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The mechanism of the tertiary amine catalysed isomerisation of endoperoxides to hydroxyketones: synthesis and chemistry of the intermediate postulated in the peroxide attack mechanism

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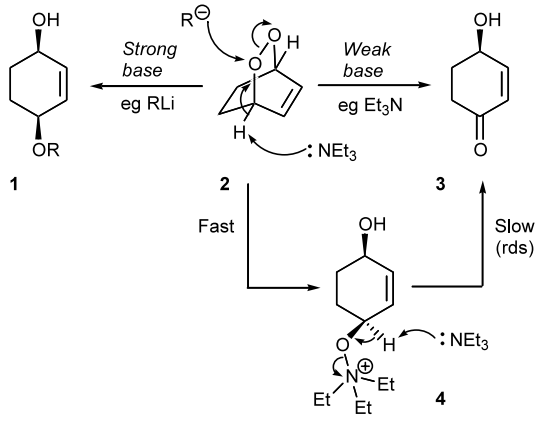
Abstract—Evidence is presented which demonstrates that the Kornblum–DeLaMare rearrangement does not proceed via nucleophilic attack of the peroxide linkage.

Primary and secondary **2** peroxides react with nucleophiles/bases by two main pathways (Scheme 1). Organolithiums and Grignard reagents attack the peroxide linkage directly to give hydroxyethers **1**,[1] whereas weak bases catalyse isomerisation to give hydroxyketones **3**.[2] The latter reaction has enormous, unexploited, potential because catalytic, enantioselective isomerisation of prochiral endoperoxides would give synthetically versatile hydroxyketones (e.g. **3**, Scheme 1) as enantiomerically pure products in just two steps from the requisite 1,3-diene. Although the achiral reaction was first reported by Kornblum and DeLaMare in 1951,[3] it attracted little attention until the discovery, that it was a key step in the biosynthesis of prostaglandins.



Scheme 1.

The mechanism was investigated by Salomon using PGH_2 **5a** and the unsubstituted analogue **5b** (Scheme 2). Reaction with DABCO yielded the ketoaldehydes **6** (77%, levuglandins[4]), plus the β-hydroxyketones **7** and β-elimination products **8** (total 23%). Comparison of the rates of reaction of the analogue **5b** with the bridgehead-d_2 derivative and a d_6-derivative revealed substantial primary and secondary kinetic isotope effects ($k_H/k_D = 3$–4 and 7–8, respectively). Rate limiting cleavage of the bridgehead C–H bond is explicable by a mechanism in which the base (e.g. triethylamine, Scheme 1) abstracts the bridgehead proton with concerted cleavage of the peroxide bond. The ketoaldehydes **6** and the β-hydroxyketones **7** do not interconvert under the reaction conditions, which suggests that peroxide cleavage and retro-aldol cleavage are synchronous.[5] The retro-aldol cleavage is peculiar to 1,3-endoperoxides and β-hydroxyketones are only a small proportion of the products, therefore these results are not necessarily applicable to peroxides in general.

Formation of the hydroxyketone **3** can also be rationalised by an alternative mechanism in which the tertiary amine attacks the peroxide linkage directly and the adduct **4**[6] undergoes slow elimination to give the hydroxyketone **3** in a rate determining step (rds).[7] Such a process would show the requisite kinetic isotope effects and would unify the mechanisms for attack by strong and weak nucleophiles/bases. Further support for this proposal is provided by the chemistry of 1,2-dioxetanes. These react with secondary amines to give

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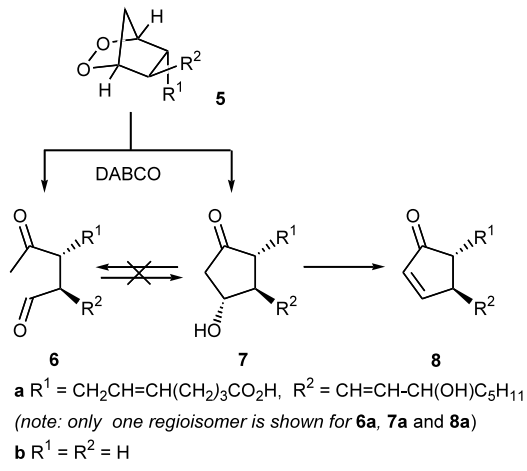
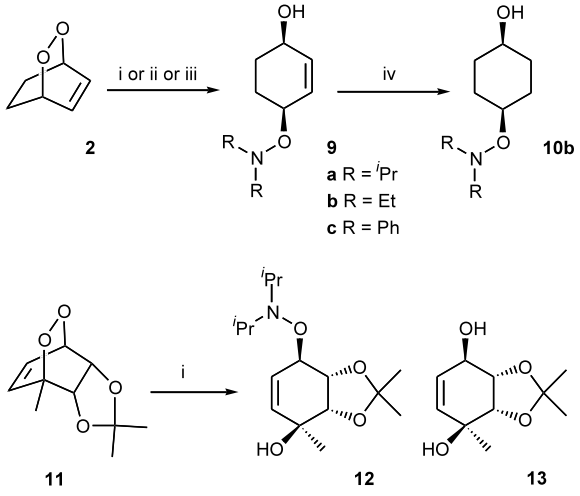


Scheme 2.

O-alkyl-hydroxylamines comparable with the adduct **9**,[8] whereas with tertiary amines, *O*-alkyl-hydroxylammonium salts related to adduct **4** are formed if the intermediate alkoxide is trapped in situ.[9]

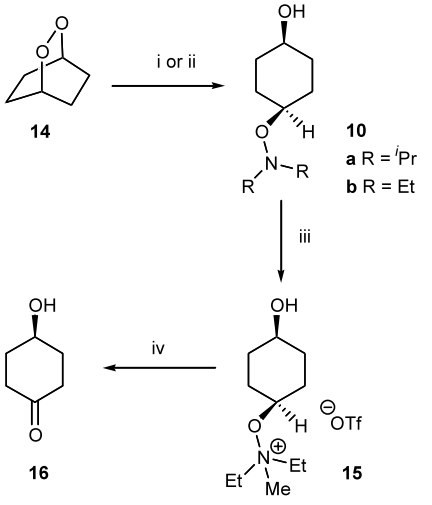
An opportunity to test this pathway was provided during studies of the enantioselective isomerisation of prochiral endoperoxides. As a prelude to the use of chiral amide bases the endoperoxide **2**[10] was treated with LDA (Scheme 3). To our surprise the anticipated hydroxyketone **3** was not formed, but instead the *O*-alkyl-hydroxylamine **9a** was isolated in fair yield. It was apparent that *N*-ethylation of the corresponding diethylamine adduct **9b** would yield an ammonium salt identical to the postulated intermediate **4** (Scheme 1). The generality of lithium amide cleavage was demonstrated with the endoperoxides **2**, **11** and **14**[11] using LDA, lithium diethylamide and lithium diphenylamide. The secondary, tertiary endoperoxide **11** derived from '*cis*-toluene glycol' also yielded a small amount of the diol **13**, which is commonly the outcome in the reaction of di-tertiary peroxides with Grignard reagents and organolithiums.



Scheme 3. *Reagents and conditions*: (i) LDA, Et_2O, −78°C, 5 min, **9a** 45%; **12** 50% and **13** 7%; (ii) Et_2NH, *n*-BuLi, Et_2O, −78°C, **9b** 48%; (iii) *n*-BuLi, Ph_2NH, Et_2O, −78°C, 10 min **9c** 27%; (iv) **9b**, H_2, Pd/C, EtOAc, 7 h, **10b** 83%.

Methylation of the diethylamine adduct **9b** with excess methyl iodide in methylene chloride was unsuccessful and dissuaded us from attempting ethylation.[12] Fearing that methylation under more severe conditions might effect elimination and/or aromatisation,[13] we shifted attention to the saturated analogue **10b**, but this was similarly unreactive (Scheme 4). Intrigued by these results, the pK_a of the aminoether **10b** was determined as an indirect measure of nucleophilicity. Titration of the free base in water:ethanol (50:50, v/v) with aqueous hydrochloric acid at ambient temperature was monitored with a pH electrode and the pH at the half equivalence point was taken as a crude measure of pK_a.[14] Using this methodology the pK_a of the hydrochloride of the aminoether **10b** was estimated to be 3.6, which is in good agreement with the reported value for *O*,*N*,*N*-trimethylhydroxylamine; pK_a 3.65[15] (infinite dilution, H_2O).

Methylation was eventually achieved with methyl trifluoromethanesulfonate and the structure of the crystalline product **15** established by X-ray crystallography. Isomerisations of the endoperoxides **2**, **11** and **14** by triethylamine are normally run in methylene chloride over 8–24 h, however, the low solubility of the salt **15** required that the reaction be run at a lower concentration than normal, which extended the reaction time. Equimolar amounts of the salt **15** and the endoperoxide **14** were individually dissolved in identical concentrations of triethylamine in methylene chloride and left at room temperature over 3 days.[17] Evaporation and ^1H NMR spectrometry in DMSO-d_6 and deuterochloroform, respectively, demonstrated that the salt **15** was unchanged and the endoperoxide **14** was completely



Scheme 4. *Reagents and conditions*: (i) LDA, THF, −78°C, 5 min, **10a** 45%; (ii) Et_2NH, *n*-BuLi, Et_2O, −78°C, **10b** 49%; (iii) CF_3SO_3Me, CH_2Cl_2, 0°C to rt, 1 h; sonocrystallisation,[16] mp 87–88°C, 47%; (iv) DBU, THF, 2 days, 58% *or* KO′Bu, THF, 15 min, 75%.

converted to the hydroxyketone **16**. ^{1}H NMR analysis of the salt reaction in deuterochloroform (in which the salt is almost insoluble) showed a trace of hydroxyketone **16**, which may have been formed during evaporation of the reaction mixture. This was confirmed when the two reactions and a blank were repeated with monitoring by IR. The endoperoxide isomerisation showed a smooth increase in absorption at 1717 cm^{-1} due to the carbonyl group of the hydroxyketone **16**, but there was no change in the salt reaction. Perturbation of the carbonyl absorption by the presence of the salt was excluded by a control experiment, in which an aliquot of the salt reaction was spiked with 10 mol% of the hydroxyketone **16**. This mixture showed the expected carbonyl absorption. Finally, treatment of the salt **15** with stronger bases such as potassium *t*-butoxide or DBU in THF caused conversion to the hydroxyketone within 15 min and 2 days, respectively. These results quite clearly exclude the *O*-alkyl-hydroxylammonium salt **4** as an intermediate in the isomerisation of the endoperoxide **2**. Efforts are continuing to develop catalysts for the enantioselective Kornblum–DeLaMare rearrangement of prochiral endoperoxides.

Note: All new compounds described in this paper were fully characterised by 360 MHz ^{1}H NMR, 90 MHz, ^{13}C NMR, IR, mass spectrometry and combustion analysis or HRMS.

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