Stereoselectivity in the Fe(II)/Cu(II)-mediated Homolytic Decomposition of the *cis*- and *trans*-Isomers of Pinane Hydroperoxide

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The outcome of the $FeSO_4/CuSO_4$-mediated homolytic decomposition of 2,6,6-trimethylbicyclo[3.1.1]heptane-2-hydroperoxide (pinane hydroperoxide, PHP) was found to be markedly dependent on its stereochemical configuration. The *cis*-isomer gave exclusively 1-(2,2-dimethyl-3-vinylcyclobut-1-yl)ethanone via beta-scission of the intermediate alkoxy radical followed by oxidation of the ensuing alkyl radical by $CuSO_4$. In contrast, *trans*-PHP afforded the tricyclic ether 1,4-dimethyl-3-oxatricyclo[5.2.0.$0^{4,9}$]nonane, via intramolecular hydrogen abstraction and $CuSO_4$ oxidation of the resulting alkyl radical, as the major product.

We became interested in the use of PHP on the basis of its commercial availability from the autoxidation of pinane.[1] Catalytic reduction to pinanol and subsequent pyrolysis affords linalool, which has applications in flavours and fragrances and vitamin E synthesis.[1]

Homolytic decomposition of PHP via a one-electron transfer reaction with iron(II)sulfate is described in the literature.[2] The alkoxy radical intermediate undergoes β-scission to form a carbon-centered radical (see Figure 1). The major product is formed by dimerisation of the latter. In the presence of halide or pseudohalide, in contrast, facile ligand transfer oxidation of the intermediate alkyl radical by Fe(III) (pseudo)halide occurs,[3] analogous to that observed with 1-methylcyclohexyl hydroperoxide.[4,5] When the homolytic decomposition of PHP is carried out in the presence of both copper(II) and iron(II) the intermediate alkyl radical undergoes facile oxidation by copper(II)[6] to afford the corresponding alkene **I** (Figure 1).[3]

In our initial studies of this Fe(II)/Cu(II) mediated reaction we used PHP which consisted of 87% *cis*-PHP and 13% *trans*-PHP (*cis*/*trans* with reference to the methyl and the bridging dimethyl).[7] After reaction, the crude mixture consisted of 90% of product **I** and 10% of an unknown impurity. Work-up of this crude mixture, by silica gel column chromatography or distillation, afforded pure **I** but the unknown material was always contaminated with **I** and could not be identified.

In order to determine the structure of the unidentified compound and to discover if the formation of this compound was dependent on the configuration of PHP we prepared samples of pure *cis*- and *trans*-PHP from the crude *cis*/*trans*-PHP mixture, by silica gel chromatography using ethylacetate/hexane as eluent.[8] The major *cis*-PHP could be purified in a single run while the minor *trans*-isomer needed a second run over silica gel. Fe(II)/Cu(II) mediated conversion of the *cis*-PHP gave **I** in quantitive yield (Figure 1).[9] The formation of this product can be rationalized by invoking one electron reduction of the hydroperoxide by Fe(II) giving a PHP-alkoxy radical with concominant formation of Fe(III)OH. The PHP-alkoxy radical undergoes ring opening to afford a keto-functionalized alkyl radical, which is oxidized by Cu(II) to an olefin, with concomitant formation of a proton and copper(I).

Fe(II)/Cu(II) mediated conversion of the *trans*-isomer of PHP gives compound **I** and the second product in a ratio of about 1 : 4.[10] ^{1}H of the latter showed two protons at δ 3.80 and 3.38 ppm, and the presence of only six protons which originate from a methyl. Hence, one of the three methyl groups from *trans*-PHP has been converted to $-OCH_2-$ as represented in structure **II** This was confirmed by ^{13}C NMR which shows two carbons attatched to an ether oxygen, one of them having two hydrogens and one having no hydrogens as was shown by the attatched proton test (APT). The formation of this compound from the intermediate alkoxy radical can easily be rationalized by intramolecular abstraction of a hydrogen atom from one of the bridging methyl groups, which in the *trans*-configuration are favourably positioned, followed by ring-closing Cu(II) oxidation of the resulting alkyl radical (Figure 2). In both the homolytic decomposition of *cis*- and *trans*-PHP some minor impurities were observed, which were assigned as dimerization products. Hydroxy compounds, formed as a result of water attack on alkyl radicals were not observed.

In short, this is a good example of how the stereochemistry of the intermediate alkoxy radical determines the outcome of the metal-mediated homolytic decomposition of an alkyl hydroperoxide.

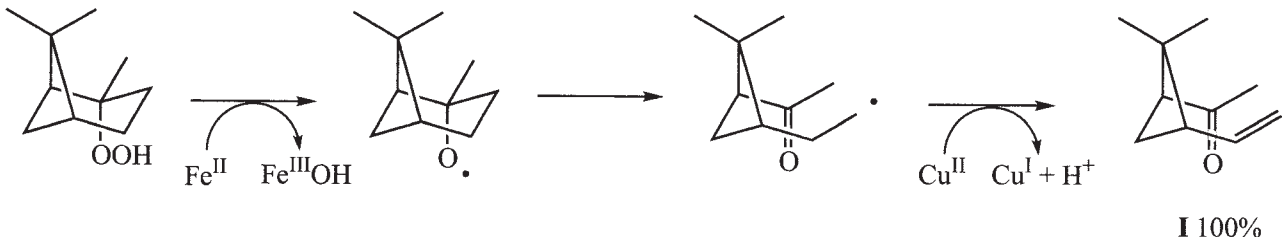

Figure 1.

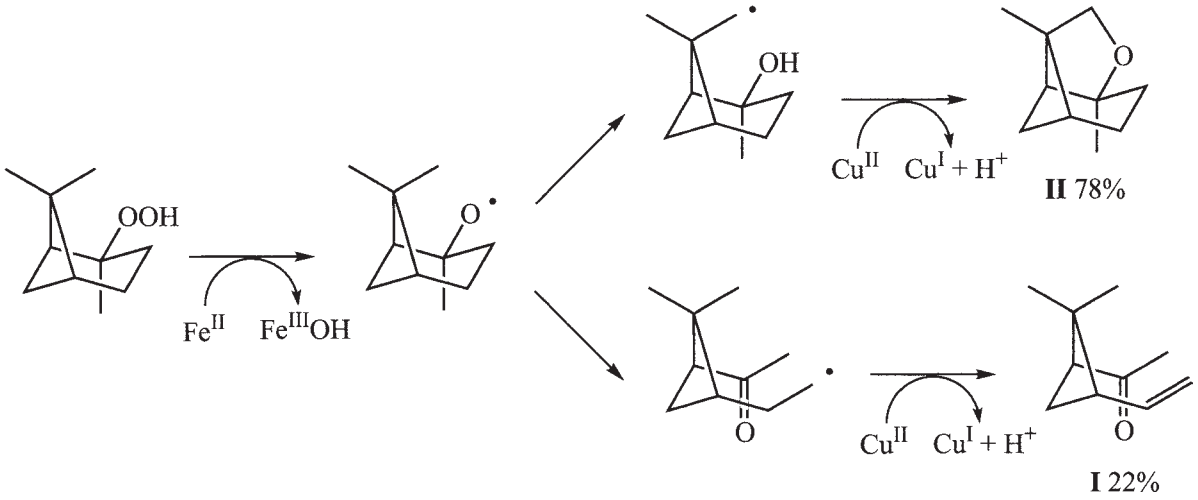

Figure 2.

References and Notes

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8 All chemicals were analytical grade products purchased from commercial suppliers and were used without further purification. PHP was obtained from Quest International (Ashford, the United Kingdom). Gas chromatography analyses were performed using a Varian Star 3600 gas chromatograph with a flame-ionisation detector and a CP Sil 5 CB (50 m × 0.53 mm, df = 2) column. Silica column chromatograpy was performed using Merck silica gel 60 (70 230 mesh). ^{1}H NMR spectra of solutions in $CDCl_3$ were recorded using an INOVA-300 spectrometer at 300 MHz. ^{13}C NMR spectra of solutions in $CDCl_3$ were recorded using an INOVA-300 spectrometer at 75 MHz. The chemical shifts are reported in parts per million (ppm) downfield to tetramethylsilane (TMS). ^{13}C NMR signals were further assigned by using the attached proton test (APT). *cis*-2,6,6-Trimethylbicyclo[3.1.1]heptan-2-hydroperoxide (*cis*-PHP): *cis*-PHP was purified from a mixture of *cis*- and *trans*-PHP in pinane(*cis*-PHP/*trans*-PHP/pinane = 47/7/46 by silica-gel column-chromatograpy (hexane/ethylacetate 90/10, 100 g SiO_2, 15 g PHP. Yield 2.2 g colourless liquid, purity 95.3%. ^{1}H NMR ($CDCl_3$) δ 7.80 (br OOH); 2.20 (m, 2H); 1.90–1.65 (m, 6H); 1.36 (s, 3H); 1.29 (s, 3H) 0.96 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 86.9, 49.1, 40.6, 37.8, 27.8, 27.5, 26.4, 25.4, 24.6, 23.4. GC/MS m/z (%) after reduction with tributylphosphine 154 (14), 139 (34), 136 (23), 109 (80), 84 (100). *trans*-2,6,6-Trimethylbicyclo[3.1.1]heptan-2-hydroperoxide (*trans*-PHP): A fraction of 1.5 g (*trans*-PHP/*cis*-PHP = 75/25) was obtained in the purification of *cis*-PHP. This fraction was further purified by silica-gel column chromatograpy (hexane/ethylacetate = 95/5), 15 g SiO_2. Yield 200 mg colourless liquid, purity 98.1%. ^{1}H NMR δ 7.80 (br, OOH); 2.29 (q, 1H); 2.14 (t, 1H); 1.91 (m, 2H); 1.85–1.65 (m, 4H); 1.31 (s, 3H); 1.21 (s, 3H) 1.04 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 88.2, 48.9, 40.9, 38.2, 27.7, 27.5, 27.1, 25.3, 24.1, 23.0. GC/MS m/z (%) after reduction with tributylphosphine 154 (13), 139 (28), 136 (18), 109 (78), 84 (100).
9 1-(2,2-dimethyl-3-vinylcyclobut-1-yl)ethanone: 1.7 g of *cis*-PHP (10 mmol) was added to a solution of 15 mmol of $CuSO_4$ in 30 ml of water at 0 °C. To this solution was added in one hour 10 mmol of $FeSO_4$ solution in 10 ml of water. When the addition was complete the reaction mixture was allowed to warm to room temperature and extracted with 3 portions of 25 ml CH_2Cl_2 The combined extracts were dried over $MgSO_4$ and solvent was evaporated under vacuo. The residue was purified from some high boiling components by SiO_2-gel column chromatograpy (hexane/ethylacetate = 95/5). Yield 1.2 g colourless liquid, purity 100%. ^{1}H NMR ($CDCl_3$) δ 5.75 (m, 1H); 5.04 (dd, 2H); 2.85 (t, 1H); 2.53 (q, 1H); 2.53 (q, 1H); 2.05 (s, 3H); 1.85 (m ,1H); 1.31 (s, 3H); 0.81 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 207.8, 137.4, 115.8, 54.0, 45.5, 44.9, 30.1, 30.1, 21.9, 18.0. GC/MS m/z (%) 152 (10), 137 (15), 118 (34) 70 (100).
10 1,4-dimethyl-3-oxatricyclo[5.2.0.0^{4,9}]nonane: 200 mg of *trans*-PHP (1.17 mmol) was added to a solution of 2 mmol of $CuSO_4$ in 10 ml of water at 0 °C. To this solution was added in one hour 1.5 mmol of $FeSO_4$ solution in 5 ml of water. When the addition was complete the reaction mixture was allowed to warm to room temperature and extracted with 3 portions of 5 ml CH_2Cl_2 The combined extracts were dried over $MgSO_4$ and solvent was evaporated under vacuo. Yield 154 mg colourless liquid, purity 78%. ^{1}H NMR ($CDCl_3$) δ 3.80 (dd, 1H); 3.38 (dd, 1H), 2.05 (m, 1H); 2.00 (m, 2H); 1.78 (m, 2H); 1.60 (m, 2H); 1.36 (dd, 1H) 1.25 (s, 6H).). ^{13}C NMR ($CDCl_3$) δ 87.7, 72.6, 52.3, 51.9, 41.3, 32.1, 25.6, 22.8, 22.9, 19.7. GC/MS m/z (%) 152 (7) 137 (15), 122 (34), 84 (100).