172. Singlet-Oxygen Ene Reactions of (E)-4-Propyl[1,1,1-²H₃]oct-4-ene

Short Communication

by **Valentin Rautenstrauch***, **Walter Thommen**, and **Karl H. Schulte-Elte**

Firmenich SA, Research Laboratories, CH–1211 Geneva 8
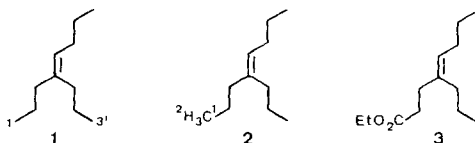
Rose bengal-sensitized photooxygenation of 4-propyl-4-octene (**1**) in MeOH/Me₂CHOH 1:1 (*v/v*) and MeOH/H₂O 95:5 followed by reduction gave (E)-4-propyl-5-octen-4-ol (**4**), its (Z)-isomer **5**, (E)-5-propyl-5-octen-4-ol (**6**), and its (Z)-isomer **7**. Analogously, (E)-4-propyl[1,1,1-²H₃]oct-4-ene (**2**) gave (E)-4-propyl[1,1,1-²H₃]oct-5-en-4-ol (**14**), its (Z)-isomer **15**, (E)-5-[3′,3′,3′-²H₃]propyl-5-octen-4-ol (**16**), its (Z)-isomer **17**, and the corresponding [8,8,8-²H₃]-isomers **18** and **19** (see *Scheme 1*). The proportions of 4–7 were carefully determined by GC between 10% and 85% conversion of **1** and were constant within this range. The labeled substrate **2** was photooxygenated in two high-conversion experiments, and after reduction, the ratios **16/18** and **17/19** were determined by NMR. Isotope effects in **2** were neglected and the proportions of corresponding products from **1** and **2** assumed to be similar (% **4** ≈ % **14**; % **5** ≈ % **15**; % **6** ≈ % (**16 + 18**); % **7** ≈ % (**17 + 19**)). Combination of these proportions with the ratios **16/18** and **17/19** led to an estimate of the proportions of hydroperoxides formed from **2**. Accordingly, singlet oxygen ene additions at the disubstituted side of **2** are preferred (*ca.* 90%). The previously studied trisubstituted olefins **20-25** exhibited the same preference, but had both CH₃ and higher alkyl substituents on the double bond. In these substrates, CH₃ groups *syn* to the lone alkyl or CH₃ group appear to be more reactive than CH₂ groups at that site beyond a statistical bias.

We [1] and *Stephenson et al.* [2] reported in 1978–80 that singlet-oxygen ene additions to trisubstituted olefins occur largely on their more substituted, crowded side. This finding has proved to be a new clue to the mechanism of the ene additions [3].

All acyclic, trisubstituted olefins with different geminal substituents examined so far have both CH₃ and higher alkyl substituents. Their global reactivities, therefore, reflect the statistical bias for reaction at the CH₃ groups and possibly also differences in the intrinsic reactivities of CH₃- and CH₂-bound C–H bonds. The only symmetrically trisubstituted olefins used are ²H-labeled 2-methyl-2-butenes in which the reaction directly involves the labeled sites [2] [4].

We wanted to know the reactivity of at least one olefin with three CH₂ groups on the double bond and investigated such a case in 1979–81 but did not publish the results because of certain experimental shortcomings. In view of the echo [3] of the earlier papers [1] [2], we now report them nevertheless.

Our substrate **2** is a 4-propyl-4-octene (**1**) in which C(1) is labeled with ²H. To obtain **2**, (E)-ester **3** was prepared by an orthoester *Claisen* rearrangement [5] and reduced (see below).
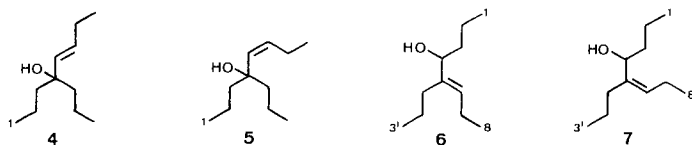
A careful product analysis was carried out with the unlabeled olefin **1**. Standard rose bengal-sensitized photooxygenation at 18–20° and reduction of the resulting hydroperoxides afforded the alcohols **4–7**. The oxygenations were run in two standard media, MeOH/Me$_2$CHOH 1:1 (v/v) and MeOH/H$_2$O 95:5, and, to our surprise, the proportions of the hydroperoxides, measured as the proportions of the corresponding alcohols obtained by reduction, differed distinctly for the two media. The proportions and the estimated analytical errors are listed in *Table 1*. At the time, this finding was unexpected. We tried a number of other media with **1** and another substrate, citronellol [6]. We found similar solvent effects and are now convinced that they are the rule. *Manring* and *Foote* [7] have since reported similar solvent effects and also weak temperature effects with 2-methyl-2-pentene. The variations in the reported product distributions for the 3-methyl-2-pentenes summarized below *(Scheme 2)* are now recognized to be solvent effects. Unfortunately, the effects are too small to be synthetically useful.

Olefin **1** was photooxygenated in 0.25M solution with the rose bengal stabilized by 0.012M NaOAc. Between *ca.* 10% and *ca.* 85% conversion of **1**, samples were withdrawn, treated with Ph$_3$P or Me$_2$S, and analyzed by GC. The proportions of **4–7** were constant within this range of conversion, although traces of diols were seen at conversions > *ca.* 40%. The diols were identified after uptake of > 1 equiv. of O$_2$. There were three pairs of diastereoisomers, **8–13**. The proportions of **4–7** measured on uptake of > 1 equiv. of O$_2$ suggest that the bishydroperoxides corresponding to **8–13** are formed from the hydroperoxides corresponding to both **6** and **7**.
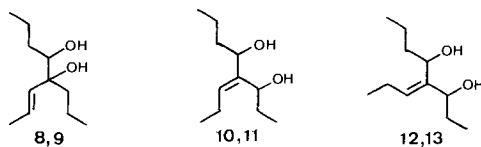

Table 1. *Proportions of Alcohols Obtained from* **1** *and* **2** *by Photooxygenation and Reduction of the Resulting Hydroperoxides*

Alcohol	MeOH/Me$_2$CHOH 1:1			MeOH/H$_2$O 95:5		
	GC[a])	NMR[b])	Combined[c])	GC[a])	NMR[b])	Combined[c])
4 14	63.5 ± 1		63.5 ± 1	58.5 ± 1		58.5 ± 1
5 15	*ca.* 0.5		*ca.* 0.5	*ca.* 0.5		*ca.* 0.5
6 16	20 ± 1	84 ± 10	17 ± 3	24.5 ± 1	84 ± 10	21 ± 3
18		16 ± 10	3 ± 2		16 ± 10	4 ± 3
7 17	16.5 ± 1	60 ± 10	10 ± 2	17 ± 1	53 ± 10	9 ± 2
19		40 ± 10	7 ± 2		47 ± 10	8 ± 2

[a])　Mol fractions of **4–7** from **1**, in %.
[b])　Ratios **16/18** and **17/19** from **2**, in %, from *Table 2*.
[c])　Mol fractions in %.

We have not done a thorough product analysis for **2**, assuming instead that the proportions of corresponding products from **1** and **2** (see below) are virtually the same and thus neglect any secondary isotope effects due to the remote labeled CH_3 group in **2**. Two high-conversion photooxygenations were run with **2**. The proportions found in these fit those for **1** but lie in the conversion range where secondary oxygenations distort the proportions of the monohydroperoxides (see above).

The oxygenations of **2** were run in the same two media and under the same conditions as those of **1**. Reduction of the resulting hydroperoxides gave the alcohols **14–19** *(Scheme 1)*. Pairs **16**, **18**, and **17**, **19** differ only in the location of the label (at C(3′) or C(8), respectively) and each pair was not separated by GC. Each unseparated mixture, **16 + 18** and **17 + 19**, was isolated by GC and the ratios **16/18** and **17/19** were determined by ¹H-NMR spectrometry, by integration of the *triplets* attributed to C(8)H₃ and C(3′)H₃.

Scheme 1. *Singlet-Oxygen Ene Reactions of* **2**.
Proportions (mol fractions in %) of products
(R = H: alcohols **14–19**, R = OH: corresponding
hydroperoxides) in MeOH/Me₂CHOH[a]) 1:1
and MeOH/H₂O[b]) 95:5. The * denotes
the C[²H₃] group.
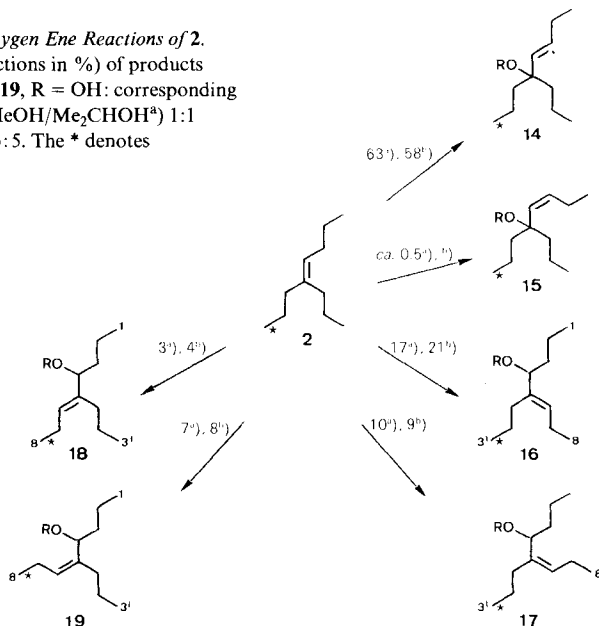
The three CH_3 signals of **6** and **7** and the two CH_3 signals of **16–19** were assigned as follows. Corresponding CH_3 signals in each set **6, 16, 18**, and **7, 17, 19**, have the same chemical shifts. In both sets, the signals of the C(8)H₃-groups, which are separated from the double bond by only one CH_2 unit, are at lowest field and are thus identified by their chemical shift. This was expected and confirmed by decoupling along the chain starting from C(6)H. The C(1)H₃ signals at higher field – the C(1)H₃ and C(3′)H₃ groups are separated from the CHOH unit and the double bond, respectively, by two CH_2 units – can be identified in the mixtures **16 + 18** and **17 + 19**, by means of the label at C(3′) and C(8). In the mixtures **16 + 18**, the common C(1)H₃ integral must be equal to the sum of the C(8)H₃ integral of **16** and the C(3′)H₃ integral of **18** and is thus identified by its size. The smaller signal at lowest field is the C(8)H₃ signal of **16** (see above), and the remaining smaller signal the C(3′)H₃ signal of **18**. The same arguments hold for the other set **7, 17, 19**.

Table 2 lists the measured chemical shifts and integrals. The sum of the three CH_3 integrals is counted as 3.00 for **6** and **7**, and as 2.00 for **16 + 18** and **17 + 19**. For **16 + 18** and **17 + 19**, the C(1)H₃ integral and the sum of the C(8)H₃ and C(3′)H₃ integrals should each be 1.00. The measured values show sizable analytical errors. The ratios of the C(8)H₃ and

Table 2. *Chemical Shifts and Integrals* (in parentheses) *of the CH₃ Signals of* **6, 16 + 18, 7,** *and* **17 + 19**[a])

	C(1)H₃	C(8)H₃	C(3′)H₃	Medium
6	0.926	0.973	0.929	
	(0.95)	(0.94)	(1.11)	
16		0.970	–	
+	0.924			
18	(0.97)	–	0.927	MeOH/Me₂CHOH
			(0.17)	
16		0.972	–	
+	0.925			
18	(1.10)	–	0.929	MeOH/H₂O
			(0.14)	
7	0.934	0.963	0.929	
	(0.98)	(0.98)	(1.04)	
17		0.963	–	
+	0.934			
19	(0.89)	–	0.929	MeOH/Me₂CHOH
			(0.44)	
17		0.965	–	
+	0.936			
19	(0.91)	–	0.932	MeOH/H₂O
			(0.51)	

[a]) Chemical shifts (C²HCl₃ solution) in ppm downfield from TMS as internal standard. *Bruker AM 360* (360.13 MHz), sweep width 400 Hz, 0.024 Hz/point, digital resolution, CD (convolution difference) resolution enhancement (*Bruker* software library DISNMRP (1981)).

C(3′)H₃ integrals for the mixtures are those of the components, thus **16/18** = 0.86:0.17 = 84:16 (MeOH/Me₂CHOH), *etc. Table 1* lists these ratios and the estimated analytical errors.

By assuming that the proportions of corresponding products from **1** and **2** are virtually the same, thus % **4** ≈ % **14**, % **5** ≈ % **15**, % **6** ≈ % (**16 + 18**), % **7** ≈ % (**17 + 19**), and combining these proportions with the ratios **16/18**, **17/19**, we obtain an estimate of the complete proportions of alcohols and hydroperoxides from **2**. These are listed in *Table 1* and shown in *Scheme 1*. The solvent effect is now only seen in the proportions of **14**. Because of the large error of the NMR analysis, the other values for the two solvents are the same within the analytical error.

The singlet-oxygen ene reactions of **2** can now be compared with those of the substrates **20–25** studied earlier [1] [2] [7]. *Scheme 2* summarizes the available data in simplified form. The arrows indicate the sites at which H-atoms are abstracted in the course of the ene additions. The geometries of the resulting hydroperoxides are neglected[1]). The numbers before the parentheses are the measured proportions in % and the numbers in brackets are statistically corrected for the number of H-atoms at that site[2]).

Our previous conclusion was that ene additions at the disubstituted side of the olefin, at sites B and C in general structure **26**, are preferred. *Tanielian* and *Mechin* [8] have formulated this somewhat differently: the reactivities of the three sites in the general structure **26** decrease in the order C > B > A. The reactions of **2** conform to both

---

[1]) The exact proportions of the various geometric isomers from **20** to **25** have not been reported.
[2]) The observed mol fractions were divided by the number of H-atoms/site and the resulting fractions are expressed in %.

Scheme 2. *Reactions of* **2**, **20–25**, *and* **28** *with* $^1O_2$
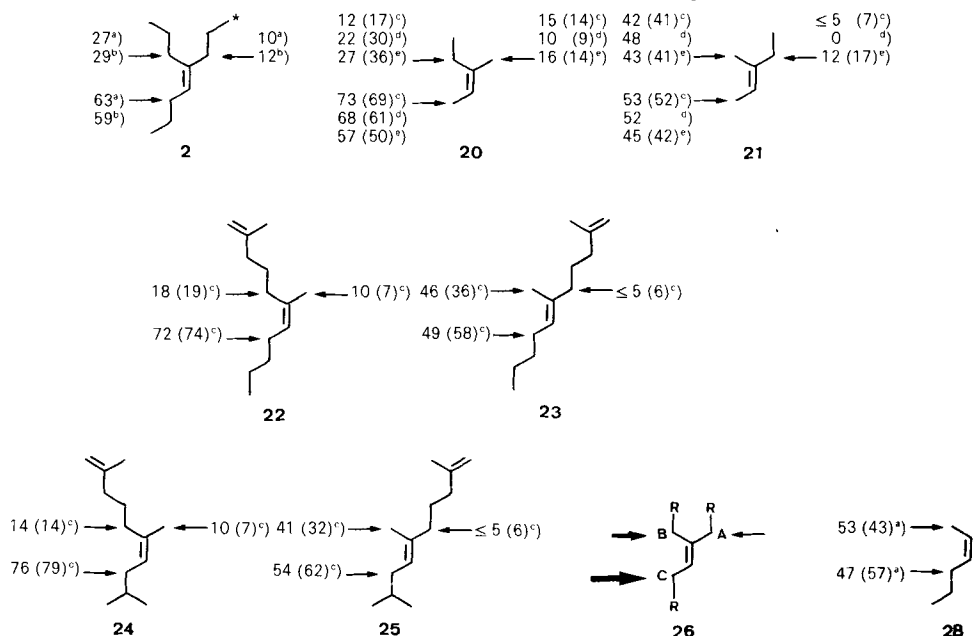
a) In MeOH/Me₂CHOH;   b) In MeOH/H₂O;   c) [1]: in EtOH/Me₂CHOH;   d) [2]: in [²H₆]Me₂CO;   e) [8]: in CHCl₃.

formulations. We note that the proportions for **2** and the statistically corrected proportions for **20–25** are all different but that CH_3 groups at site B (in **21**, **23**, **25**) appear to be significantly more reactive than CH_2 groups at that site (in **20**, **22**, **24**) beyond the statistical bias. We had already noted this in the earlier data but wished to compare them with those for **2**.
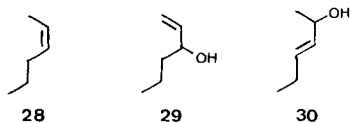
We wondered, whether there is a similar effect in disubstituted olefins, and there appears to be no information on this in the literature. We tried standard rose-bengal-sensitized photooxygenation of (*E*)- and (*Z*)-2-hexene (**27** and **28**, respectively) in MeOH/Me₂CHOH 1:1. There was no discernible uptake of O_2 in the case of **27** (3 h). With **28**, O_2 uptake ceased after *ca.* 25% conversion (1 h) but Ph₃P reduction gave **29** and **30** in a constant 53:47 ratio up to this point. This ratio and the statistically corrected one are included in *Scheme 2*. The CH_3 group in **28** is not more reactive than the CH_2 group.

The synthesis of **2** is outlined in *Scheme 3*. *Wittig* olefination of 2-pentanone gave a 1:1 mixture **31/32** in 28% combined yield. Epoxidation of this mixture with 3-chloroperbenzoic acid followed by chromatography furnished the epoxides **33**, **34** in 46% combined yield. We isolated a 42:58 mixture but did not identify which isomer was which. Treatment of this mixture with Li(i-Pr)₂N (1.7 equiv.)/t-BuOK (1.7 equiv.)/hexamethylphosphoric triamide (0.33 equiv.) [9] in THF (−75°, 48 h) and hydrolysis led to a 83:17 mixture **35/36** in *ca.* 90% combined yield. A geometric isomer of **36** was not detected, but the geometry of **36** not determined. Heating the mixture **35/36** with

Scheme 3. *Synthesis of* 2
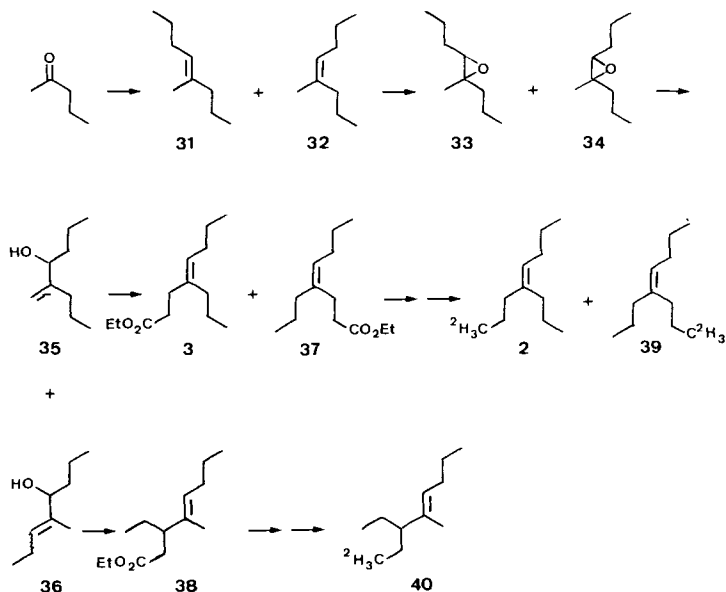
triethyl orthoacetate (4.5 equiv.) [5] and 2-nitrophenol (0.23 equiv.) [10] afforded a mixture of 84% of 3, 4% of its (Z)-isomer 37 (3/37 = 96:4), and 12% of 38, plus ca. 7 unidentified minor components, the combined yield of 3, 37, and 38 being 80% (GC). Purification by chromatography led to a mixture of 91% of 3, 2.5% of 37 (3/37 = 97:3), and 6.5% of 38, in 29% combined yield. Treatment of this mixture with $LiAl^2H_4$ gave the corresponding mixture of alcohols. Tosylation and again $LiAl^2H_4$ treatment (THF, reflux, 20 h) followed by hydrolysis and chromatography furnished a mixture of 91% of 2, 2.5% of its (Z)-isomer 39 (2/39 = 97:3, the ratio determined for the esters 3, 37), and 6% of 40 in 56% combined overall yield for the last three steps. This mixture was used in the photooxygenations. Alcohols derived from 40 were removed in the isolation of 16 + 18, and 17 + 19. Corrections of the proportions of hydroperoxides from 2 for the presence of 3% of 39 are negligible.

REFERENCES

[1] K. H. Schulte-Elte, B. L. Muller, V. Rautenstrauch, *Helv. Chim. Acta* **1978**, *61*, 2777; K. H. Schulte-Elte, B. L. Muller, H. Pamingle, *ibid.* **1979**, *62*, 816; K. H. Schulte-Elte, B. L. Muller, G. Ohloff, *Nouv. J. Chim.* **1978**, *2*, 427; K. H. Schulte Elte, V. Rautenstrauch, *J. Am. Chem. Soc.* **1980**, *102*, 1738.
[2] M. Orfanopoulos, B. Grdina, L. M. Stephenson, *J. Am. Chem. Soc.* **1979**, *101*, 275.
[3] K. N. Houk, J. C. Williams, P. A. Mitchell, K. Yamaguchi, *J. Am. Chem. Soc.* **1981**, *103*, 949; J. R. Hurst, G. B. Schuster, *ibid.* **1982**, *104*, 6854; **1983**, *105*, 4501; A. A. Gorman, I. R. Gould, I. Hamblett, *ibid.* **1982**, *104*, 7098; J. R. Hurst, S. L. Wilson, G. B. Schuster, *Tetrahedron* **1985**, *41*, 2191.
[4] B. Grdina, M. Orfanopoulos, L. M. Stephenson, *J. Am. Chem. Soc.* **1979**, *101*, 3111.
[5] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.* **1970**, *92*, 741.
[6] G. Ohloff, E. Klein, G. O. Schenck, *Angew. Chem.* **1961**, *73*, 578.
[7] L. E. Manring, C. S. Foote, *J. Am. Chem. Soc.* **1983**, *105*, 4710, 7004.
[8] C. Tanielian, R. Mechin, *Tetrahedron* **1985**, *41*, 2139, and ref. therein.
[9] B. Rickborn (Univ. of California, Santa Barbara), personal communication (1979); S. Raucher, G. A. Koolpe, *J. Org. Chem.* **1978**, *43*, 3794; B. Renger, H. Hügel, W. Wykypiel, D. Seebach, *Chem. Ber.* **1978**, *111*, 2630.
[10] V. Rautenstrauch, Ger. Offen. 2,657,903 (07.07.1977) (*CA:* **1977**, *87*, 167605j).