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REVERSIBLE COUPLING OF A SUBSTITUTED ALLYLIC RADICAL WITH MOLECULAR OXYGEN IN A TOCO REACTION OF 5-METHYLHEPTA-1,3,6-TRIENE

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Abstract: p-Toluenethiol/oxygen co-oxidation of 5-methylhepta-1,3,6-triene (1) gives inter alia only one (6a) of four possible diastereoisomeric dioxolanes, and the threo- and erythro- isomers of the 1,4-addition product (10, 11). The variation in relative yields with thiol concentration indicates that coupling of the allylic radical (2) with oxygen is reversible.

The interaction of 5-methylhepta-1,3,6-triene (1) with benzenethiol and oxygen (TOCO reaction) has been reported[1] to afford only one of the four possible diastereoisomers of the 1,2-dioxolane (6a). Its formation involves ring closure of an intermediate alkenylperoxy radical. We now examine in detail the mechanism of this remarkable regio- and stereo-specific process and show that a key step, namely coupling of the substituted allyl radical (2) with molecular oxygen, is reversible.

The overall sequence of mechanistic steps as previously reported[1,2] involves: (i) addition of ArS$^{\bullet}$ to the diene moiety in (1), (ii) coupling of the allyl radical (2) so formed with molecular oxygen, (iii) 1,5-ring closure of the resultant peroxy radical, and (iv) coupling of the cyclised radical with oxygen followed by hydrogen-atom transfer from thiol to afford the hydroperoxide (6a). Quantitative reduction of (6a) to the alcohol (6b) is effected by treatment with triphenylphosphine during workup. The relative stereochemistry of the methyl and arene-thioalkenyl substituents in (6) is defined at the time of the oxygen coupling reaction of the allyl radical (2); i.e. the cyclic product arises from only one (3) of the two diastereoisomeric peroxy radicals (3) and (5). The question arises, therefore, of whether the coupling process is stereospecific.[3]

An answer to this question can be provided by a stereochemical examination of the hydroperoxides formed from peroxy radicals by the hydrogen-atom transfer process which competes with ring closure. Accordingly, the triene (1) was co-oxidised with p-toluenethiol in dilute solution (4×10^{-3}M) as previously described,[1,2] and the crude product, after reduction with

triphenylphosphine was chromatographed on t.l.c. grade silica to afford a mixture (80:20 by ^{13}C n.m.r.) of the diastereoisomeric alcohols (8b) and (9b). This mixture was subjected to ozonolysis followed by treatment with hydrogen peroxide and the product was then methylated with diazomethane. The components of the mixture were identified by gas chromatographic comparison (three columns) with samples synthesised by unambiguous routes,[4] as the methyl esters of threo-1-hydroxy-2-methylsuccinic acid (10; 85%) and its erythro diastereoisomer (11; 15%). We conclude, therefore, that the coupling of the allylic radical (2) with oxygen is not stereospecific. Both diastereoisomeric peroxy radicals (3) and (5) are formed but the erythro form undergoes mainly ring closure under these experimental conditions whereas the threo form (5) is exclusively converted into the acyclic hydroperoxide (8a) by hydrogen atom transfer.

Repetition of the experiment at a higher thiol concentration (4×10^{-2}M) gave further information concerning the reaction mechanism. Since its rate is dependent on thiol concentration, hydrogen atom transfer to the peroxy radical (3) competes more effectively with ring closure under these experimental conditions. No cyclic product was isolated and the yield of acylic alcohols was increased (see Table 1). The ^{13}C n.m.r. spectrum of the mixture revealed the presence of two isomers (60:40) identified by ozonolysis as described above as the threo alcohol (8b; 60%) and the erythro alcohol (6b; 40%). Both experiments afforded the alcohol (7b) arising from coupling of oxygen at the 2-position of the allylic radical. In each case it contained equal amounts of the threo and erythro isomers as estimated by ^{13}C n.m.r. spectroscopy.

Since the cyclic product (6a) is derived exclusively from the erythro peroxy radical (3), and since the stereochemistry of the acyclic products is known it is possible to deduce the stereochemistry of the addition steps under both sets of experimental conditions. The data are given in Table 2. They show that both the 1,4-:1,2-addition ratio and the erythro:threo ratio for 1,4-addition increase with decreasing thiol concentration. A reasonable explanation for this behaviour is that the oxygen coupling step is reversible. At very low thiol concentration the peroxy radicals (3), (4), and (5) are inefficiently trapped by hydrogen atom transfer and interconversion between them can occur via the allylic radical (2). Only the rate of ring-closure of the peroxy radical (3), a first order process, is unaffected by thiol concentration. Consequently, formation of the cyclic product (6a) becomes increasingly dominant as the thiol concentration is lowered.

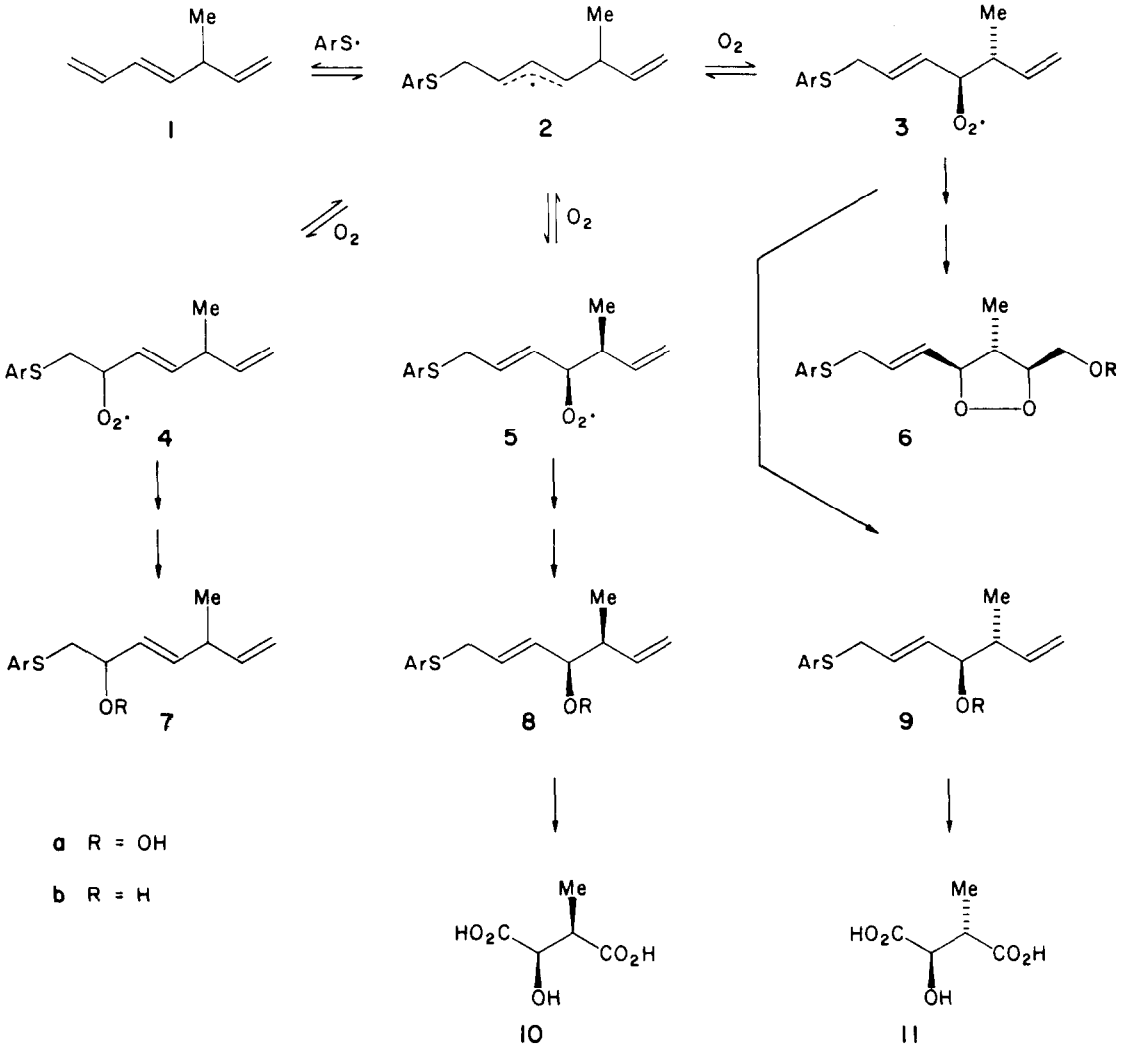

TABLE 1. Yields (%) of products from TOCO reactions of 1.

[ArSH]/M	7	8b + 9b	6b	total
4.0×10^{-2}	47	29	<3	76
4.5×10^{-3}	44	21	26	91

Table 2. Relative yields and stereochemistry of adducts formed from 2 by coupling with molecular oxygen.

[ArSH]/M	1,2-adduct (4) formation			1,4-adduct (3+5) formation		
	total	threo	erythro	total	threo	erythro
4.0×10^{-2}	63	31	31	37	22	15
4.5×10^{-3}	48	24	24	52	19.5	32.5

Finally, we turn to the question of why ring closure of the threo radical (5) is less favoured than that of its erythro isomer (3). Recently published guidelines[5] suggest that ring closures of 3-substituted hexenyl radicals and related systems preferentially afford cis-disubstituted products whilst 4-substituted systems afford trans. The peroxy radical (3) corresponds to a 3,4-disubstituted system in which the two substituents are correctly stereochemically disposed to allow ring closure to proceed in conformity with the guideline. This is not so for the peroxy radical (5). Because of the stereochemical relationship between the two substituents, ring closure cannot conform to the guidelines; each of the two possible chair-like transition states will contain one of the substituents in an axial position. Furthermore, one of them will lead to the formation of a highly-strained, all-cis trisubstituted product.

Other evidence for the reversibility of the coupling of molecular oxygen with dienylic radicals has recently been obtained[6] from studies of autoxidation of polyolefins. This reversibility complicates kinetic analysis of such sytems and must be taken into account in designing biomimetic experiments involving molecular oxygen, e.g. prostaglandin biosynthesis.

REFERENCES AND NOTES

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