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Selectron Transfer-Initiated Epoxidation and Isomerization Chain Reactions of β-Caryophyllene

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Abstract: The abundant sesquiterpene β -caryophyllene can be epoxidized by molecular oxygen in the absence of any catalyst. In polar aprotic solvents, the reaction proceeds smoothly with epoxide selectivities exceeding 70%. A mechanistic study has been performed and the possible involvement of free radical, spin inversion, and electron transfer mechanisms is evaluated using experimental and computational methods. The experimental data—including a detailed reaction product analysis, studies on reaction parameters, solvent effects, additives and an electrochemical investigation—all support that the spontaneous epoxidation of β -caryophyllene constitutes a rare case of unsensitized electron

Introduction

β-Caryophyllene (bC) is a very abundant naturally occurring sesquiterpene. This semivolatile compound possesses a unique bicyclic structure composed of a fused cyclobutane and *trans*-cyclononene ring. It can be found in the essential oils of herbs and spices such as clove, hop, cannabis, cinnamon, and black pepper. The abundance and specific reactivity of β-caryophyllene make it the largest sesquiterpenoid contributor to formation of secondary organic aerosols.^[1] The use of β-caryophyllene as a natural anti-inflammatory or antibacterial compound is being explored,^[2] and it is currently employed as an aromatizing agent in foods (e.g. chewing gum can contain up to 500 ppm of β-caryophyllene) and cosmetics. On the European market, 30% of the available cosmetics contain β-caryophyllene.^[3] The total annual consumption of β-caryophyllene amounts to up to 5 tons.^[4]

 β -Caryophyllene is not only a valuable natural product in its own right, but it also serves as intermediate for the synthesis

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transfer from an olefin to triplet oxygen under mild conditions (80 °C, 1 bar O₂). As initiation of the oxygenation reaction, the formation of a caryophyllene-derived radical cation via electron transfer is proposed. This radical cation reacts with triplet oxygen to a dioxetane via a chain mechanism with chain lengths exceeding 100 under optimized conditions. The dioxetane then acts as an in situ-formed epoxidizing agent. Under nitrogen atmosphere, the presence of a one-electron acceptor leads to the selective isomerization of β -caryophyllene to isocaryophyllene. Observations indicate that this isomerization reaction is a novel and elegant synthetic pathway to isocaryophyllene.

of oxygenated sesquiterpenoid compounds. Caryophyllene oxide-the corresponding endocyclic epoxide of β -caryophyllene—and other oxygenated derivatives have strong antibacterial and antifungal activities.^[2c,5] The reactivity of β -caryophyllene and the selectivity of chemical transformations of β -caryophyllene are often attributed to the strain of its trans-cyclononene ring.^[6] The chemistry of β -caryophyllene and caryophyllene oxide and especially their rearrangement to other bi- and tricyclic structures in (super)acid medium have been the subject of many studies.^[7] However, little information is available concerning the spontaneous oxidation of $\beta\mbox{-}caryophyllene. A$ common observation is that upon oxidative degradation of β caryophyllene, levels of caryophyllene oxide rise.^[8] In a recent study by Sköld, neat β -caryophyllene was exposed to air at room temperature during several months.^[9] At full conversion of β -caryophyllene, caryophyllene oxide was formed with a selectivity of 40%.

In our attempt to synthesize oxygenated caryophyllene-derived sesquiterpenoids, the spontaneous oxidation of β -caryophyllene in the presence of molecular oxygen as investigated. We found that it is epoxidized under mild conditions in the presence of molecular oxygen in polar aprotic solvents with a selectivity of up to 70% without the addition of any catalyst or co-reactant. According to the widely accepted Twigg epoxidation mechanism, epoxidation of olefins involves stoichiometric coproduction of alkoxy radical-derived products—typically alcohols—resulting in a maximal theoretical epoxide selectivity of 50%.^[10] Furthermore, we found that the reaction of β -caryophyllene in the presence of dioxygen can be steered towards isomerization to isocaryophyllene instead of oxygenation by the addition of certain types of initiators and/or altering the re-

Chem. Eur. J. 2015, 21, 2146-2156

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action conditions. Given the high selectivity of the reaction of β -caryophyllene in the presence of molecular oxygen, we attempted to elucidate the mechanism that lies at the base of these unusual observations. With both experimental and theoretical means, the possible involvement of a free-radical mechanism, a spin-forbidden pathway or an electron transfer mechanism was studied. The results strongly support the formation of the radical cation of β -caryophyllene via an electron transfer from β -caryophyllene to dioxygen as a common initiating step for both its isomerization and epoxidation.

Results

Quantitative analysis of reaction products

The reaction of bC in the presence of molecular oxygen was monitored with GC-FID, GC-MS, and ¹H NMR spectroscopy. The concentration profiles of the reaction products and bC as a function of reaction time (acquired in acetonitrile at 80 °C and 1 bar O_2) are depicted in Figure 1. 1,4-di-*tert*-butylbenzene (DTB) was used as internal standard.

A small amount of 2,6-di-tert-butyl-p-cresol (or butylated hydroxytoluene, BHT) was added to every sample to ensure no further reaction would take place after the sample was taken. Reduction of the samples with an excess of trimethylphosphine prior to GC analysis did not result in the detection of other products (hydroperoxides are smoothly reduced to their respective alcohols upon reaction with trimethylphosphine). As can be seen from Figure 1, a lag time precedes the formation of oxidation products. In Scheme 1, the structures of the detected products are given. Among the reaction products, β -caryophyllene oxide (bCO) was the dominant product, whereas isocaryophyllene oxide (iCO)-the geometrical isomer of bCO-was formed in minor amounts. A constant bCO/iCO ratio of around 10:1 was observed. At prolonged reaction times, caryophyllene-derived diepoxides were formed. In addition to epoxides, minor amounts (< 5%) of isocaryophyllene (iC)-the geometrical isomer of bC itself-and a caryophyllene-derived dicarbonyl product (CDC) were formed.

The epoxide selectivity and mass balance, as determined by GC-FID, of the oxygenation reaction of β -caryophyllene are







Figure 1. Spontaneous oxidation of β-caryophyllene. Concentration profiles of A) β-caryophyllene (bC), β-caryophyllene oxide (bCO) and isocaryophyllene oxide (iCO) and B) caryophyllene-derived dicarbonyl products (CDC), caryophyllene-derived diepoxides (CDE), and isocaryophyllene (iC). Reaction conditions: $[bC]_0 = 0.1 \text{ M}$, [DTB] = 0.01 M, 1 bar O₂, 80 °C, solvent = MeCN.

plotted as a function of the β -caryophyllene conversion in Figure 2. Conversion and epoxide selectivity values were confirmed by quantification with ¹H NMR spectroscopy.

The total epoxide selectivity, which comprises the combined yield of bCO, iCO, and CDE, increases steeply as the conversion increases, whereas, upon approaching full conversion, the selectivity slightly decreases. After the initial stage of the reaction, the epoxide selectivity exceeds 65%, even at full conversion.

A maximum epoxide selectivity of 73% was attained at 27% conversion. The selectivity for iC varies between 1% and 2% during the reaction, leading to an iC yield of 1.5% at full conversion. The mass balance as determined by GC-FID decreased as the reaction proceeded, which we attribute to the formation of nonvolatile products. These nonvolatile products could not be identified with ¹H NMR spectroscopy and are most likely oligomerization products.

The oxygenation of iC was attempted under the same conditions; however, only 7% conversion was achieved after 24 h

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100

80

60

40

20

0

0

20

40

bC Conversion / %



80

100

Figure 2. Total epoxide selectivity (S_{epox}), selectivity for isocaryophyllene (S_{isom}) and mass balance of β -caryophyllene oxygenation as a function of β -caryophyllene conversion. Reaction conditions: [bC]₀=0.1 M, [DTB]=0.01 M, 1 bar O₂, 80 °C, solvent=MeCN.

60

with a selectivity for epoxides of 43%. Two additional control experiments were performed. First, bC was purified and re-isolated by silica column chromatography and subjected to the same reaction conditions; identical observations were made as for the unpurified commercial bC. Second, limonene and valencene—two terpenic components with both an endocyclic trisubstituted C=C and exocyclic C=C bond—were subjected to the reaction conditions but conversion levels remained below 5% for both components after 20 h; no unusually high epoxide selectivities were observed.

Variation of reaction parameters

The influence of the reaction conditions on the rate and selectivity of the oxygenation reaction of bC was evaluated. At a temperature below 70 °C, no conversion could be detected whereas no induction time was observed when the oxygenation was performed at 100 °C. Irradiation of the glass reactor with a 150 W halogen lamp or performing the oxygenation in the absence of light did not result in different reaction rates or selectivities compared to the standard conditions.

The influences of oxygen pressure and concentration of bC on the conversion and selectivity of the reaction are given in Table 1. When the standard reaction conditions were applied (Table 1, entry 1), a conversion level of about 20% was attained after 4.5 h with a corresponding selectivity for epoxides of 70% and a selectivity for iC of 1.5%. No reaction took place if the solution was saturated with N₂ (Table 1, entry 2). If the reaction was performed under air instead of pure dioxygen (Table 1, entry 3), the reaction rate decreased and the selectivity for iC increased to 3.5%. No induction period could be observed when the reaction was performed in a stainless steel autoclave at elevated oxygen pressure (Table 1, entry 4), and only a trace of iC (< 0.5%) was formed. If the initial concentration of bC was lowered (Table 1, entry 5), the reaction proceeded significantly more slowly; the mass balance remained

on reaction rate and selectivity. Entry $[bC]_0 [M] p_{O2} [bar] X^{(a)} [\%] S_{epox}^{(b)} [\%] S_{epox}/S_{isom}^{(c)}$ (t [h])									
1	0.1	1	22 (4.5)	70	52:1				
2	0.1	0 ^[d]	< 0.5 (10)	_	_				
3	0.1	0.2	19 (6.2)	67	20:1				
4	0.1	10	21 (2.0)	71	223:1				
5	0.02	1	19 (14)	76	68:1				
6	0.25	1	20 (2.5)	69	49:1				
Reaction conditions, unless stated otherwise: $[bC]_0 = 0.1 \text{ M}$, $[DTB] = 0.01 \text{ M}$, 1 bar O ₂ , 80 °C, solvent = MeCN. [a] X = conversion; [b] S _{epox} is the total se- lectivity for epoyides including bCO iCO and CDE: [c] S is the selectivity									

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higher than 95%, even at higher conversion levels and an increased epoxide selectivity was observed. If a higher initial concentration of bC was used (Table 1, entry 6), no induction phase was observed, the reaction was complete after 15 h, and a mass balance <75% was obtained.

ty for iC; [d] the solution was saturated with N_2 prior to reaction.

The effect of additives

To gain insight into the mechanism of the oxygenation reaction of bC, the reaction was performed in the presence of different additives (Table 2). First, BHT, 1,2,4-trimethoxybenzene (TMB), and 1,4-diazabicyclooctane (DABCO) were tested. Upon addition of BHT (Table 2, entry 2), the reaction was effectively inhibited and even after 24 h, no product formation was detected. In the presence of TMB (Table 2, entry 3), the lag phase increased significantly but at prolonged reaction time, the reaction proceeded with a rate and selectivity comparable to that of the reference reaction. The additive DABCO (Table 2, entry 4) resulted in an overall slower reaction but no observable lengthening of the induction phase. Next, the effect of a number of commonly used oxidation initiators was tested; 2,2'-azobis(2-methylpropionitrile) (AIBN), N-hydroxyphthalimide (NHPI), ceric ammonium nitrate (CAN), and Co(acac)₃ were selected. When AIBN was added to the reaction mixture (Table 2, entry 5), no induction phase could be observed and the reaction proceeded significantly faster albeit with comparable selectivity compared to the reference reaction. A remarkable feature of the reaction is that iC was the main product when NHPI or CAN were used as additives in MeCN (Table 2, entries 6 and 8-10).

The reaction with CAN was very fast but was unselective, as evidenced by the low mass balance value. Performing the reaction with CAN under N₂ atmosphere, however, resulted in a very selective reaction towards iC with a mass balance exceeding 95%, even at high conversion levels, with 95% iC yield. Irrespective of the composition of the atmosphere, the yellow-orange-colored CAN solution became colorless over the course of 5 min, indicating the rapid consumption of the cerium salt.

When NHPI was used under an N_2 atmosphere, no products were formed. Strikingly, when NHPI was added in DMAc

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Table 2. Effect of additives on the conversion, selectivity and mass balance of the reaction of β -caryophyllene with molecular oxygen.

Entry	Additive (concentration [mol %])	<i>t</i> [h]	X [%]	S _{epox} [%]	S _{isom} [%]	Mass balance [%]			
1 ^[a]	none	3	13	68	1	97			
		10	67	70	1	84			
2	BHT (2)	3	< 0.5	—	—	>99			
		10	< 0.5		—	>99			
3	TMB (20)	3	1	60	1	98			
		10	18	73	1	91			
4	DABCO (20)	3	< 0.5	—	—	>99			
		10	5	71	1	98			
5	AIBN (2)	1	44	72	< 0.5	89			
		3	78	71	< 0.5	84			
6	NHPI (10)	1	19	12	78	>99			
		3	98	15	64	81			
7 ^[b]	NHPI (10)	1	2	72	5	>99			
		3	26	78	6	>99			
8	CAN (10)	1	56	29	34	69			
		3	87	28	32	65			
9 ^[c]	CAN (10)	1	63	< 0.5	96	>99			
		3	>99	< 0.5	95	98			
10 ^[c]	CAN (0.5)	3	25	< 0.5	91	98			
		10	71	< 0.5	96	98			
11	Co(acac) ₃ (2)	3	2	19	2	98			
		10	3	27	< 0.5	98			
12	$Bu_4N(PF_6)$ (10)	1	27	70	2	93			
		3	61	66	1	81			
13 ^[d]	DCA (0.1)	3	8	35	< 0.5	95			
		6	50	49	< 0.5	79			
14 ^[d]	Rose Bengal (0.5)	1	60	$< 0.5^{[e]}$	$< 0.5^{[e]}$	>99			
		3	>99	$< 0.5^{[e]}$	$< 0.5^{[e]}$	>99			
15	KO ₂ (20)	3	< 0.5	_	_	>99			
	18-crown-6 (20)	10	< 0.5	_	_	>99			
Deactiv	Prostion conditions unless otherwise stated, [b(] = 0.1 ·· [DTP] 0.01 ··								

Reaction conditions, unless otherwise stated: $[bC]_0 = 0.1 \text{ M}$, [DTB] = 0.01 M, 1 bar O₂, 80 °C, solvent = MeCN; amounts of additives are given relative to the concentration of β -caryophyllene). [a] Reference; [b] Solvent = DMAc; [c] 1 bar N₂; [d] RT, $h\nu$; [e] allylic hydroperoxides—typical singlet oxygenation products—were formed.

(Table 2, entry 7; see also next section), epoxidation became the main reaction pathway again. The use of $Co(acac)_3$ (Table 2, entry 11) resulted in the inhibition of the oxygenation reaction. A very short induction phase (<5 min) and a significant rate enhancement were observed if the ammonium salt Bu₄NPF₆ (Table 2, entry 12) was used as additive. The selectivity of the reaction remained however unaffected. The photo-oxygenation of bC in the presence of 9,10-dicyanoanthracene (DCA; Table 2, entry 13) yielded epoxides as the main oxidation products. Photo-oxygenation in the presence of methylene blue (Table 2, entry 14) yielded allylic hydroperoxides, as reported in the literature,^[11] and no bCO or iC were detected. Finally, the effect of the superoxide anion on the reaction was tested by addition of a premixed solution containing KO₂ and a crown ether to the reaction mixture (Table 2, entry 15). The reaction was completely inhibited in the presence of superoxide anion; moreover, when KO₂ was added to an ongoing reaction (Table 2, entry 8 after 1 h) the reaction was effectively stopped and no further products were formed.

Solvent effects

The oxygenation of bC was performed in different solvents in order to gain further insight into the nature of the reaction (Table 3). Three classes of solvents were tested: Heptane, tolu-

Table 3. Solvent effects on the oxygenation of $\beta\text{-caryophyllene}.$								
Entry	Solvent (type)	X _(t=5h) [%]	S _{epox} [%]	$S_{\rm epo}/S_{\rm isom}$				
	Apolar							
1	Heptane	< 0.5	—	_				
2	Toluene	< 0.5	—	_				
3	Iodobenzene	< 0.5	—	—				
	Protic Polar							
4	Water	< 0.5	_					
5	MeOH	< 0.5	—					
6	PrOH	< 0.5	—					
7	NMAc	< 0.5	_	—				
	Aprotic Polar							
8	MeCN	27	72	52:1				
9	EtOAc	21	43	49:1				
10	DMF	< 0.5	—	_				
11	DMAc	30	81	> 500:1				
12	NMP	83	75	> 500:1				
Reaction c	onditions: $[bC]_0 = 0$.	1 м, [DTB]=0.01	м, 1 bar O ₂ , 80°	°C.				

ene, and iodobenzene as apolar solvents; water, methanol (MeOH), propanol (PrOH), and *N*-methylacetamide (NMAc) as protic polar solvents; and acetonitrile (MeCN), ethyl acetate (EtOAc), *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacet-amide (DMAc), and *N*-methylmorpholine (NMP) as aprotic polar solvents.

For none of the tested apolar (Table 3, entries 1-2), halogenated apolar (entry 3), or protic polar solvents (entries 4-7), could product formation be observed after 5 h. Even after 24 h, the conversion level did not exceed 5 % in these solvents. Performing the reaction in aprotic polar solvents did result in an active system (Table 3, entries 8, 9, 11, and 12). Interestingly, using an 80:20 MeCN/H₂O mixture instead of neat MeCN as the reaction medium rendered the system inert. The reaction proceeded more slowly in EtOAc than in MeCN and resulted in lower selectivities for both epoxides and iC after 5 h (Table 3, entry 9). The iC and epoxide selectivity in EtOAc did increase up to 1% and 70%, respectively, when the conversion exceeded 50%. Neither with MeCN nor EtOAc could solvent-degradation products be detected over the course of the reaction. Among the tested amide solvents, no reaction took place in DMF (Table 3, entry 10), whereas in both DMAc and NMP the spontaneous epoxidation of bC proceeded smoothly and selectively (Table 3, entries 11 and 12). With epoxide selectivities of 81% and 75% after 5 h in DMAc and NMP respectively, the reaction in these amide solvents was significantly more selective than that in the non-amide polar aprotic solvents. Furthermore, only traces of iC (< 0.05%) could be detected in these solvents and when the additive NHPI was used in DMAc (Table 2, entry 7), only minor amounts of iC were formed. In

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DMAc and NMP, solvent degradation did occur. NMAc was the main degradation product formed from DMAc, whereas 1-methyl-2,5-pyrrolidinedione and 2-pyrrolidinone were formed if NMP was used as the solvent.

Discussion

Free-radical autoxidation

The epoxidation of bC is inhibited by radical inhibitors such as BHT and is accelerated in the presence of the typical radical initiator AIBN. This clearly indicates the involvement of radical species in the formation of bCO. The plausibility of a "classic" autoxidation mechanism was therefore verified. Autoxidation of olefins is performed in most cases at elevated temperatures and oxygen pressures and the use of transition metals as catalysts is common practice.^[12] Olefin autoxidation proceeds via a free-radical mechanism (Scheme 2). During initiation, precur-

Initiation

(1)	ROOH				→	RO	+	•он	
Propag	ation								
(2)	RO	+	RH		→	ROH	+	R	
(3)	ОН●	+	RH		►	H ₂ O	+	R	
(4)	R	+	O ₂		→	RO0 [•]			
(5)	ROO	+	RH		→	ROOH	+	R	
(6)	ROO	+	R ₁ -C=C-	R ₂		R ₁ -	-C(C	OR)-C-R2	
(7)	R ₁ -C(O	OR)-C-R ₂			R ₁ -	с -с́-) C-R ₂ +	RO
Termin	ation								
(8)	RO0 [•]	+	RO0 [•]		►	NRP	+	O ₂	
(9)	ROO	+	₽		►	ROOR			

Scheme 2. Free-radical autoxidation mechanisms.

sors of free radicals are formed and little or no substrate is converted [Scheme 2, reaction (1)], which typically leads to an induction phase. In the propagation, chain-carrying peroxy radicals are formed [Scheme 2, reactions (1)–(5)]. These peroxy radicals react either via H-atom abstraction [Scheme 2, reaction (5)], or alternatively they react via addition to the C=C

double bond [Scheme 2, reaction (6)]. H-atom abstraction by peroxy radicals at the weaker allylic C–H bond leads to the formation of allylic hydroperoxides. These species can decompose homolytically at the elevated reaction temperature, resulting in the formation of more radicals. This subsequently causes an exponential increase of the reac-

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Scheme 3. Proposed free-radical epoxidation mechanism.

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tion rate and a lower selectivity for the primary hydroperoxide oxidation products. Secondary products associated with this abstraction pathway are alcohols and ketones. Addition of a peroxy radical to an olefin results in a radical peroxo adduct. This adduct reacts further via the so-called Twigg mechanism by homolytic cleavage of the peroxo bond into an epoxide and an alkoxy radical [Scheme 2, reaction (7)].^[10] Formation of epoxides via known autoxidation mechanisms therefore cannot occur with a selectivity that is higher than 50%. The residual alkoxy radical can re-enter the propagation chain via reaction (2). Recombination of two radical species results in the formation of non-radical products (NRP) which effectively terminates the chain propagation [Scheme 2, reactions (8) and (9)].

The abstraction-to-addition ratio has been found to be very structure dependent. Cyclohexene is a well-known example of an olefin which reacts primarily via abstraction, whereas addition is the main pathway for the autoxidation of cyclooctene.^[13] In the present case of spontaneous bC oxidation, no allylic functionalized reaction products were detected and sample reduction with trimethylphosphine prior to GC analysis did not result in a different product composition. These findings indicate that H-atom abstraction is not a major pathway and that hydroperoxides are not formed in our system. However, even if bC would react exclusively via the addition pathway, the observed epoxide selectivity in our system still cannot be rationalized by the reactions depicted in Scheme 2.

We subsequently considered the possibility of an alternative epoxidation pathway. To achieve an epoxide selectivity above 50%, this new route would have to avoid co-formation of other products. Therefore an epoxidation mechanism was suggested in which the peroxy radical carries a catalytic role (Scheme 3). Initially, a peroxy radical adds to the C=C double bond, forming the radical peroxo adduct [Scheme 2, reaction (6)]. Dioxygen may add to this peroxo adduct, forming a peroxoperoxy radical [Scheme 3, reaction (10)], which may in turn convert bC into bCO according to the known Twigg mechanism, yielding a residual oxoperoxy radical [Scheme 3, reactions (11) and (12)]. This oxoperoxy radical could then decompose into bCO upon the release of the original peroxy fragment [Scheme 3, reaction (13)]. There are, however, two difficulties with this mechanism. First of all, it is known for monoterpenes that reaction (10) is only able to kinetically compete with reaction (7) at higher O_2 pressures. Although it is possible that the size and configuration of the trans-cyclononene ring of bC stabilize the radical peroxo adduct, making re-

(6)	$ROO^{\bullet} + R_1 - C = C - R_2$		\rightarrow	R ₁ -C(OOR)-C-R ₂	
(10)	R ₁ -C(OOR)-C-R ₂	+ O ₂		R ₁ -C(OOR)-COO-R ₂	
(11)	R ₁ -C(OOR)-COO-R ₂	+ R ₁ '-C=C-R ₂ '		R ₁ -C(OOR)-COO(C(R ₁ ')	-(C-R ₂ '))-R ₂
(12)	R ₁ -C(OOR)-C(OOC(R ₁ ')(C-R ₂ '))-R ₂		R ₁ -C(OOR)-C(0)-R ₂ +	0 R ₁ '-C-C-R ₂ '
(13)	R ₁ -C(OOR)-C(0)-R ₂			$R_1 = C = C = R_2 + C_2$	ROO



action (10) more favorable,^[14] there is still the difficult subsequent unimolecular step leading to bCO. We therefore computationally characterized the release of the peroxy fragment and subsequent formation of bCO from the peroxo adduct [Scheme 3, reaction (13)]. Unfortunately DFT predicts an activation energy larger than 25 kcal mol⁻¹, in line with the formation of the strained oxirane ring. This implies that this reaction cannot kinetically compete with the bimolecular H-atom abstraction by the oxoperoxy radical, featuring an estimated barrier of only 5–10 kcal mol⁻¹. This analysis evidences that epoxide formation via the steps in Scheme 3 is unlikely. No other free-radical mechanisms were identified that could account for the high epoxide selectivity in the reaction of bC with dioxygen. Other mechanistic possibilities were therefore explored.

Spin inversion mechanism

The direct addition of triplet dioxygen to organic substrates in their singlet ground state, for example, via C–H insertion or [2+2] cycloaddition, is spin-forbidden. Examples of olefins that are oxygenated by direct reaction with molecular triplet oxygen are however known in the literature,^[15] but, to our knowledge, there is no example of a nonconjugated trisubstituted olefin that displays this remarkable reactivity. Direct reaction of olefins with triplet oxygen is initiated by the formation of a charge-transfer complex. Two hypothetical mechanisms have been proposed for the formation of a ground-state oxygenated product starting from this charge-transfer complex (Scheme 4; adapted from ref. [16]). The first is the recombina-



Scheme 4. Direct reaction of an olefin A with triplet dioxygen.

tion of dioxygen with the olefin resulting in the formation of a triplet diradicaloid species (³D). This diradicaloid species may then undergo intersystem crossing (ISC) through spin inversion, yielding the ground-state oxygenation product. The second hypothesis proposes that spin inversion precedes the collapse of the charge-transfer complex with consequent formation of singlet oxygen. Both members of the charge-transfer complex are now in a singlet state and may react to form the oxygenation product, typically via a zwitterionic singlet intermediate (¹Z).

Although the reaction of bC with dioxygen is inhibited by DABCO—a potent quencher of singlet oxygen—most of the experimental data do not support a spin inversion mechanism. In the presence of singlet oxygen, no epoxides were formed.

The observed solvent effects do not correspond with the formation of either a diradicaloid species or a zwitterionic intermediate. The inhibition of the reaction in polar protic solvents like MeOH and PrOH seems to exclude a zwitterionic intermediate, whereas the rate-accelerating effect of polar aprotic solvents like MeCN and DMAc is not in line with the formation of a neutral diradicaloid species. Iodine-containing solvents can be used to detect the involvement of a spin inversion step by their accelerating effect on the reaction due to the heavy atom effect.^[15c, 17] When iodobenzene was used as solvent however, no reaction took place. Spin inversion usually requires input of thermal energy or photons. Irradiating the transparent reaction vessel with visible or UV light did not, however, have an effect on the reaction.

Electron transfer

Electron transfer (ET) may occur between an organic compound and a suitable electron acceptor interacting with each other in a charge-transfer complex.^[18] Reported reduction potential values for dioxygen to the superoxide anion in aprotic solvents range from -0.50 V to -0.65 V vs. standard hydrogen electrode (SHE), making it a mediocre electron acceptor.^[19] Electron transfer to triplet oxygen is feasible for electron-rich compounds with sufficiently low ionization potentials. The electron transfer results in the formation of the radical cation– superoxide anion pair. Possible reactions following the actual electron transfer are summarized in Scheme 5. The ion radical



Scheme 5. Olefin (A) oxygenation via electron-transfer to triplet dioxygen.

pair may recombine into a zwitterionic singlet $({}^{1}Z)$ or diradicaloid singlet $({}^{1}D)$ intermediate, resulting in the oxygenation of the organic substrate via a non-chain mechanism. If the organic radical cation is sufficiently stable, it may diffuse out of the solvent cage and initiate a chain reaction.

The endoperoxidation of ergosteryl acetate—a polycyclic conjugated diene—and the conversion of adamantylideneadamantane to its dioxetane are well-known examples of oxygenations of olefins operating via $\text{ET.}^{[20]}$ In both cases, the addition of a potent electron acceptor (EA), such as tris(4-bromophenyl)aminium hexachloroantimonate, is required to initiate the reaction. There are accounts of olefin oxygenation in the literature in which ET to triplet oxygen itself is the initiating step; in this case, ${}^{3}O_{2}$ is the EA. For instance, Correa et al. reported that the uncatalyzed oxidation of *trans*-stilbene and *trans*- β -methoxystyrene at a temperature in the range of 100–125 °C and



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an O₂ pressure higher than 25 bar yields oxidative C=C cleavage products due to dioxetane decomposition and minor amounts of epoxides.^[21] The autoxidation is initiated by electron transfer to dioxygen and a strong correlation was found between the one-electron oxidation potential of the olefin and the observed oxidation rate. The oxygenation of conjugated dienes, adamantylidene derivatives and common olefins under harsh reaction conditions occurs via a common chain mechanism.^[19] The formed radical cation reacts with triplet oxygen, giving the peroxy radical cation. This peroxy radical cation then abstracts an electron from an unreacted olefin, forming the oxygenated product—either a dioxetane or an endoperoxide—and regenerating the radical cation. These reaction steps are given for bC in Scheme 6.

To our knowledge, only one account of selective epoxidation via electron transfer to dioxygen is known. The spontaneous epoxidation of a tetrasubstituted norbornylene derivative was reported by Bartlett and Banavali.^[22] This strained olefin was epoxidized in 70% yield at room temperature and ambient pressure of O₂. The only reported side product was a diketone product. Electron transfer to dioxygen was suggested as initiating step; however, no chain mechanism seemed to operate. Lastly, we would like to mention the selective epoxidation of 2,3-dimethyl-2-butene at 5 bar O₂ and 100 °C, which was reported in the patent literature.^[23] Even at 80% conversion, the selectivity for tetramethyloxirane exceeded 70%, with coproduction of minor amounts of an allylic alcohol. Unfortunately, no further mechanistic information is available.

In the present case of spontaneous epoxidation of bC, the experimental data indeed seem to support an electron transfer mechanism. TMB is an efficient one-electron donor and its addition to the reaction mixture results in a significantly longer induction phase. BHT and other para-activated phenols efficiently quench free radicals via H-atom transfer and they can consequently guench radical cations by proton-coupled electron transfer.^[24] DABCO has been suggested to act as an electron shuttle between the radical cation and the superoxide anion, restoring the reactants to their neutral state and dissipating the energy as heat.^[25] The addition of CAN - a one-electron acceptor - causes a clear rate-enhancing effect. Furthermore, the observed discoloration of the bright orange CAN is indicative for the one-electron reduction of Ce^{IV} to Ce^{III}. Other additives known in the literature to act as initiators for electron transfer chain reactions such as Co^{III}-based salts and tris(4-bromophenyl)aminium hexachloroantimonate were tested as well, but with little success.^[20b] Co(OAc)₃ was found to be insoluble under the conditions reported in Table 2 (not shown). The inhibitory effect of Co(acac)₃ may be explained by its reduction to Co^{II} and the consequent guenching of peroxo radicals by Haber-Weiss type chemistry. The addition of tris(4-bromophenyl)aminium hexachloroantimonate to the reaction mixture resulted in the formation of a mixture of bC-derived skeletal isomerization and oxidation products, but no epoxides were detected. Formation of epoxides during the DCA-sensitized photo-oxygenation of bC is further evidence for the involvement an electron transfer step. It is well known that DCA acts as a one-electron acceptor in type I photosensitized oxygenations of dienes and diarylcyclopropanes.^[19] The formation of charged species is energetically unfavorable in an apolar medium, explaining the inhibitory effect of the solvents heptane and toluene and rationalizing the accelerating effect of salts. The oxidation reaction only occurs in aprotic polar solvents such as MeCN. The beneficial effect of these solvents is twofold. First, according to the Marcus theory,^[26] the activation energy of electron transfer is lowered in solvents with high polarizability and second, it is well known that these solvents facilitate the dissociation of the radical cation-superoxide anion pair and thus shift the electron transfer equilibrium to the right.^[18] There is no straightforward rationalization for the inhibition of the reaction in DMF, but a strong rate-retarding effect of DMF was also observed in the work of Bartlett on the spontaneous epoxidation of a norbornylene derivative.^[22] Diffusion of the radical cation out of the solvent cage leads to a chain mechanism, which is consistent with the conversion profile as a function of the reaction time, with a clear induction phase. The induction phase was shortened significantly if the bC concentration or the dioxygen pressure were increased. The fact that no reaction took place if the reaction vessel was purged with N₂ is strong evidence for dioxygen acting as the EA.

The susceptibility of bC to electron transfer was evaluated by performing an electrochemical study. The cyclic voltammograms of bC and iC in MeCN at 30 °C and ambient atmosphere are compared in Figure 3. The one-electron oxidation of bC appeared to be irreversible in all of the conditions tested. The maximum current for bC was at 1.3 V vs. Ag/Ag¹. For reference, *trans*-stilbene, which readily undergoes one-electron oxidation, has a one-electron oxidation potential of 1.6 V vs. Ag/Ag¹.^[21] The low oxidation potential of bC is reflected in the relatively mild reaction conditions required for the spontaneous oxygenation of bC when compared to those used in the oxidation of the substrates in the work of Correa.^[21] Furthermore, the oxidation peak of iC appeared at a potential about 0.2 V higher



Figure 3. CV curves for β -caryophyllene (bC) and Isocaryophyllene (iC). Experimental conditions: Substrate (5 mM), Bu₄NPF₆ (0.1 M), solvent = MeCN, 30 °C, ambient atmosphere, scan rate = 50 mV s⁻¹, Pt working and counter electrode.

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than for bC. We suggest therefore that the lower oxidation rate of iC in the same experimental conditions can be attributed to its higher oxidation potential.

The synthesis of the observed reaction products under the standard reaction conditions was attempted electrochemically in potentiostatic mode (Table 4). A potential interval of 1.7 V

Table 4.Electrochemical conversion of β -caryophyllene.									
Entry	E vs. Ag/Ag ^ı [V]	<i>t</i> [h]	Atmosphere	X [%]	S _{epox} [%]	S _{isom} [%]			
1 2	1.7 1.7	1.5 0.5	1 bar O_2 1 bar N_2	>99 13	15 < 0.5	< 0.5 97			
Reaction conditions: $[bC]_0 = 5 \text{ mm}$, $Bu_4 \text{NPF}_6$ (0.1 m), solvent = MeCN, 80 °C, 0.5 h, Pt working and counter electrode.									

was applied to a solution of bC in MeCN at 80 °C. If the solution was saturated with dioxygen, full conversion was attained after 1.5 h, with bCO and CDC as the main products detected by GC-MS. However, the mass balance did not exceed 20%. When the potentiostatic experiment was performed under N₂ atmosphere, 13% of bC was converted selectively to iC with a complete mass balance; no other products were detected. The combined information extracted from the effects of additives, the solvent effects, the variation of reaction conditions and the electrochemical study provides compelling evidence for an electron transfer from bC to dioxygen as initiating step and the subsequent formation of bCO via a chain mechanism.

For the formation of bCO, we propose a two-step mechanism in which initially, a bC-derived dioxetane (CDO or iCDO) is formed (Scheme 6). The radical cation of bC (bC⁺⁻) reacts with dioxygen to form a peroxy radical cation. This peroxy radical cation then may abstract an electron from bC, resulting in cyclization to CDO and regeneration of bC⁺⁻.

The oxygenation of bC is inhibited by addition of KO_2 . We attribute this to quenching of bC^{+} with superoxide, effectively terminating the propagation chain (Scheme 5). This supports



Scheme 6. Isomerization and oxygenation of the β -caryophyllene-derived radical cation.

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our hypothesis on the formation of bCO via a chain mechanism and not via the direct recombination of the radical cation of bC with superoxide anion. Attempts to perform the oxygenation in protic solvents all failed and even when 10 vol% of water was added to MeCN, no oxidation products were detected. Nucleophilic attack of these protic solvents is suspected to quench the chain-carrying radical cation and results in termination of the propagation chain. The dioxetane product CDO was not detected directly by GC-MS but its thermal decomposition product CDC was. It is indeed very likely that CDO decomposes in the injection port to form CDC. With ¹H NMR spectroscopy, a small signal with a shift of 4.5 ppm was observed, but the low concentration of suspected CDO allows only a tentative identification.

Isomerization of bC⁺⁺ leads to the less strained *cis*-cyclononene configuration. Addition of dioxygen to this stabilized radical cation results in the formation of iCDO whereas transfer of an electron from bC gives iC and a new molecule of bC⁺⁺ (Scheme 6). Isomerization of bC to iC becomes the dominant pathway if CAN is added to the reaction mixture under N₂ atmosphere. In fact, the isomerization of bC in the presence of CAN under N₂ atmosphere constitutes an elegant and highyielding synthesis route to iC (see Table 2, entry 9) when compared to the currently known routes which require light or toxic metals.^[27] When only 0.005 molar equivalents of CAN were added under N₂, a conversion of 71% was attained after 10 h, suggesting a chain length of at least 140.^[28]

Isomerization of bC is also the main reaction when NHPI is used in MeCN under an oxygen atmosphere. It is known that NHPI is converted to the corresponding phthalimide *N*-oxyl radical (PINO) via in situ H abstraction by dioxygen.^[29] In most of the cases studied to date, PINO functions as an H-atom shuttle between carbon-centered radicals and peroxy radicals, enhancing the rate of hydrocarbon autoxidation.^[30] However, besides this H-atom shuttling function, PINO is also capable of accepting electrons, as was proven recently in a study on electron-transfer-catalyzed amine demethylation.^[31] The NHPImediated isomerization of bC to iC in MeCN then can be ex-

> plained by an electron transfer from bC to PINO, followed by isomerization of the radical cation and an electron transfer from a fresh molecule of bC to the isomerized radical cation (Scheme 6, left). The high epoxide selectivity, even at low oxygen pressures, seems to indicate that the consecutive addition of dioxygen to bC⁺⁺ and formation of CDO are kinetically more favorable than the isomerization of the radical cation. The lack of isomerization in DMAc and NMP can then be attributed to the electron transfer properties of these solvents.[32]





Scheme 7. Proposed route for the selective formation of β -caryophyllene oxide.

The steep increase of the epoxide selectivity with conversion suggests the initial formation of an epoxidizing species; epoxidation becomes kinetically relevant only after the concentration of this epoxidizing species reaches a sufficient level. We therefore suggest that the ET products CDO or iCDO react in a second step with another molecule of bC forming two molecules of bCO and/or iCO; the proposed mechanism is given in Scheme 7. There is little literature available on the reaction of dioxetanes with olefins. Adam et al. studied the reaction of disubstituted dioxetanes with substituted ethylenic components.^[33] The obtained products depend on the employed olefin and solvent. The use of electron-poor olefins mainly gave 1,6-cycloaddition products or ene-type products. If electron-rich olefins were employed, minor amounts of epoxides were also detected. We propose an epoxidation mechanism according to the original hypothesis by Adam and co-workers.^[33] CDO reacts with bC to form a zwitterionic 1,6-dipolar transition state that may rearrange to a 1,4-dipole. Intramolecular nucleophilic attack of this 1,4-dipole results in the formation of two molecules of bCO. The facilitating effect of aprotic polar solvents is consistent with the proposed zwitterionic transition state. Although epoxides were only minor products in the report by Adam et al., the strained configuration of bC may provide an additional driving force for epoxidation.^[34] iCO formation may then be explained by either the 1,6-cycloaddition by iCDO instead of CDO to bC, or by rotation of the R_1-R_2 axis. The observed high bCO/iCO ratio points however to the unfavorable formation of iCO and is consistent with the proposed high barrier for isomerization.

Conclusions

The epoxidation of β -caryophyllene—an abundant sesquiterpene—in the presence of molecular oxygen without the addition of any catalyst was studied. In aprotic polar solvents, the reaction proceeded spontaneously with selectivities for epoxides exceeding 70%. The isomerization product isocaryophyllene was formed in minor amounts during the reaction but it became the main product if *N*-hydroxyphthalimide was added to the reaction mixture, or if ceric ammonium nitrate was used as an additive under N₂ atmosphere. The latter system provides a novel, elegant, and high-yielding route to isocaryophyllene. The high epoxide selectivity and the absence of allylic abstraction products are not consistent with any of the known free-radical autoxidation mechanisms and a hypothetical catalytic function of a peroxy radical was found to be improbable by computational methods. The observed solvent effects and the lack of epoxide formation in the presence of singlet oxygen excluded a spin inversion mechanism. An electron transfer from β -caryophyllene to dioxygen was proposed as the initiating step, forming the radical cation of β -caryophyllene and superoxide anion. This mechanism is supported by (i) the facilitating effect of aprotic polar solvents, (ii) the inhibitory effect of diazabicyclooctane (a guencher of charge-transfer complexes), 1,2,4-trimethoxybenzene (a quencher of radical cations) and 2,6-di-tert-butyl-p-cresol (a radical inhibitor), (iii) shortening of the induction phase upon increase of the β caryophyllene or dioxygen concentration in the solution, (iv) the accelerating effect of one-electron acceptors, (v) the epoxidation of bC during type I photosensitized oxidation, and (vi) the low oxidation potential of β -caryophyllene. The radical cation carries the propagation chain, in which addition of triplet oxygen results in the formation of the caryophyllene-derived dioxetane. Inhibition of the oxygenation reaction by nucleophilic protic solvents, cobalt salts and superoxide, as well as the detection of the decomposition product of the dioxetane, further support this mechanism. In a final step, the dioxetane reacts with β -caryophyllene via a dipolar 1,6-cycloaddition, forming two equivalents of the epoxide. Isomerization of β -caryophyllene to isocaryophyllene is unfavorable and only becomes a dominant route if the radical cation is formed in the absence of oxygen via the addition of one-electron oxidants. Future work will be devoted to a thorough EPR spectroscopic study of this system and possible synthetic applications of these findings.

Experimental Section

All of the used chemicals were acquired commercially and were of highest purity available. Solvents were dried over molecular sieves before use. bC (1 g, 4.9 mmol) was purified by flash chromatography with heptane as the eluent over SiO_2 gel (50 g, 220–440 mesh) and re-isolated by removing the solvent under reduced pressure. Oxygenation reactions at ambient pressure and below 85 °C were



performed in a glass vial. Reactions at elevated pressure and/or temperature were performed in a stainless steel autoclave equipped with a manometer and sampling valve. Autoclaves were passivated with saturated sodium pyrophosphate in between different reactions. In a typical oxidation procedure, β -caryophyllene (0.060 g, 0.30 mmol) and 1,4-di-tert-butylbenzene (0.006 g, 0.03 mmol) were added to acetonitrile (3 mL) in a glass vial with a septum. The solution was purged with O₂ and a balloon of oxygen was attached to the glass vial with a needle. The solution was heated to 80°C with stirring. We emphasize that the experiments were performed above the flash point of acetonitrile and appropriate safety precautions had to be taken, especially during sampling. At regular intervals, aliquots of the solution were taken, a small quantity of BHT was added and the samples were analyzed with GC-FID, GC-MS, and ¹H NMR spectroscopy. Concentration profiles were determined by GC-FID and concentrations were quantified versus 1,4-di-tert-butylbenzene as an internal standard. Products were identified by GC-MS and ¹H NMR spectroscopy; the obtained spectra were compared and matched with those reported in the literature. In a preparative isomerization procedure, bC (0.2 g, 1.0 mmol) and CAN (0.055 g; 0.1 mmol) were added to acetonitrile (10 mL) and the mixture was stirred at 80 °C and under 1 bar of oxygen for 2 h. After reaction, the mixture was extracted *n*-heptane (2×20 mL). The combined heptane layers were washed with brine (20 mL) and dried over MgSO₄ and the solvent was removed by evaporation under reduced pressure. The residual colorless oil was purified by flash chromatography on silica gel with nheptane (100 mL), yielding isocaryophyllene (0.17 g, 85% yield, 98% GC purity). Calculations were performed at the B3LYP/6-31G(d,p) level of theory using the Gaussian09 software package.^[35] Cyclic voltammetries and potentiostatic experiments were run in a small electrochemical cell under controlled temperature and atmosphere. A platinum-coated silicon wafer was used as working electrode, while a platinum coil and a home-made Ag/Ag^I (3 м KCl) electrode were used as counter and reference, respectively. All the experiments were controlled by a galvanostat/potentiostat EG&G 273.

Acknowledgements

B.S. is grateful to IWT, Flanders, for providing a research grant. D.D.V. thanks Belspo (IAP 7/05) and KULeuven (Methusalem grant CASAS) for support. N.C., J.F. and D.D.V. are thankful to IWT for the funding of the MOFShape project.

Keywords: epoxidation · isomerization · radical ions · reaction mechanisms · sesquiterpenes

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- [32] The use of NHPI in DMAc did not lead to isomerization but to a more selective epoxidation and the demethylation product NMAc was detected after reaction by GC-MS. These striking results can be rationalized by the demethylating properties of PINO; in DMAc, the solvent itself is a one-electron donor and undergoes demethylation via ET to PINO. This reaction of DMAc with PINO renders ET from bC to PINO kinetically uncompetitive. This has two consequences: (1) No viable isomerization route is present and (2) the presence of the methyl radicalformed via the demethylation of DMAc-opens up an additional route for bC epoxidation via reactions (4), (6), and (7) in Scheme 2, resulting in a higher epoxide selectivity. An analogous role is suspected for the solvent NMP. The high epoxide selectivity, even at low oxygen pressure, seems to indicate that the concurrent addition of dioxygen to the generated radical cation and formation of CDO are kinetically more favorable than the isomerization of the radical cation. Additionally, the higher S_{epox}/S_{isom} ratio in DMAc compared to MeCN can be rationalized in terms of the EA properties of DMAc and the apparent high barrier for isomerization. The quenching of the radical cation by DMAc prevents its rearrangement to its more stable cis-cyclononene configuration, whereas in MeCN the solvent has no EA-properties and a few percent of iC can form.
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Received: August 3, 2014 Published online on November 27, 2014