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# Studies on the Mechanism of Base-Catalyzed Decomposition of Bicyclic Endoperoxides

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Kinetic studies were performed to clarify the Kornblum-Delamare reaction mechanism of bicyclic endoperoxides. Ascaridol and 1,4-diphenyl-2,3-dioxa-bicyclo[2.2.2]oct-5-ene, not having $\alpha$-protons, did not provide any reaction with bases. Reaction with different bases has revealed that reaction rates for the base-catalyzed decomposition of 2,3-dioxa-bicyclo[2.2.2]oct-5-ene depend strongly on the base strength. The stronger the base used, the faster the conversion rate. Reaction rate values $k$ of endoperoxides with different skeletons were also studied with $NEt_3$. It has been noted that the strength of the base plays the dominant role in determining the rate of the reactions.

**Key Words:** Bicyclic endoperoxides, Kornblum-Delamare reaction, base-catalyzed decomposition, kinetic study.

## Introduction

Kornblum and Delamare[1] showed the first decomposition of dialkyl peroxides by base-catalyzed rearrangement. They reported that 1-[1-(*tert*-butylperoxy)ethyl] benzene **1** gives acetophenone and tert-butanol by treatment with bases such as KOH, NaOEt, and piperidine. Milas and Surgenor[2] reported previously the stability of 2-(*tert*-butylperoxy)-2-methylpropane against strong bases. Kornblum and Delamare proposed a three-step mechanism for the base-catalyzed decomposition of 1-[1-(*tert*-butylperoxy)ethyl]benzene (**1**) as outlined in Scheme 1.

The first step of the reaction includes an abstraction of the $\alpha$-proton to give an intermediate carbanion **2**. In the second step the electron pair of the carbanion **2** displaces *tert*-butoxide to form a ketone (acetophenone). These steps presumably are synchronous. Finally, in the third step *tert*-butoxide captures the proton from the base to give *tert*-butanol. In view of this mechanism, only those dialkylperoxides and alkyl hydroperoxides having an $\alpha$-proton next to the peroxide linkage should undergo base-catalyzed rearrangement.

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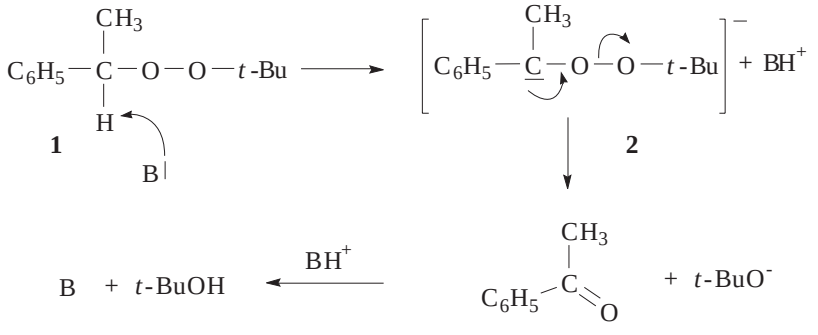



**Scheme 1**

This reaction was exploited as a very useful tool in synthetic organic chemistry. It was shown that many cyclic endoperoxides give 4-hydroxy ketones by base-catalyzed rearrangements[3]. Tropone[4] and tropone derivatives[5] were readily prepared via the Kornblum-Delamare reaction of endoperoxides. Most recently, we have shown that some unsaturated bicyclic endoperoxides resulted in the formation of the saturated diketones upon treatment with bases, instead of the expected hydroxy-enones[6].

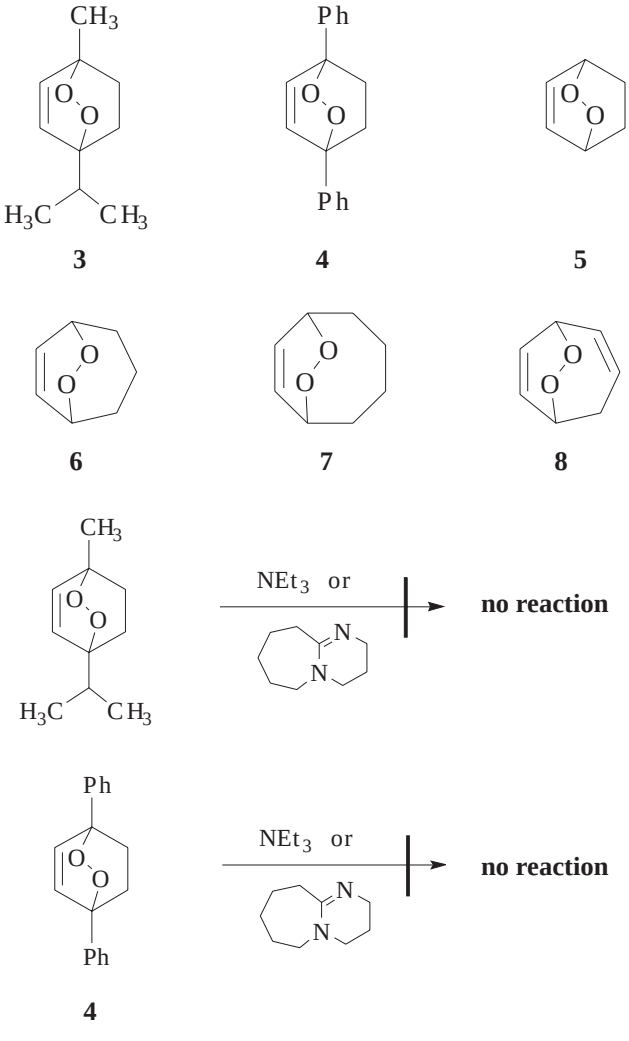
Besides having synthetic importance, the Kornblum-Delamare reaction has biological aspects. Prostaglandin $H_2$ that includes a [2.2.1] bicyclic endoperoxide moiety is converted to prostaglandin $E_2$ having a 3-hydroxy-cyclopentanone moiety by in situ reaction without any change in the other parts of the molecule[7]. Salomon and coworkers studied the mechanism of this conversion using 2,3-dioxa-bicyclo[2.2.1]heptane as a model system. Their studies, mainly based on kinetic isotope effects, showed supporting evidence for the classical Kornblum-Delamare reaction mechanism[7]. Nojima and coworkers[8] studied the base-catalyzed rearrangements of 3,3,5-trisubstituted [1,2]dioxolanes and observed a retro aldol reaction that also supported the classical mechanism.

However, there are some mechanisms proposing electron-transfer from base to peroxide giving Kornblum-Delamare products. For example, Dixon and Schuster[9] inspected the thermolysis of 1-phenylethyl peroxyacetate using bases such as N,N-dimethyl-dihydrodibenzo[ac]phenazine and N,N-diphenyl-1-aminopyrene. They showed that these bases accelerate the rate of reaction without themselves being consumed. Pobedimskii et al.[10] investigated the mechanism of the reaction of peroxides (dicyclohexyl peroxydicarbonate, benzoyl peroxide, etc.) with aromatic amines by ESR spectroscopy. They reported that the primary stage of the reaction is the transfer of an electron from the amine to the peroxide with the formation of a radical-cation derived from the amine. These various examples demonstrate that the mechanism of the Kornblum-Delamare rearrangement is under debate.

In this paper, we investigated the base-catalyzed reactions of bicyclic endoperoxides **3** and **4**, do not bear an abstractable $\alpha$-proton and bicyclic endoperoxides **5-8**, having an $\alpha$-proton next to the peroxide linkage.

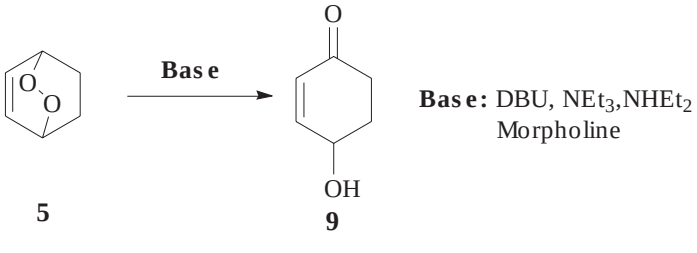
## Results and Discussion

In the first part of this work, the reactions of the bicyclic unsaturated endoperoxides of **3** and **4** with $NEt_3$ and diazabicycloundacene (DBU), a strong amine base, were investigated. The treatment of endoperoxide **3** as well as **4** with $NEt_3$ (for 220 h) and DBU (for 156 h) at room temperature did not give any reaction. The starting materials were recovered unchanged.




**Scheme 2**

The non-reactivity of these endoperoxides **3** and **4** may be attributed to them not having $\alpha$-hydrogen atoms. From these two experiments, it may be concluded that the base-catalyzed Kornblum-Delamare rearrangement requires the existence of an abstractable $\alpha$-proton next to the peroxide linkage, as proposed before. In the second part of this work, we investigated the reactions of cyclic unsaturated endoperoxides bearing an $\alpha$-proton at the bridgehead with different bases and in different solvents. 2,3-dioxa-bicyclo[2.2.2]oct-5-ene **5** was chosen as a model system.




**Scheme 3**

We used five different bases having different strengths: DBU, triethylamine, diethylamine, morpholine and pyridine. The base-catalyzed reaction of **5** with morpholine and pyridine in $CCl_4$ did not provide any

trace of the expected hydroxyketone **9**. However, **5** was rearranged smoothly to **9** in chloroform in the presence of morpholine (Scheme 3). Pyridine in chloroform was not effective in performing this conversion. The different behavior of morpholine in chloroform and carbontetrachloride may be attributed to the change of the base strength of morpholine depending on the solvation effect. In order to find a correlation between the base strength and the rate of the rearrangement we performed some kinetic studies. Kinetic measurements were done in an NMR tube in the cavity of the NMR-probe at room temperature. The endoperoxide **5** has been converted to the hydroxy-enone **9** in the presence of bases such as DBU, triethylamine, diethylamine, and morpholine. The rearrangement of **5** can be followed conveniently by NMR spectroscopy. The results are shown in Figure 1.

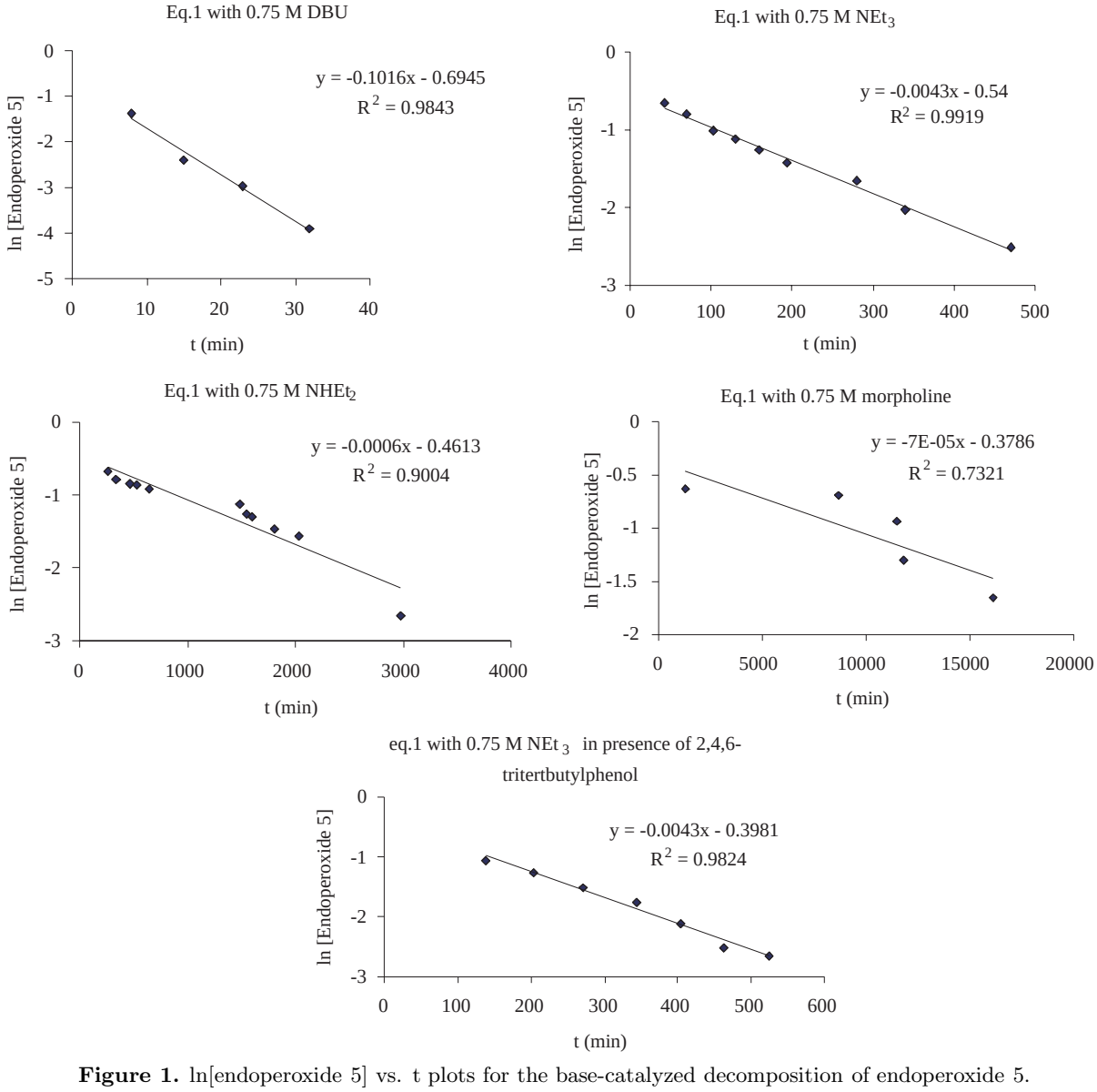



**Figure 1.** ln[endoperoxide 5] vs. t plots for the base-catalyzed decomposition of endoperoxide 5.

Comparison of the $k$ values obtained with different bases clearly demonstrates that the decomposition rates of endoperoxide **5** depend directly on the strength of the used bases (see Table 1). The highest $k$ value was obtained for DBU (relative $k$ value 1430).

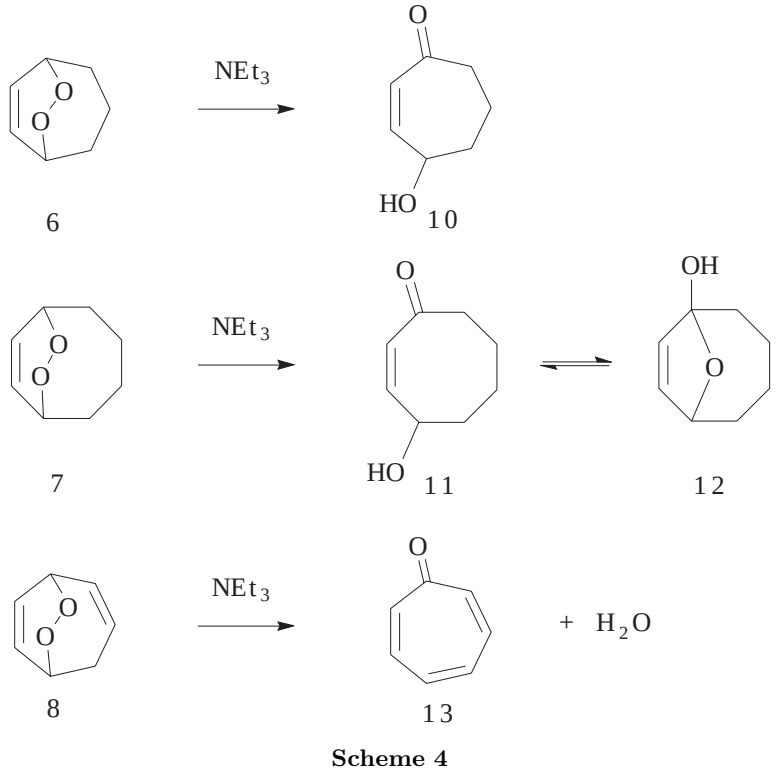
**Table 1.** Kinetic values for the conversion of endoperoxide 5 to 9 in the presence of different bases (0.75 M base in $CDCl_3$, room temperature).

| Base | pKa calculated[a] | pKa values in the literature | k ($min^{-1}$) | Relative k |
|---|---|---|---|---|
| DBU | 12.84 ± 0.20 | 23.9 [b] | $1.0 \times 10^{-1}$ | 1430 |
| $NEt_3$ | 10.62 ±0.25 | 10.77-11.39 [c] | $4.3 \times 10^{-3}$ | 61 |
| $NHEt_2$ | 10.76 ± 0.10 | 10.50-11.12 [c] | $6.0 \times 10^{-4}$ | 9 |
| Morpholine | 8.97 ± 0.20 | 7.96-8.11 [c] | $7.0 \times 10^{-5}$ | 1 |
| Pyridine | 5.32 ± 0.10 | 5.07-5.43 [c] | No Reaction | |

[(a)]The predicted value of the pKa was obtained using the ACD/I-Lab Web service. [(b)] Ref. 11; [(c)] This information was obtained using the ACD/I-Lab Web service.

These results support the classical Kornblum-Delamare reaction mechanism including H-abstraction by base: The greater the base strength, the faster the reaction. Pyridine was the weakest base used. The basicity of pyridine (pKa = 5.07 - 5.43) is probably not enough to abstract the bridge proton to initiate the rearrangement.

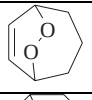
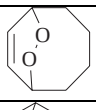
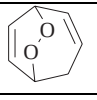
After obtaining valuable information between the basicity of the base and the reaction rate, we decided to measure the rate constants of different endoperoxides **5-8** (Scheme 4). Bicyclic endoperoxides with different briding modes were chosen as model compounds, since we expected that the strain inserted in the molecule should influence the acidity of the bridgehead protons that should be reflected in the reaction rate. The kinetic measurements were performed under the same reaction conditions as reported above. $NEt_3$ was used as a base in all cases. The reaction with DBU was unfortunately too fast to evaluate the kinetic data.




**Scheme 4**

Experimental and relative $k$ values for the decomposition of endoperoxides **5-8** are presented in Table. 2. Typical graphics are shown in Figure 2. Comparison of the measured $k$ values of the conversion **5→9** with that of **6→10** shows that the later reaction is 3.7 times faster than the first one. Actually, it was expected that the decomposition of **5** should be faster. It is well established that the strain in the molecule causes rehybridization at the bridgehead carbon atoms where the *s*-character of the C-H bond is increased. As a consequence of that, the acidity of the bridgehead protons is generally increased. On that basis we expected that **5** would undergo rearrangement faster than **6**. Therefore, we claim that the basicity of the base primarily affects the reaction rates. Furthermore, some steric interactions may play a second role in the rate of the decompositions. In fact, all these measured values for **5-8** do not vary greatly from each other. The ring strain in **8** must be greater than that in **6** and **7.** That **8** has the smallest $k$ value demonstrates again that the acidity of the bridge proton is not as important as thought.

**Table 2**. Kinetic values for decomposition of endoperoxides in 0.75 M $NEt_3$ solution.

| Endoperoxide | $k$(min-1) | Relative $k$ |
|---|---|---|
|  **6** | $1.6 \times 10^{-2}$ | 6.7 |
|  **7** | $4.8 \times 10^{-3}$ | 2 |
|  **5** | $4.3 \times 10^{-3}$ | 1.8 |
|  **8** | $2.4 \times 10^{-3}$ | 1 |

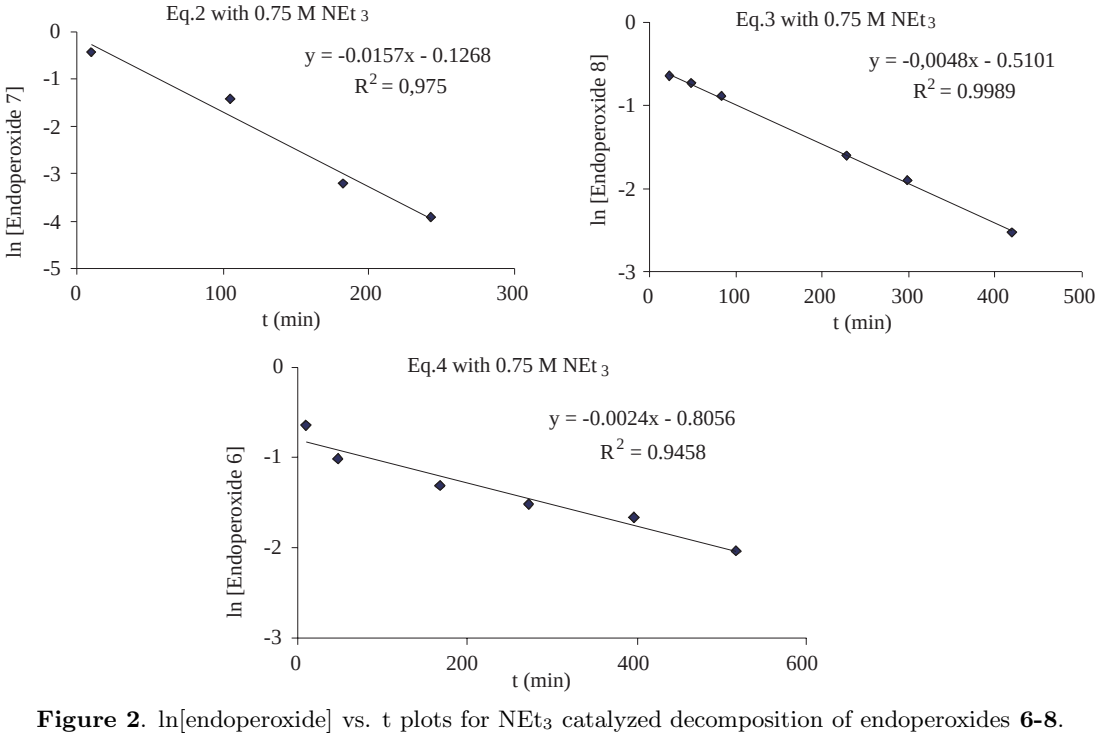



**Figure 2**. ln[endoperoxide] vs. t plots for $NEt_3$ catalyzed decomposition of endoperoxides **6-8**.

In order to gain further information on the Kornblum-Delamare mechanism, we independently investigated the $NEt_3$-catalyzed decomposition of endoperoxide **5** in the presence of 2,4,6-tri-tertbutylphenol, a radical quenching reagent. The determined $k$ value was the same as that found in the absence of 2,4,6-tri-tertbutylphenol. This observation indicates that radical intermediates are not involved during the decomposition of endoperoxides, at least in the cases of the endoperoxides so for examined.

In conclusion, our findings revealed the following important points: (i) Endoperoxides should have $\alpha$-proton(s) to undergo the Kornblum-Delamare reaction. (ii) The reaction rate depends on the strength of the base used as catalyst. The most efficient base is DBU. Morpholine is not suitable because it is a weak base and gives further reaction.

# Materials and Methods

## General procedure for preparation of endoperoxides

To a stirred solution of the corresponding diene in $CCl_4$ was added a small amount of tetraphenylporphyrine (TPP). The resulting mixture was irradiated with a projection lamp (150-watt) while oxygen was being passed through the solution. The mixture was magnetically stirred at room temperature and the reaction was monitored by $^1$H-NMR spectrum. After completion of the reaction the solvent was evaporated at room temperature to give the crude endoperoxide. Chromatography of the crude endoperoxide on a silica gel column eluting with suitable solvent gave pure endoperoxide. $^1$H-NMR spectra of all endoperoxides were identical with those reported in the literature.

**1-Isopropyl-4-methyl-2,3-dioxabicyclo[2.2.2]oct-5-ene**[12] (**3**) was prepared by TPP sensitized photooxygenation of $\alpha$-terpinene. Chromatography eluting with ethyl acetate/hexane (8:92) and evaporation of solvent gave **3** in 70% yield.

**1,4-Diphenyl-2,3-dioxa-bicyclo[2.2.2]oct-5-ene**[13] (**4**) was prepared by TPP sensitized photooxygenation of 1,4-diphenyl-cyclohexa-1,3-diene[14]. Chromatography eluting with chloroform: hexane (40:60) and evaporation of solvent gave **4** (30%).

**2,3-Dioxa-bicyclo[2.2.2]oct-5-ene**[15] (**5**) was prepared by TPP sensitized photooxygenation of cyclohexa-1,3-diene. Chromatography with chloroform/hexane (40:60) and evaporation of solvent gave endoperoxide **5** (57%).

**6,7-Dioxa-bicyclo[3.2.2]non-8-ene**[16] (**6**) was prepared by TPP sensitized photooxygenation of cyclohepta-1,3-diene. Chromatography with ether/hexane (40:60) and evaporation of solvent gave endoperoxide **6** (71%).

**7,8-Dioxa-bicyclo[4.2.2]dec-9-ene**[17] (**7**) was prepared by TPP sensitized photooxygenation of cycloocta-1,3-diene. Chromatography eluting with ether/hexane (40:60) and evaporation of solvent gave endoperoxide **7** (71%).

**6,7-Dioxa-bicyclo[3.2.2]nona-2,8-diene**[18] **(8)** was prepared from photooxygenation of cycloheptatriene following the procedure described by Adam and Balci[3d,18] (26%).

**General procedure for studies of base-catalyzed decomposition kinetics of endoperoxides** 0.5 mL of 1.04 M Endoperoxide (0.52 mmol) in $CDCl_3$ was placed in an NMR tube. To this solution was added 0.3 mL of 2 M base (0.60 mmol) in $CDCl_3$, while stirring with a small magnetic bar. Periodically the

bar was taken out and $^1$H-NMR spectra of the mixture were recorded. The concentration of the starting materials was determined as a function of reaction time. Data were evaluated according to first-order and other simple reaction kinetics methods. It was observed that experimental data were in good agreement with first-order reaction kinetics.

The formed rearranged products (4-hydroxy-cyclohex-2-enone (**9**)[19], 4-hydroxy-cyclohept-2-enone (**10**)[16], 4-hydroxy-cyclooct-2-enone (**11**) $\rightleftarrows$ 9-oxa-bicyclo- [4.2.1]non-7-en-1-ol (**12**)[19] and tropone (**13**)[20]) were characterized by a comparison of their $^1$H-NMR spectra with those reported in the literature.

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