

ON THE GEOMETRIC REQUIREMENTS FOR CONCERTED 1,2-CARBONYL MIGRATION IN α,β -EPOXY KETONES

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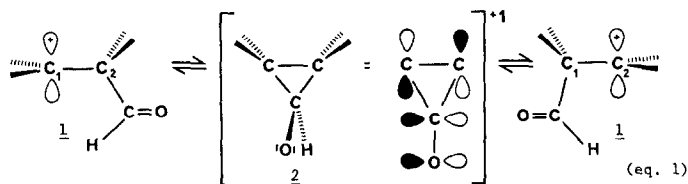
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Summary: The stabilizing influence of neighboring group participation by the carbonyl group in concerted 1,2-acyl migration is related to the ability of the molecule to assume a transition stage geometry resembling a cyclopropyloxonium ion.

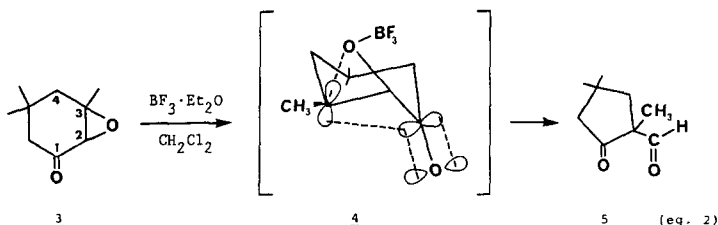
The unusual migratory aptitude of the carbonyl group in Lewis acid catalyzed rearrangements of α,β -epoxy ketones was first disclosed by House¹ in a series of papers concerning the mechanism of acyl migration. Labeling studies established the reaction to be intramolecular, and it was also found that very little positive charge developed in the transition state ($\rho \sim -1$).^{1a} Our more recent studies have shown that 1,2-carbonyl migration is a concerted process that proceeds with inversion of configuration at the migration terminus without loss of optical purity.² We have suggested that the reaction involves neighboring group participation (NGP) at the carbonyl carbon.³

Despite the numerous examples of carbonyl migration that have been reported,¹ application of this transformation to organic synthesis has not been exploited. We ascribe the lack of utilization of this reaction in more complicated molecules to the fact that it is difficult to predict with any degree of certainty when acyl migration will occur in high yield. If one is to include this transformation in the planning of strategies for multistep syntheses, then our ability to assure the successful outcome of a carbonyl migration must be improved. Very subtle and seemingly inconsequential changes in the structure of the epoxy ketone can have a profound effect upon the reaction pathway. We have chosen two structurally related α,β -epoxy ketones to illustrate this point. Both substrates involve acyl migration within a cyclic structure to a developing positive tertiary center at the migration terminus. We now address the question of the geometric requirements for a concerted carbonyl migration. If the proper orbital orientation for NGP at carbonyl carbon cannot be achieved due to steric interactions or bond angle deformation, then competing halohydrin formation or alkyl (hydrogen) migration will be observed. In a kinetically separate step, carbonyl migration of the halohydrin can occur.

We attribute the facility with which certain acyl migrations occur to a unique stabilization of the transition state by delocalization of the developing positive charge through a **reverse polarization of the carbonyl π -bond** and formation of a cyclopropyloxonium ion (eq. 1).⁴ We suggest that ion 2 lies on the reaction pathway and that the geometric requirements for its formation can serve as a model to suggest that facile acyl migration could be expected when the carbonyl moiety can participate in nonclassical bonding as in 2.



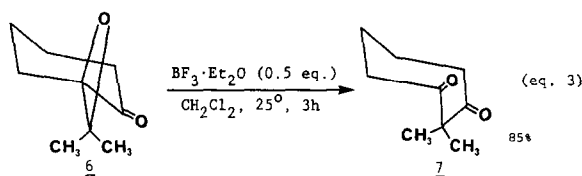
When isophorone oxide **3** was treated with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in CH_2Cl_2 solvent, we observed essentially quantitative 1,2-carbonyl migration with attendant ring contraction affording **5**



(eq. 2). This is a synthetically useful transformation that can be achieved on a preparative scale. In a typical experiment 5.0 g (0.032 mol) of **3** was added to a 100 ml of CH_2Cl_2 containing 2.0 ml of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at 25° . After 1 min, the reaction was quenched by addition of aqueous NaHCO_3 , extracted with $\text{NaCl}_{(\text{aq})}$ and dried (MgSO_4). We isolated 4.4 g (88%) of **5** upon careful distillation. Several experiments are outlined in Table 1.

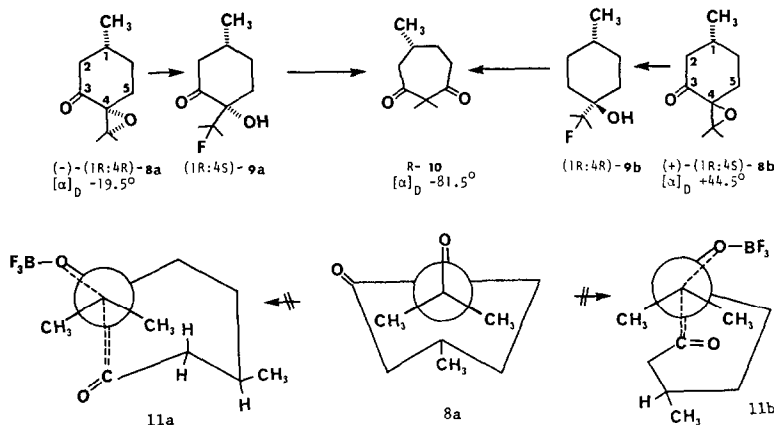
We suggest that this extremely facile transformation proceeds without the intervention of a fluorohydrin intermediate and with total exclusion of hydrogen migration. For such a concerted 1,2-carbonyl migration to occur, the carbon-carbon σ bond ($\text{C}_2\text{-C}=\text{O}$) at the migration origin must be parallel, or nearly so, to the developing vacant carbon p orbital at C_3 .^{2,3} The atomic p orbital at the carbonyl carbon must also be capable of attaining coplanarity with the $\text{C}_2\text{-C}_3$ bond axis in order for developing Walsh orbitals (as in **2**) to effectively disperse the positive charge in the transition state. If a delocalized ion such as **2** lies at or near the transition state and its formation is a necessary condition for a concerted acyl migration, then the geometric requirements for such a reaction are rather specific. Examination of molecular models suggests that isophorone oxide (**3**) can easily achieve these specific orbital alignments by a $\text{C}_3\text{-C}_4$ bond rotation that has the carbonyl moiety poised in the proper manner for $\text{C}_1\text{-C}_2$ bond migration where the carbonyl carbon can initiate bonding at the migration terminus early on the reaction coordinate as depicted in **4**. At this point the $\text{C}_2\text{-C}_1$ and $\text{C}_3\text{-O}$ σ bonds are extensively elongated. As the 1,2-carbonyl migration proceeds, the positive charge at C_3 may be stabilized from the top face by the departing oxygen and from the bottom by the neighboring carbonyl carbon.

We also observed carbonyl migration in the exo-oxide **6** upon treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in a nonplanar solvent (eq. 3). However, Reusch⁵ has reported that treatment of pulegone oxide **8** with 1.25 eq of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in benzene afforded fluorohydrin **9** after 5 min. Thermal rearrangement of **9** (150°) afforded the 1,3-diketone **10** (50%). In contrast, Watanabe⁶ reported ZnBr_2 catalyzed rearrangement of pulegone oxide in refluxing benzene (6h) to afford **10** via carbonyl migration in yields of 90%. These divergent observations prompted us to closely examine the Lewis acid catalyzed rearrangement of **8**.



Treatment of a mixture of pulegone oxides **8a** and **8b** with 2.0 eq of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in refluxing benzene yielded 2,2,5-trimethylcycloheptane-1,3-dione **10** in 1 min (99%). The optically pure diastereomers **8a** and **8b** were separated by spinning band distillation. After purification by recrystallization (petroleum ether), **8a** had $[\alpha]_D^{25} -19.5^\circ$ (c 1.5 EtOH); mp 52.5-54.5° and **8b** had $[\alpha]_D^{25} +44.5$ (c 1.5 EtOH); mp 57-58°. Treatment of **8a** or **8b** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in refluxing benzene followed by sublimation (0.01 mm, 25°) gave **10** that had $[\alpha]^{24.5} -81.8^\circ$ (c 1.5 EtOH) and $[\alpha]^{24.5} -81.2^\circ$ (c 1.5 EtOH) (lit.⁶ $[\alpha]_D^{25} -81.6$ (c 1.15 EtOH), respectively. However, glpc analysis of the reaction mixture clearly indicated that the kinetic product formed from pulegone oxide (and **6**) is a fluorohydrin (Scheme 1).

Scheme 1



Isolation of fluorohydrins **9a** and **9b** by preparative glpc and subsequent treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in refluxing benzene afforded **10** arising from carbonyl migration in 1 min in quantitative yield as determined by glpc. The fluorohydrins can readily achieve the required conformation for concerted 1,2-acyl rearrangement. With all three substrates, initial oxirane cleavage was much faster than subsequent carbonyl migration. The overall rate of rearrangement for **8a** was approximately twenty times faster than **8b** as a consequence of a steric interaction of the remote methyl group at C₁ in **9b**. Failure to observe the one-step concerted pathway from either **8a** or **8b** may be attributed to the inability of either compound to attain a geometry where the atomic p orbital at the carbonyl carbon can overlap with the incipient p orbital at the migration terminus early on the reaction coordinate.

Since the migrating carbonyl group in **8a** (or **8b**) has two distinct π -faces, two transition states are possible for a concerted carbonyl migration. Examination of molecular models suggests that formation of **11b** requires considerable internal angular strain in the methylene chain. Although migration of the opposite face of the carbonyl moiety may be readily achieved from **8a** by C₄-C₅ bond rotation, a severe steric interaction of a methylene group with a CH₃ group destabilizes transition state **11a**. These same arguments apply to **8b** since the methyl substituent at C₁ is far removed from the migration terminus. We, therefore, suggest that the geometric requirements for forming a uniquely stabilized transition state resembling **2** are too severe and an alternate pathway resulting in fluorohydrin formation obtains. We have been able to achieve carbonyl migration in **8** with other catalysts under more forcing reaction conditions (Table 1).

In conclusion, if molecular models indicate that the requisite geometry for NGP at carbonyl carbon is attainable, then a concerted acyl migration should be anticipated.

Table 1
LEWIS ACID CATALYZED CARBONYL MIGRATION

Epoxy Ketone	Catalyst Equivalents	Solvent	Reaction Time	Temperature	Product	Yield
3	BF ₃ ·Et ₂ O(0.5) ^a	CH ₂ Cl ₂	25 min.	25°	5	97(88) ^b
3	BF ₃ ·Et ₂ O(0.2)	CH ₂ Cl ₂	25 min.	25°	5	97
3	BF ₃ ·Et ₂ O(0.1)	CH ₂ Cl ₂	30 min.	reflux	5	97
8 ^c	BF ₃ ·Et ₂ O(0.5)	CH ₂ Cl ₂	4 hr.	25°	10	93(64)
8	BF ₃ Et ₂ O(0.5)	CH ₂ Cl ₂	1 hr.	reflux	10	83(70)
8	BF ₃ ·Et ₂ O(2.0)	C ₆ H ₆	1 min.	reflux	10	99(85)
8	BF ₃ ·Et ₂ O(0.2)	C ₆ H ₆	1 hr.	reflux	10	97(73)
8	BF ₃ ·Et ₂ O(0.5)	C ₆ H ₆	22 hr.	25°	10	93(71)
8	CuCl ₂ (2.0)	C ₆ H ₆	3 hr.	reflux	10	92(60)
8	ZnCl ₂ (2.0)	C ₆ H ₆	46 hr.	reflux	10	97(79)

- a) Ratio of catalyst to epoxyketone. b) Isolated yield in parentheses, percent.
c) A mixture of **8a** and **8b** was utilized.

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