCHDOH obtained from the reaction of PhCHO with Bu_3SnD and BINOL; d) PhCHDOH obtained by conversion of the alcohol from c) into chiral **1** (R = benzyl-α-[D]), partial rearrangement into **2** (R = benzyl-α-[D]), and treatment of the recovered **1** with NaOMe; e) PhCHDOH obtained upon treatment of **2** (R = benzyl-α-[D]) (from d) with Zn/HOAc; f) PhCHDOH recovered from freshly prepared **1** (R = benzyl-α-[D]) following treatment with NaOMe; g) PhCHDOH obtained upon treatment of the alcohol from c) with Zn/HOAc. The spectra b) – g) have been deuterium-decoupled.

0947-6539/98/0405-0896 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 5

unreacted **1** and the product **2** (R = CHDPh) were isolated. Benzyl alcohol was recovered from the product by reduction with zinc and acetic acid,[8] and from the reactant by treatment with NaOMe/MeOH. Figures 18d and 18e are the benzylic regions of the MTPA esters of the alcohol from **1** and the alcohol from **2**, respectively. Figures 18g and 18f refer to control samples obtained after Zn/HOAc treatment of the original sample of benzyl-α-[D]alcohol and after NaOMe/MeOH treatment of the initial sample of **1**, respectively. There is no significant racemization during the recovery of benzyl-α-[D]alcohol from the reactant or the product, and there is no significant racemization of **1** during the course of the rearrangement. 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 DMF 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 observations of Schöllkopf and Hoppe,[5, 8] who used polarimetry. The rearrangement of chiral **1** (R = CHDPh) was, therefore, also examined under their experimental conditions (chloroform, 0.3 M, 140 °C).

*H. Kinetics and stereochemistry of the rearrangement of **1** (R = benzyl) in chloroform*: Figure 19 shows the deuterium decoupled benzylic protons in the ^{1}H NMR spectra of the

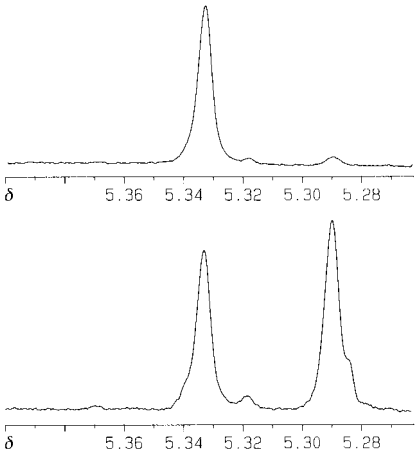


Figure 19. Deuterium-decoupled ^{1}H NMR spectra. Top: the Mosher ester of the benzyl-α-[D]alcohol recovered from chiral **1** (R = benzyl-α-[D]) after 60% rearrangement of a 0.3 M chloroform solution at 140 °C. Bottom: the Mosher ester of the benzyl-α-[D]alcohol recovered from chiral **2** (R = benzyl-α-[D]) after complete rearrangement of a 0.3 M chloroform solution of **1** at 140 °C.

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 racemization of the reactant, but the product is formed with apparent racemization. The usual interpretation of racemization, that is, that an achiral intermediate must have been produced, would be incorrect in this case. In fact, two reactions have occurred. One, by means of channel B, has given the product with net retention of configuration; the other, through 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

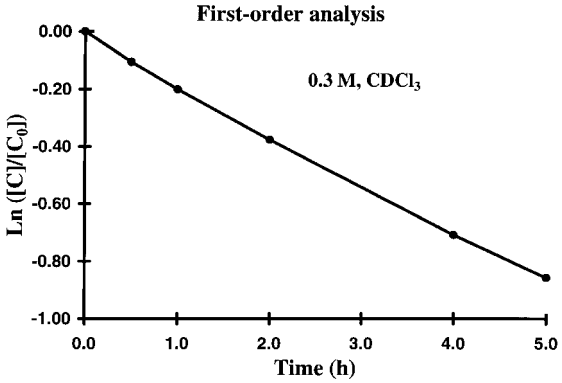


Figure 20. First-order plot of the kinetic data for the rearrangement of a 0.3 M chloroform solution of 2-benzyloxypyridine-1-oxide at 140 °C.

a first-order plot of the data of presented in Table 9. The plot is curved; however, if the curvature is ignored, the apparent first-order rate constant is $4.9 \times 10^{-5}\,s^{-1}$, in reasonable agreement with the first-order rate constant reported by Hoppe,[8] $6.64 \times 10^{-5}\,s^{-1}$. Figure 21 is a concentration–time plot of the data in Table 9. The theoretical plot has been generated from Scheme 4, with the following rate constants: $k_1 = 1.5 \times 10^{-4}\,M^{-1}\,s^{-1}$, $k_2 = 8 \times 10^{-4}\,s^{-1}$, and $k_3 = 8 \times 10^{-4}\,s^{-1}$.

Table 9. Rearrangement of **1** (R = benzyl) at 140 °C in deuteriochloroform.

Time [h]	Concentration of **1** [M]
0.0	0.299
0.5	0.268
1.0	0.244
2.0	0.205
4.0	0.147
5.0	0.127

*I. 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 through 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.[2a, 29] 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,[30] we attempted to determine this isotope effect.

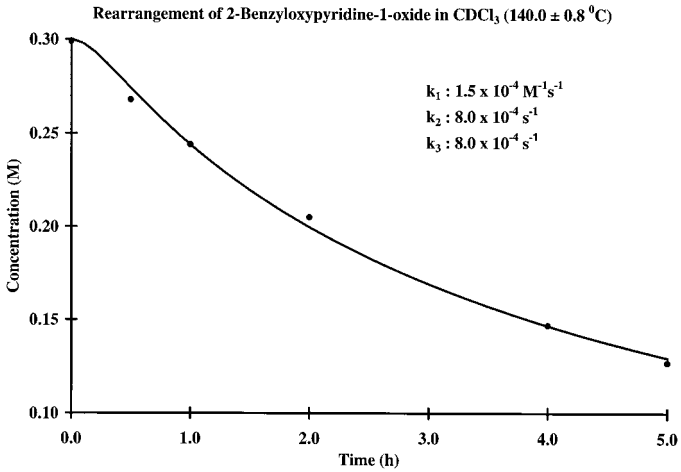


Figure 21. Concentration-time plot of the data of Figure 20. The theoretical curve has been calculated from Scheme 4, with channels B and D contributing equally to the formation of the product.

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[8] 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 °C, at which time the mole fraction of unconverted **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, recrystallized, and the EI-MS was measured (*b*). The results are summarized in Table 10, and the secondary isotope effects were calculated

Table 10. Competition experiments to determine the secondary CH_3/CD_3 kinetic isotope effect in the rearrangement of **1** (R = methyl).[a]

Time [h]	125/128 Ratio	Mole fraction of **1**	k_H/k_D[b]
0.0	1.206	1.000	–
8.0	1.194	0.768	1.03
16.0	1.253	0.508	0.94

[a] 0.45 M in chloroform. [b] Calculated from Equation (1), see text.

by use of Equation (1), where *a*, *b*, and *c* are as defined above. The average isotope effect is 0.99.

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

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 3. 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.[2]

J. Solvent effects: The evidence presented so far has shown that the rearrangements of **1** (R = methyl) 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 DMF, leads to changes in the rate constants of the individual steps, but does not alter the mechanism.

Ballesteros et al[11] has 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 nonpolar 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 °C in toluene, anisole, and nitrobenzene. Although under these conditions the rearrangement of **1** is 70 percent complete in 4 h in DMF, there was no significant reaction after 24 h in toluene, or after 4 h in the polar aromatic solvents.

Conclusions

The central thesis of this work has been confirmed. Retention of configuration in nucleophilic displacement at carbon should be regarded as a priori 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 center, leading to net retention of configuration, compete kinetically with single inversions at two centers, leading to net inversion of configuration.

All previous studies of this rearrangement are consistent with this mechanism. These include the crossover studies of Litster and Tieckelmann[4a] and of Ballesteros et al,[11] the rearrangement of **6** to **7**,[6] the *p*-substituent effect in the rearrangement of 2-benzyloxypyridine-1-oxides,[7] the negative volume of activation,[12] and the disputed skeletal isomerization in the rearrangement of the cyclopropylcarbinyl substituent.[4a, 5]

Experimental Section

General: Solvents were dried by standard procedures and redistilled prior to use. ^1H NMR and ^{13}C NMR were obtained on Bruker model SY-100 or

0947-6539/98/0405-0898 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 5

AMX 400 spectrometers. Chemical shifts are recorded with reference to 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 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 analyzer. Analytical thin-layer chromatography (tlc) was performed on precoated Merck silica gel 60 F-24 plates with aluminum backing. Spots were observed under ultraviolet light and were visualized with 1% ceric sulfate. Column chromatography was carried out with 230–400 mesh silica gel (Merck). Kinetic studies were performed in a Fisher high temperature oil bath (silicone oil) fitted with a Thermotronic Devices Model 51 proportional temperature controller. The temperatures of kinetic experiments varied between 139.2 and 140.8 °C, and are reported as 140 ± 0.8 °C. Details of the kinetic experiments and the analytical procedures employed have been given earlier.

2-Chloropyridine-1-oxide: Chloroform (70 mL) and *m*-chloroperbenzoic acid (14.6 g, 85 mmol) were added to a 250 mL three-necked flask fitted with magnetic stirrer, condenser, and dropping funnel. 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 over 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, whilst being strirred, into ice-cold 3 N 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 × 150 mL), and 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 2-chloropyridine-1-oxide as white plates. M.p. 63–65 °C (lit. m.p. 67–68.5 °C,[24] evacuated capillary); ^{1}H NMR ($CDCl_3$): $\delta = 8.34$–8.36 (m, 1H, H6), 7.49–7.51 (m, 1H, H4), 7.18–7.23 (m, 2H, H3, H5); ^{13}C NMR ($CDCl_3$): $\delta = 140.8$ (C2), 127.2 (C3, C5) 125.6 (C6), 123.9 (C4); MS (EI): *m/z*: 131, 129 (ratio = 25:75); C_5H_4NOCl (129.546): calcd C 46.36, H 3.11, N 10.81; found C 46.45, H 3.14, N 10.74.

2-Methoxypyridine-1-oxide. Methanol (15 mL) and sodium metal (390 mg, 17.0 mg-atom) were added to a round-bottomed flask fitted with magnetic stirrer and condenser. When the sodium had dissolved, a solution of 2-chloropyridine-*N*-oxide (2.0 g, 15.4 mmol) in methanol (10 mL) was added dropwise over 10 min. The solution was refluxed for 1 h (after the addition was complete), cooled, and the solvent was removed under reduced pressure. The product was dissolved in water (30 mL) and extracted with chloroform (4 × 100 mL). The combined organic extracts were dried and evaporated to afford a light yellow solid, which was purified by chromatography (methanol/ethyl acetate, 1:1). Crystallization from ethyl acetate afforded white needles of 2-methoxypyridine-1-oxide, 0.97 g (50%). M.p. 73–76 °C (lit. m.p. 78–79 °C[21]); $C_6H_7NO_2 \cdot 1.0\,H_2O$ (143.142): calcd C 50.35, H 6.33, N 9.79; found C 50.46, H 6.22, N 9.84. Dissolution of a sample in boiling toluene, followed by slow crystallization at room temperature gave a single large colorless tabular crystal, which was submitted for x-ray crystallographic analysis.[18] ^{1}H NMR ($CDCl_3$): $\delta =$ 8.27–8.29 (m, 1H, H6), 7.28–7.32 (m, 1H, H4), 6.89–6.95 (m, 2H, H3,H5), 4.08 (s, 3H, O*CH*$_3$); ^{13}C NMR ($CDCl_3$): $\delta = 158.87$, 140.18, 127.72, 117.63, 108.34, 57.25; IR (KBr): $\tilde{\nu} = 1606$, 1522, 1348 cm^{-1}; MS (EI) *m/z*: 125.

2-[D$_3$]Methoxypyridine-1-oxide: Repetition of the above reaction with CD_3OD (10 mL), sodium metal (177 mg, 7.7 mg-atom) and 2-chloropyridine-*N*-oxide (1.0 g, 7.7 mmol) gave 0.42 g (43%) of product. M.p. 73–76 °C; ^{1}H NMR ($CDCl_3$): $\delta = 8.27$–8.29 (m, 1H), 7.28–7.32 (m, 1H), 6.89–6.95 (m, 2H); MS (EI): *m/z*: 128.

2-[D$_3$]Methoxy-6-[D]pyridine-1-oxide: The above reaction was repeated with CD_3OD (10 mL), sodium metal (210 mg, 9.2 mg-atom) and 2-chloropyridine-1-oxide (1.0 g, 7.7 mmol). When the addition was complete, the reaction mixture was refluxed for 12 h. Isolation gave 0.36 g (36%) of 2-[D$_3$]methoxy-6-[D]pyridine-1-oxide. M.p. 73–76 °C; ^{1}H NMR ($CDCl_3$): $\delta = 8.25$–8.27 (m, 0.2H, H6), 7.26–7.30 (m, 1H, H4), 6.88–6.93 (m, 2H); MS (EI): *m/z*: 129, 128 (ratio, 4:1).

1-Methoxy-2-pyridone: Five equal portions of a solution of **1** (R = Me, 50.3 mg) in [D$_7$]DMF (2.5 mL) were sealed in NMR tubes, and heated at 140 °C. The initial spectrum exhibited peaks at $\delta = 8.24$–8.27 (d, 1H), 7.30–7.35 (t, 1H), 7.23 (d, 1H), 7.04 (t, 1H), 4.03 (s, 3H). After 8.7 h, only the spectrum of the product was evident, at $\delta = 7.95$–7.97 (dd, 1H), 7.40–7.46 (dt, 1H), 6.51–6.53 (dd, 1H), 6.21–6.24 (m, 1H), 4.00 (s, 3H). In a second experiment, a solution of **1** (R = Me, 200 mg, 0.15 mmol), in DMF (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}H NMR ($CDCl_3$): $\delta = 7.50$–7.52 (dd, 1H), 7.28–7.32 (dt, 1H), 6.65–6.67 (dd, 1H), 6.11–6.15 (dt, 1H,), 4.06 (s, 3H,); ^{13}C NMR ($CDCl_3$): $\delta = 158.1$, 138.4, 135.1, 122.5, 105.0, 64.3; MS (EI): *m/z*: 125; $C_6H_7NO_2 \cdot 0.75\,H_2O$ (134.134): calcd C 52.00, H 6.14, N 10.11; found C 52.23, H 6.20, N 11.22.

2-Benzyloxypyridine-1-oxide: THF (10 mL), sodium metal (60.5 mg, 2.6 mg-atom), and benzyl alcohol (2.1 g, 19 mmol) were added to a round-bottomed flask fitted with a magnetic stirrer and a condenser. 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, stirred for 3 h, cooled to room temperature, and treated with water (10 mL). Extraction with chloroform, drying, and evaporation gave a white solid which was purified by column chromatography (ethyl acetate, followed by methanol/ethyl acetate, 1:2). Crystallization from ethyl acetate/hexane gave 0.34 g (73%) of 2-benzyloxypyridine-1-oxide. M.p. 108–109 °C (lit. m.p. 107 °C[8]); ^{1}H NMR ($CDCl_3$): $\delta = 8.26$–8.28 (m, 1H, H6), 7.43–7.46 (m, 2H, Ph*H*), 7.33–7.40 (m, 3H, Ph*H*), 7.13–7.17 (m, 1H, H4), 6.88–6.92 (m, 1H, H5), 6.83–6.85 (m, 1H, H3), 5.44 (s, 2H, benzyl C*H*$_2$); ^{13}C NMR ($CDCl_3$): $\delta = 157.95$, 140.45, 135.03, 128.78, 128.65, 127.72, 126.98, 118.48, 112.58, 72.51; MS (EI): *m/z*: 201; $C_{12}H_{11}NO_2$ (201.224): calcd C 71.63, H 5.51, N 6.96; found C 71.73, H 5.64, N 6.79.

2-Benzyl-α,α-[D$_2$]oxy-6-[D]pyridine-1-oxide: THF (10 mL) and lithium aluminum deuteride (0.8 g, 19 mmol) were added to a round-bottomed flask fitted with a magnetic stirrer and a dropping funnel. A solution of freshly recrystallized benzoic acid (3 g, 24.6 mmol) in THF (15 mL) was added dropwise over 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 × 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}H NMR ($CDCl_3$): $\delta = 7.32$–7.39 (m, 5H, Ph*H*), 2.57 (s, 1H, O*H*); MS (EI): *m/z*: 110. In the next step, THF (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 °C; ^{1}H NMR ($CDCl_3$): $\delta = 8.26$–8.28 (m, 0.3H, H6), 7.44–7.46 (m, 2H, Ph*H*), 7.32–7.39 (m, 3H, Ph*H*), 7.13–7.17 (m, 1H, H4), 6.88–6.89 (m, 1H, H5), 6.82–6.85 (m, 1H, H3); MS (EI): *m/z*: 204, 203 (ratio, 4.5:1).

1-Benzyloxy-2-pyridone: A solution of 2-benzyloxypyridine-1-oxide (100 mg, 0.5 mmol) in DMF (2 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 87 mg (87%) of a white solid. M.p. 82–84 °C (lit. m.p. 77 °C[8]); ^{1}H NMR ($CDCl_3$): $\delta = 7.36$–7.40 (m, 5H, Ar), 7.24–7.28 (dt, 1H), 7.09–7.11 (ddd, 1H), 6.68–6.70 (ddd, 1H), 5.90–5.94 (dt, 1H), 5.29 (s, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 158.9$, 138.5, 136.7, 133.9, 130.0, 129.3, 128.7, 122.9, 104.3, 78.4; MS (EI): *m/z*: 201; $C_{12}H_{11}NO_2$ (201.224): calcd C 71.63, H 5.51, N 6.96; found C 71.48, H 5.35, N 7.03.

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 °C, stirred for 16 h, and then cooled and evaporated under reduced pressure. Crystallization from chloroform/hexane (1:5) gave 48 mg (54%) of an off-white product. M.p. 148–149 °C (lit. m.p. 148–149 °C[21]); ^{1}H NMR (D_2O): $\delta = 7.81$–7.73 (m, 1H), 7.46–7.50 (m, 1H), 6.62–6.65 (m, 1H), 6.45–6.48 (m, 1H,); MS (EI): *m/z*: 111.

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 suspension of 2-hydroxypyridine-1-oxide (20.3 mg, 0.18 mmol) in THF (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}H NMR ([D$_7$]DMF): $\delta = 7.93 - 7.94$ (br d, 1H), 7.29 – 7.33 (br t, 1H), 6.45 – 6.48 (br d, 1H), 6.21 – 6.24 (br d, 1H).

1,2-Dimethoxypyridinium trifluoromethanesulfonate: Methyl triflate (0.4 mL, 3.5 mmol) was injected into a solution of 2-methoxypyridine-1-oxide (146.8 mg, 1.2 mmol) in THF (15 mL) and chloroform (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 °C; ^{1}H NMR ($CDCl_3$): $\delta =$ 8.55 (dd, 1H, H6), 8.42 (dt, 1H), 7.75 (dd, 1H, H3), 7.54 (dt, 1H), 4.36 (s, 3H, OCH_3), 4.30 (s, 3H, OCH_3); $C_8H_{10}NO_5SF_3$ (289.231): calcd C 33.22, H 3.48, N 4.84; found C 33.19, H 3.37, N 4.75.

Reaction of the lithium salt with the triflate salt.

A) In [D$_7$]DMF: 1,2-Dimethoxypyridinium trifluoromethanesulfonate (5.1 mg, 0.018 mmol) was added to a solution of the lithium salt (2.2 mg, 0.018 mmol) in [D$_7$]DMF (0.5 mL). The ^{1}H NMR spectrum, taken immediately after the addition, showed the peaks of the two reactants at $\delta = 9.20$ (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 $\delta = 7.96 - 7.98$, 7.42 – 7.46, 6.51 – 6.54, 6.22 – 6.25, and 4.00. After 22 h, the conversion to **2** was greater than 95%.

B) In D$_2$O: NaOD-D$_2$O (0.11 mL, 1.43 N solution, 0.16 mmol) was added to a solution of 1-hydroxy-2-pyridone (20.2 mg, 0.18 mmol) in D$_2$O (0.5 mL). The resulting solution, designated solution A, exhibited NMR peaks at $\delta =$ 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$_2$O (0.5 mL). This solution exhibited peaks at $\delta = 8.66 - 8.68$ (d, 1H), 8.35 – 8.40 (t, 1H), 7.65 – 7.67 (d, 1H), 7.46 – 7.50 (t, 1H), 4.32 (s, 3H) and 4.24 (s, 3H). To begin the reaction solution A (0.16 mL, 0.044 mmol) 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 ($\delta = 3.27$) and 1-methoxy-2-pyridone. ^{1}H NMR: $\delta = 7.83 - 7.85$ (d, 1H), 7.51 – 7.55 (t, 1H), 6.61 – 6.65 (d, 1H), 6.44 – 6.48 (t, 1H), 3.95 (3H).

Reaction of 1 (R = CD$_3$) with methyl iodide: Methyl iodide (75 mL, 171.0 mg, 1.2 mmol) was added to a solution of **1** (R = CD$_3$, 50.8 mg, 0.4 mmol), in chloroform (3 mL). The solution was refluxed for 27 h, and the solvent was removed. The ^{1}H NMR spectrum of the product ($CDCl_3$) was identical to that of **2** (R = CH$_3$).

Reaction of 1 (R = CH$_3$) with benzyl chloride: A solution of benzyl chloride (50 mL, 60 mg, 0.4 mmol) and 2-methoxypyridine-1-oxide (50.2 mg, 0.4 mmol) in [D]chloroform (2 mL) was heated to reflux. After 20 h, the ^{1}H NMR spectrum showed conversion to a 4:1 mixture of **2** (R = benzyl) and **2** (R = methyl).

Chiral benzyl-α-[D]alcohol:[28] 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 methylene chloride, 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 while the solution was stirred. The reaction mixture was cooled to −78 °C, and a solution of tributyltin deuteride (3.6 mL, 13.5 mmol) in ether (15 mL) was added dropwise. Stirring was continued for 10 min at −78 °C after the addition was complete, and the reaction mixture was then stored for 20 h at −20 °C. The stirred reaction was quenched by addition of saturated sodium bicarbonate solution (20 mL). 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 × 100 mL), the organic layer was dried and evaporated, and 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.

MTPA ester of benzyl alcohol.[25] Oxalyl chloride (5 μL, 7.27 mg, 0.057 mmol) was added to a solution of (S)-(−)-methoxytrifluoromethylphenylacetic acid (2.8 mg, 0.012 mmol) and DMF (1.0 mL, 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 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (one crystal) in [D]chloroform (0.5 mL). The resulting solution was transferred to a NMR tube, shaken vigorously, and the ^{1}H NMR spectrum was recorded (see Figure 18).

Chiral 2-benzyl-α-[D]oxypyridine-1-oxide: THF (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) were stirred together for 10 min. Then 2-chloropyridine-1-oxide (1.21 g, 9.2 mmol) was added in one portion. The mixture was warmed to 55 – 65 °C, stirred for 4.5 h, cooled, and water (20 mL) was added. Extraction with chloroform (4 × 70 mL) followed by drying and evaporation gave a white solid, which was purified by chromatography (ethyl acetate, then methanol/ethyl acetate 1:2). Crystallization from ethyl acetate-hexane gave 1.06 g (57%), m.p. 108 – 109 °C.

Recovery of benzyl alcohol from chiral 2-benzyl-α-[D]oxypyridine-1-oxide: The *N*-oxide (0.1 g, 0.5 mmol) was added to a solution prepared from sodium hydride (48 mg of 60% dispersion in mineral oil, 1.2 mmol) and methanol (10 mL). The resulting solution was refluxed, whilst stirred, for 7 h and the solvent was then removed under reduced pressure. The residue was treated with water (5 mL) and extracted with ethyl acetate (3 × 50 mL). The organic extract was dried, concentrated, and the residue was purified by preparative layer chromatography (ethyl acetate:hexane, 1:3) to give 35 mg (65%) of benzyl-α-[D]alcohol.

Rearrangement of chiral 2-benzyl-α-[D]oxypyridine-1-oxide: A solution of the *N*-oxide (0.8 g, 4.0 mmol) in DMF (9.0 mL) was heated at 140 – 150 °C for 3 h. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (ethyl acetate, followed by ethyl acetate/methanol 1:1) to give recovered 2-benzyl-α-[D]oxypyridine-1-oxide (0.18 g) and the product 1-benzyl-α-[D]oxy-2-pyridone (0.43 g).

Recovery of benzyl alcohol from chiral 1-benzyl-α-[D]oxy-2-pyridone:[8] The pyridone (0.3 g, 1.5 mmol) was added to a suspension of zinc dust (freshly activated with 1 N HCl, 0.22 g, 3.3 mg-atoms) in 30% acetic acid (10 mL). The reaction mixture was refluxed, with stirring, for 5.5 h, cooled to room temperature, and saturated sodium bicarbonate (30 mL) was added cautiously. Extraction with ethyl acetate (3 × 100 mL), followed by drying and evaporation of the extract and chromatography (ethyl acetate/hexane, 1:3) afforded benzyl-α-[D]alcohol (122 mg, 75%).

Solvent effect studies: A solution of 2-methoxypyridine-1-oxide (2.5 mg, 0.02 mmol) in toluene (0.2 mL) was sealed in a glass tube under nitrogen and heated at 140 °C for 24 h. The solvent was then removed, and the ^{1}H NMR spectrum recorded in deuteriochloroform. The spectrum was identical with that of the starting material. In a second experiment, a solution of 2-methoxypyridine-1-oxide (20.5 mg, 0.16 mmol) in anisole (0.5 mL) was heated at 140 °C for 4 h. The solvent was then removed and the ^{1}H NMR spectrum was recorded. The spectrum was again identical with that of the starting material. In a third experiment, a solution of 2-methoxypyridine-1-oxide (20.0 mg, 0.16 mmol) in nitrobenzene (0.5 mL) was heated at 140 °C for 4 h, cooled, and the infrared spectrum was recorded. This showed strong peaks at 1522 and 1348 cm^{-1} and very weak absorption at 1666 and 1499 cm^{-1}. The infrared spectrum of 2-methoxypyridine-1-oxide in nitrobenzene shows strong peaks at 1522 and 1348 cm^{-1}; the infrared spectrum of 1-methoxy-2-pyridone has strong peaks at 1666 and 1499 cm^{-1}. The spectrum of a 95:5 mixture of **1** and **2** was the same as that of the rearrangement product.

Theoretical procedures: Transition structures were located by the reaction coordinate method. The C···O bonds of the entering and leaving groups were fixed at several values near 1.9 Å, all other geometrical parameters were optimized, and the magnitudes and signs of the gradients of the two reaction coordinates were used to improve the trial values. When a structure close to the saddle point was reached, a final refinement was usually achieved with the OPT = CALCALL option of Gaussian 92 or Gaussian 94,[14] in which force constants are calculated in every iteration. All calculations of intermolecular alkyl transfer (alkyl = Me, Et, PhCH$_2$), of intramolecular alkyl transfer (alkyl = Me, Et, PhCH$_2$), and of CH$_3$/CD$_3$ isotope effects were performed at the 3-21G level, and all of the stationary structures computed at this level were characterized by vibrational analysis. These data, and details of all structures, are available as Supporting Information. The Supporting Information also includes the vibrational analysis of intramolecular methyl transfer at the 3-21 + G level. Vibrational analysis was not performed on the MP2/6-31 + G* calculations of intra-

0947-6539/98/0405-0900 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 5

molecular methyl transfer. For calculations of CH_3/CD_3 isotope effects, the frequencies employed as input to the Bigeleisen equation[15] were obtained by scaling of the computed values by 0.9.

Acknowledgements: The authors thank Dr. Inga Hoppe for kindly providing a copy of her 1971 Göttingen Dissertation, Professor Robert F. Hudson for his interest and encouragement, Professor Maurice Kreevoy for an interesting comment, Dr. Raymond Batchelor and Professor F.W.B. Einstein for determination of the crystal structure of **1** (R = Me), and the Natural Sciences and Engineering Research Council of Canada for financial support.

Received: July 15, 1998 [F764]

[1] a) L. Deng, V. Branchadell, T. Ziegler, *J. Am. Chem. Soc.* **1994**, *116*, 10645; b) S. Harder, A. Streitwieser, J. T. Petty, P. von R. Schleyer, *ibid*. **1995**, *117*, 3253; c) M. N. Glukhovtsev, A. Pross, H. B. Schlegel, R. D. Bach, L. Radom, *ibid*. **1996**, *118*, 11258; d) S. Wolfe, C.-K. Kim, K. Yang, N. Weinberg, Z. Shi, *Can. J. Chem.* **1998**, *76*, 114.

[2] a) H. G. Floss, S. Lee, *Acc. Chem. Res.* **1993**, *26*, 116; b) See also: D. Alker, W. D. Ollis, H. Shahriari-Zavareh, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1623, and references therein.

[3] L. Tenud, S. Farook, J. Seibl, A. Eschenmoser, *Helv. Chim. Acta.* **1970**, *53*, 2059; V. I. Minkin, L. P. Olekhanovich, Y. A. Zhdanov, *Molecular Design of Tautomeric Compounds,* Reidel, Dordrecht, **1988**, chapter 4.

[4] a) F. J. Dinan, H. Tieckelmann, *J. Org. Chem.* **1964**, *29*, 1650; b) J. E. Litster, H. Tieckelmann, *J. Am. Chem. Soc.* **1968**, *90*, 4361.

[5] U. Schöllkopf, I. Hoppe, *Tetrahedron Lett.* **1970**, 4527; *Liebigs Ann. Chem.* **1972**, *765*, 153.

[6] D. Alker, S. Mageswaran, W. D. Ollis, H. Shahriari-Zavareh, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1631; D. Alker, W. D. Ollis, H. Shahriari-Zavareh, *ibid*. **1990**, 1637.

[7] It should be noted that the details of these kinetic studies do not appear in ref. [5], or in the Dissertation on which ref. [5] is based.[8] Moreover, although the Hammett plot of ref. [5] is considered to be linear (Figure 22) when only the *p*-substituents are included in the plot an upward (concave) curvature results. This behavior is characteristic of S_N2 reactions of benzyl derivatives.[9]

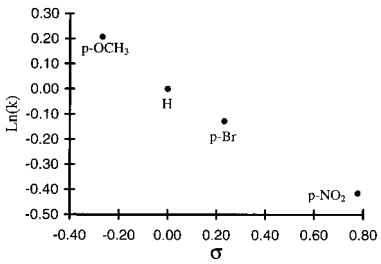


Figure 22. The Hammett plot (*p*-substituents only) ref. [5].

[8] I. Hoppe, Dissertation, Göttingen, **1971**.

[9] See: P. R. Young, W. P. Jencks, *J. Am. Chem. Soc.* **1979**, *101*, 3288; A. Pross, S. Shaik, *ibid.* **1981**, *103*, 3702, and references therein.

[10] R. B. Woodward, R. Hoffmann, *Angew. Chem.* **1969**, *81*, 797; *Angew. Chem. Intl. Ed. Engl.* **1969**, *8*, 781.

[11] P. Ballesteros, S. Senent, J. Elguero, *Bull. Soc. Chim. Belg.* **1990,** *99*, 595.

[12] W. J. le Noble, M. R. Daka, *J. Am. Chem. Soc.* **1978**, *100*, 5961.

[13] W. J. le Noble, *Progr. Phys. Org. Chem.* **1967**, *5*, 207; T. Asano, W. J. le Noble, *Chem. Rev.* **1978**, *78*, 407; R. van Eldik, T. Asano, W. J. le Noble, *ibid*. **1989**, *89*, 549.

[14] T. Clark, J. Chandrasekhar, G. W. Spitznagel, P. von R. Schleyer, *J. Comp. Chem.* **1983**, *4*, 294; W. J. Hehre, L. Radom, P. von R. Schleyer, J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, **1985**. Ab initio calculations were performed with Gaussian 92 or Gaussian 94. See: M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, S. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. DeFrees, J. Baker, J. J. P. Stewart, J. A. Pople, *Gaussian 92*, *Revision B*, Gaussian, Pittsburgh, PA, **1992**; M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. DeFrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzales, J. A. Pople, *Gaussian 94, Revision D*, Gaussian, Pittsburgh, PA. **1995**.

[15] Isotope effects were calculated with the Bigeleisen equation, J. Bigeleisen, *J. Chem. Phys.* **1949**, *17*, 675, by methods described in: a) S. Wolfe, S. Hoz, C.-K. Kim, K. Yang, *J. Am. Chem. Soc.* **1990**, *112*, 4186; b) S. Wolfe, C.-K. Kim, *ibid*. **1991**, *113*, 8056; c) R. J. Boyd, C.-K. Kim, Z. Shi, N. Weinberg, S. Wolfe, *ibid.* **1993**, *115*, 10147.

[16] J. A. Llewellyn, R. E. Robertson, J. M. W. Scott, *Can. J. Chem.* **1960**, *38*, 222; T. W. Bentley, P. von R. Schleyer, *Adv. Phys. Org. Chem.* **1977**, *14*, 1; W. J. Albery, M. M. Kreevoy, *ibid.* **1978**, *16*, 87.

[17] a) C. N. Sukenik, J. A. P. Bonapace, N. S. Mandel, P.-Y. Lau, G. Wood, R. G. Bergman, *J. Am. Chem. Soc.* **1977**, *99*, 851; b) J. D. Dunitz, *Pure Appl. Chem.* **1991**, *63*, 177; c) P. Venugopalan, K. Venkatesan, J. Klausen, E. Novotny-Bregger, C. Leumann, A. Eschenmoser, J. D. Dunitz, *Helv. Chim. Acta.* **1991**, *74*, 662; d) M. Dessolin, O. Eisenstein, M. Golfier, T. Prangé, P. Sautet, *J. Chem. Soc. Chem. Commun*. **1992**, 132; e) J. D. Dunitz, *Acta Crystallogr. B51* **1995**, 619; f) M. Smrčina, S. Vyskočil, V. Hanuš, M. Polášek, V. Langer, B. G. M. Chew, D. B. Zax, H. Verrier, K. Harper, T. A. Claxton, P. Kočovsky, *J. Am. Chem. Soc.* **1996**, *118*, 487.

[18] R. Batchelor, F. W. B. Einstein, unpublished results.

[19] S. S. Shaik, H. B. Schlegel, S. Wolfe, *Theoretical Aspects of Physical Organic Chemistry. The S_N2 Mechanism*, Wiley, New York, **1992**.

[20] For a similar approach, see: T. R. Griffin, D. B. Cook, A. Haynes, J. M. Pearson, D. Monti, G. E. Morris, *J. Am. Chem. Soc.* **1996**, *118*, 3029.

[21] J. N. Gardner, A. R. Katritzky, *J. Chem. Soc*. **1957**, 4375.

[22] 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 spectra 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 204 compounds (Scheme 2): $\beta = 0.9$ 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 (methyl or benzyl), r = undeuterated migrating group, X = deuterated ring, x = undeuterated ring. With these definitions the composition of a reactant can be described as: XR = fully

deuterated, xR or 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 ion, $\lambda\alpha[1-(1-\alpha)\beta]$; satellite ion, $(1-\lambda)\alpha[1-(1-\alpha)\beta]$

Xr: molecular ion, $\lambda\alpha(1-\alpha)\beta$; satellite ion, $(1-\lambda)\alpha(1-\alpha)\beta$

xR: molecular ion, $\lambda(1-\alpha)[1-(1-\alpha)\beta]$; satellite ion, $(1-\lambda)(1-\alpha)[1-(1-\alpha)\beta]$

XR: molecular ion, $\lambda(1-\alpha)^2\beta$; satellite ion, $(1-\lambda)(1-\alpha)^2\beta$

[23] The theoretical curves of Figures 15-17 were produced by numerical integration of the rate equations of Schemes 3 and 4. Since the experimental data of these figures were obtained from the equation $[\mathbf{1}] = [\mathbf{1}]_0\{r/(r+1)\}$, where r is the ratio of the integrals of **1** and **2**, the calculated concentrations of **1** (R = methyl or benzyl) were rescaled as $[\mathbf{1}]_0[\mathbf{1}]/([\mathbf{1}]+[\mathbf{2}])$. The computer programme is available from the authors.

[24] A. R. Katritzky, *J. Chem. Soc.* **1957**, 191.

[25] D. E. Ward, C. K. Rhee, *Tetrahedron Lett.* **1991**, *49*, 7165.

[26] As noted earlier, Hoppe reported specific rotations of less than 1° to three decimal place accuracy.[8] The apparatus that gave these results and the details of the measurements were not disclosed. In our hands, rotations of α-deuteriobenzyl compounds were found to be highly variable and, in view of our own history of problems in this area,[27] we sought an NMR alternative to measurements of rotation.

[27] See the foonote on p. 138 of S. Wolfe, A. Rauk, L. M. Tel, I. G. Csizmadia, *J. Chem. Soc. B*, **1971**, 136.

[28] G. E. Keck, K. H. Tarbet, L. S. Geraci, *J. Am. Chem. Soc.* **1993**, *115*, 8467; G. E. Keck, D. Krishnamurthy, *J. Org. Chem.* **1996**, *61*, 7638.

[29] J. W. Cornforth, J. W. Redmond, H. Eggerer, W. Buckel, C. Gutschow, *Nature* **1969**, *221*, 1212; J. Lüthy, J. Rétey, D. Arigoni, *ibid.* **1969**, *221*, 1213; H. G. Floss, S. Lee, *Acc. Chem. Res.* **1993**, *26*, 116.

[30] K. N. Houk, S. M. Gustafson, K. A. Black, *J. Am. Chem. Soc.* **1992**, *114*, 8565; J. W. Storer, L. Raimondi, K. N. Houk, *ibid.* **1994**, *116*, 9675.

[31] The reaction of (impure) cyclopropylcarbinyl bromide with sodium cyanide in aqueous ethanol produces a mixture of cyclopropylcarbinyl and cyclobutyl nitriles. See: G. E. Cartier, S. C. Bunce, *J. Am. Chem. Soc.* **1963**, *85*, 932.

0947-6539/98/0405-0902 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 5