

POSITIONAL SELECTIVITY
DURING CONTROLLED OXIDATION OF POLYOLEFINS

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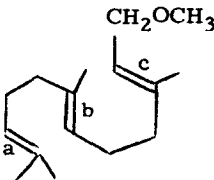
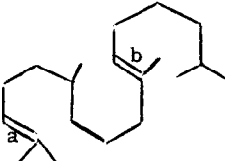
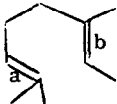
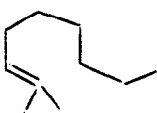
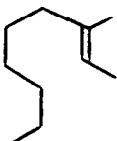
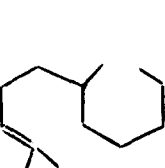
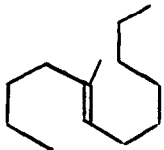
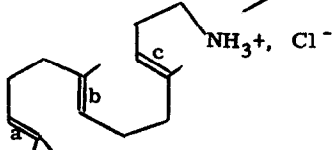
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In attempts to simulate the obligatory end double bond oxidation triggering the over-all biological conversion of squalene to sterols, van Tamelen and Curphey (1) observed several years ago the highly selective formation of terminal bromohydrin during attack of squalene by N-bromosuccinimide in aqueous ethylene glycol dimethyl ether. More recently, squalene-2, 3-oxide produced by this chemical means was shown in this (2) and another (3) laboratory to act as a biological precursor of lanosterol and cholesterol, suggesting that epoxidation at the Δ^2 position of squalene initiates the biochemical sequence. Because of its intrinsic chemical novelty, its biological implications, and its actual utility in preparing artificial substrates for biochemical mechanistic studies, the non-enzymic selective terminal oxidation of terpenes and other olefins by means of various agents was investigated in more detail.

As a means of shedding light on the oxidation phenomena, three principal variations were introduced: the structure of the olefinic substrate, the nature of the medium, and the type of oxidizing agent. In Table I and II are summarized results obtained to date, partly on the basis of which we conclude that the in vitro selectivity is due to both steric and conformational characteristics of the olefinic system ("conformational-steric effect"). As can be seen from a representative terpenoid case, trans, trans-farnesyl methyl ether (I), the selectivity is very high, 95% terminal (a) in glyme-water and greater than 99% in aqueous t-butanol. The same order of selectivity is observed in a purely synthetic case (II) where

TABLE I

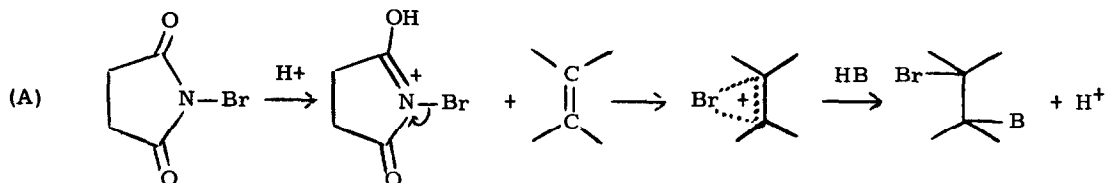
Selectivity in the Conversion of Olefins to Bromohydrins by N-Bromosuccinimideⁱ

Olefin	Attack Percentages	
	Glyme-water	Petroleum ether-acetic acid ⁱⁱ
I 	95 (a):5 (b):0 (c) 99+ (a) (aqueous t-butanol)	81 (a):19 (b):0 (c)
II 	98.5 (a):1.5 (b)	62 (a):38 (b)
III 	61 (a) : 39 (b)	
IV  vs. V 	56 (IV) : 44 (V)	50:50
VI  vs. VII 	100 (VI) : 0 (VII)	
VIII 	100 (a) : 0 (b) : 0 (c) (by n. m. r.)	

i. Except as noted, each product mixture was converted via epoxide to 1,2-glycol, which was then cleaved by periodate. V. p. c. methods were used to determine the relative composition

of either the epoxide or the resulting aldehyde-ketone mixture, the nature of which was demonstrated by comparison (v. p. c.) with authentic specimens. Yields in the glyme-water reactions fell between 60-70%, except in the case of VIII, which was essentially quantitative. In the petroleum ether-acetic acid experiments, the 1,2-bromoacetate initially produced was hydrolyzed to bromohydrin before proceeding with the normal analytical procedure.

ii. The oxidation mechanism is probably not dependent in its essentials on the media employed in these studies. We have observed that: NBS is recovered quantitatively from aqueous glyme after 24 hr. at room temperature; halohydrin formation is markedly catalyzed by acids; hypobromous acid *per se* gives distinctly different and far less satisfactory results with *e. g.*, I. Thus it appears that NBS does not act as a source of hypobromous acid in the halohydrin preparations described herein, but that a mechanism of the type (A) is involved. In glyme-water,



HB = H₂O and provides halohydrin; where HB = CH₃CO₂H, 1,2-bromoacetate is produced.

the double bonds are more widely separated. Similarly, in a competitive case involving two long chain olefins, one (VI) with a "terminal" double bond and the other (VII) with an "internal" olefinic link, the former is oxidized to the virtual exclusion of the latter. As expected, various kinds of terminal double bonds exhibit little difference in susceptibility to attack (III and IV/V). Selectivity in cases I, II and VI/VII might be ascribed only to steric effects operative in the environment of the internal double bond, except for two reasons: 1) most oxidizing agents should in this case lead to terminal selectivity—actually the N-bromosuccinimide selectivity is unusual (1), and 2) a pronounced solvent effect has been observed (Table I). In petroleum ether-acetic acid, selectivity in the case of I drops from 95-99% to 81%; and in the case of II, the change is even more marked, from 98.5% to 62%. Similar, although less dramatic, differences are observed in certain peracid oxidations (Table II), a less preferential process in general.

Although the effect of solvent on selectivity is subject to various interpretations, it seems possible that it is related to the conformation of the olefin in solution. As suggested previously (1), in certain solvents coiling of the polyolefin may be more pronounced and

TABLE II
Selectivity in the Oxidation of Olefins by Other Reagentsⁱ

Olefin (reagent)	Attack Percentages	
	Glyme-water	Methylene Dichloride
I (peracetic acid)	60 (a) : 30 (b) : 10 (c)	70 (a) : 25 (b) : 5 (c)
I (sodium tetrachloroperphthalate)	76 (a) : 20 (b) : 4 (c)	
II (peracetic acid)	58 (a) : 42 (b)	64 : 36
IV-V (peracetic acid)	50 : 50	
I (mercuric acetate) ⁱⁱ	100 : 0	
squalene (diimide) ⁱⁱⁱ	ca. random (in <i>t</i> -BuOH)	
VIII (0.5 N hydrochloric acid) ⁱⁱ	100 : 0	

therefore more effective in shielding the internal double bond(s) from oxidative attack and yet permit exposure of the terminal position for reaction. The Curtin-Hammett principle (4) does not disallow the phenomenon, since the energy increment ascribed to solvent influence could be applied to the transition, as well as to the ground, state. Alternatively, solvent-clustering at the reacting center of the reagent and olefinic molecules in the transition state may, by simple bulk effects, discourage reaction at the sterically encumbered central portion of the system. In keeping with this explanation is the low selectivity exhibited by various "neutral" oxidizing species, *e.g.*, peracids, diimide or osmium tetroxide, as contrasted

i. See footnote i, Table I.

ii. In both cases the over-all result was hydration of the terminal olefinic link, with formation of the *t*-alcohol in high yield. The composition was determined by suitable n. m. r. methods.

iii. Controlled diimide reduction, resulting in recovered squalene, a mixture of dihydrosqualenes and tetrahydrosqualenes, was carried out by addition of acetic acid to a mixture of squalene and azodicarboxylate anion in *t*-butanol. By v. p. c., a 1:2 ratio of 2,3-dihydrosqualene (authentic specimen prepared by K. B. Sharpless, unpublished work) and isomeric dihydrosqualenes was observed.

with the higher selectivity of charged (and therefore more extensively solvated) agents, such as protonated N-bromosuccinimide (see footnote i, Table I), protons (5) and mercuric acetate. Regardless of the explanation, the product ratio (a:b centers) falls in the range of ca. 20:1 - 100:1, which is equivalent to several kcal/mole advantage for terminal oxidation, a reasonable value for the kind of phenomenon involved.

Although the nature of the active epoxidizing enzyme in the squalene → lanosterol conversion is unknown, the high selectivity attainable in non-enzymic reactions suggests that the entropy requirements of the "squalene epoxidase" reaction may be lower than in the absence of such solvent effects as described above. In that case, a correspondingly lower structural specificity of the epoxidase might be anticipated, thereby permitting enzymic oxidation of various unsaturated hydrocarbons other than squalene.

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