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The Epoxidation of α,β-Unsaturated Terpene Ketones

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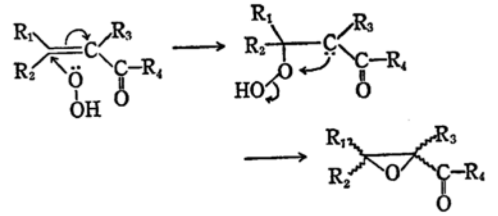
It has recently been reviewed by Klein and Ohloff[1] that in a variety of α,β-unsaturated cyclic terpene ketones, the base-catalyzed epoxidation of exocyclic double bonds in conjunction with carbonyl groups proceeds in a non-stereoselective manner to produce a mixture of two diastereomeric epoxides, whereas in endocyclic double bonds, the steric course of epoxidation is highly stereoselective, resulting in the formation of a single product. However, they did not refer to the factors which govern the steric course of the epoxidation reaction.

The epoxidation of polarized double bonds with hydrogen peroxide in aqueous alkaline media was first reported by Weitz[2] and the reaction mechanism involving the intervention of a hydroperoxycarbanionic intermediate was proposed by Bunton.[3]



Dewar[4] advanced a theory for a facile bimolecular nucleophilic displacement of halogen α to

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[1] E. Klein and G. Ohloff, *Tetrahedron,* **19**, 1091 (1963).

[2] F. Weitz and A. Scheffer, *Ber.*, **54**, 2327 (1921).

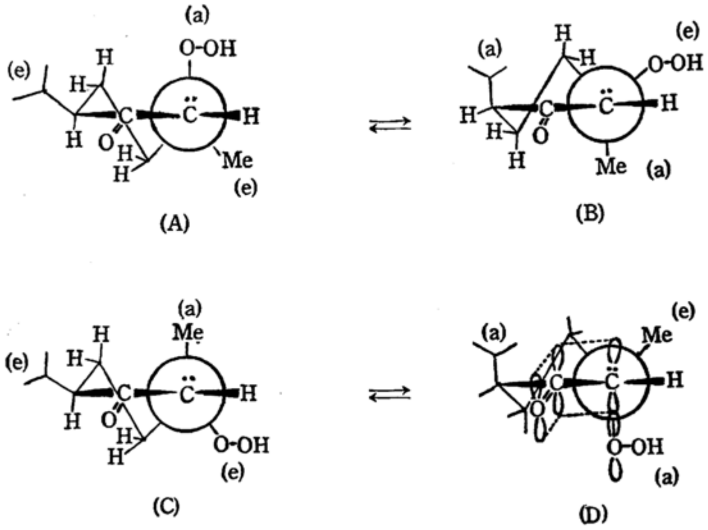
[3] C. A. Bunton and G. J. Minkoff, *J. Chem. Soc.*, **1949**, 665.

[4] M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford University Press, Oxford (1949), p. 73.

a keto group and his theory states that the transition state is stabilized by overlap and conjugation of the C=O π-orbital with the orbitals of the bonds being formed and broken at the α-carbon atom. This concept was successfully applied by Zimmerman(5) for the stereochemical interpretation of the alkaline epoxidation reaction, in which the stereochemical preference in epoxide products was overlap controlled.

We wish herewith to mention that the Zimmerman overlap-control theory holds for the epoxidation of α,β-unsaturated cyclic terpene ketones as well, and that the conformational analysis of the transition state carbanion, which fulfilled the stereoelectronic requirements for the maximum stabilization by orbital overlap and charge delocalization, may provide a useful means of assigning an absolute configuration to the epoxide to be expected from the epoxidation of cyclic terpene ketones containing either endocyclic or exocyclic ethylene linkage.

In accordance with this view, the available data(1) actually indicate that upon epoxidation, cyclic terpene ketones containing α,β-endocyclic double bonds afford stereospecifically the enantiomer to be expected from the intermediate hydroperoxy-carbanion which was stabilized by the orbital-overlap and charge delocalization in the conformation with the minimized non-bonded repulsive interactions of substituents in the preferred equatorial disposition. This may be exemplified in detail by (−)-(4R)-piperitone (**1**) which upon epoxidation, yielded exclusively (+)-(1R : 2R : 4R)-piperitone oxide (**2**): the nucleophilic attack of hydroperoxide anion to the β-carbon (here $C_{(1)}$) of the polarized double bond in **1** would produce two conceivable transition state carbanions *i. e.* **A** resulted from the attack of the anion to the 1 *re*-2 *re* face of the double bond and **C** resulted from that to the 1 *si*-2 *si* face. The transition state carbanion **A** in which both the anchoring isopropyl and methyl groups are disposed equatorially and the hydroperoxy group is in an axial position, should naturally be in a conformational equilibrium with **B** where both isopropyl and methyl groups are disposed axially and hydroperoxy group is in an equatorial position. A similar conformational equilibrium should obtain in the diastereomeric transition state conformer **C**. Of the four conceivable transition states **A**, **B**, **C** and **D**, only **A** and **D** can fulfill the stereoelectronic requirements for oxirane ring formation by intramolecular nucleophilic displacement since in these two conformations, the axial hydroperoxy group is so disposed as to permit the cyclization and also to possess the maximum stabilization by orbital overlap and charge delocalization. Further choice of these two conformers, then, would be made from a purely steric point of view, *i. e.* the comparison of relative conformational stability as demonstrated by inspection of scale models clearly indicates that the transition state carbanion **A** with both the anchoring isopropyl and methyl groups oriented equatorially should be more favored than the diastereometric counterpart **D** with the bulky isopropyl group disposed in an axial position and methyl group in an equatorial position. Since the first step of hydroperoxide anion attack is reversible, the steric course of the epoxidation should be directed to proceed through the most favored transition state **A** and the chemical consequence of this situation should naturally be the exclusive



Scheme I

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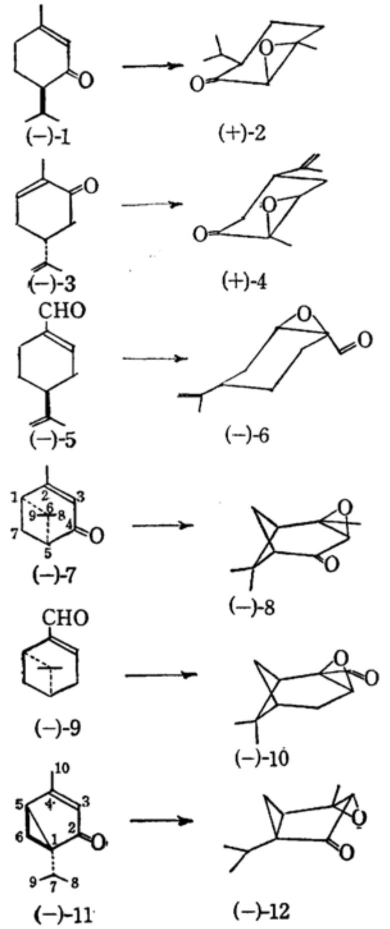
[5] H. E. Zimmerman, L. Singer and B. S. Thyagarajan, *J. Am. Chem. Soc.*, **81**, 108 (1959).

formation of (+)-(1R:2R:4R)-piperitone oxide **2**. This is just what was found experimentally by the product analysis and the absolute assignment of configuration to **2**: the conformation of the most favored transition state **A** has been reflected as such in the epoxide product **2**.

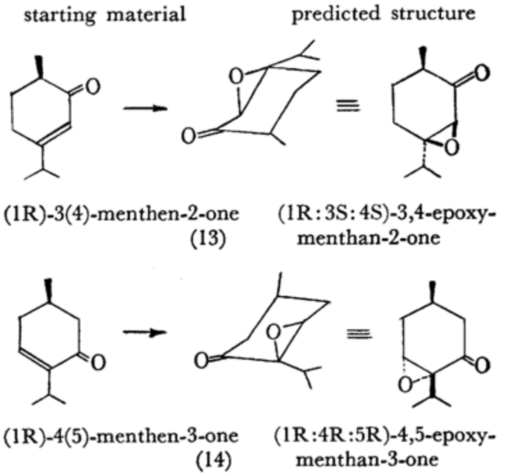
Literature[1] affords cogent support for the stereochemical interpretation of epoxidation in terms of the overlap-control stabilization combined with conformational analysis, as demonstrated by the epoxidation of (−)-(4R)-piperitone (**1**) into (+)-(1R : 2R : 4R)-piperitone oxide (**2**); of (+)-(4S)-**1** into (−)-(1S:2S:4S)-**2**; of (−)-(4R)-carvone (**3**) into (+)-(1R : 2R : 4R)-carvone oxide (**4**); of (+)-(4S)-**3** into (−)-(1S : 2S : 4S)-**4**; of (−)-(4S)-perillaldehyde (**5**) into (−)-(1S : 2R : 4S)-perillaldehyde oxide (**6**); of (−)-(1R : 5S)-verbenone (**7**) into (−)-(1R : 2R : 3S : 5S)-verbenone oxide (**8**); of (+)-(1S:5R)**7** into (+)-(1S : 2S : 3R : 5R)-8; of (−)-(1R: 5S)-myrtenal (**9**) into (−)-(1R : 2R : 3S : 5S)-myrtenal oxide (**10**); of (−)-(1R : 5S)-umbellulone (**11**) into (−)-(1R : 3S : 4S : 5R)-umbellulone oxide (12),[6,7] respectively.



Scheme II

In a manner similar to the above-mentioned piperitone (**1**), the chair conformation of the intermediate hydroperoxy-carvone anion, with the isopropyl group disposed in an equatorial position and the hydroperoxy group in an axial position and thus with the advantage of overlap stabilization, would be more favored than the othewise-conformed counterpart, so that it would result in the end product **4** with the oxirane ring *trans* to the isopropyl group. What has been mentioned with carvone holds for (−)-perillaldehyde (**5**) as well. Verbenone (**7**) permits readier access to the 2 *si*-3 *re* face of the double bond because of the smaller bulkiness of $C_{(7)}$-hydrogen than the geminal dimethyl in the opposite side, thus naturally proceeding through the overlap-stabilized intermediate and resulting in the formation of the corresponding epoxide (**8**) (*trans* relative to geminal dimethyl). The situation is also the same with myrtenal which gave the *trans*-epoxide (**8**). (−)-Umbellulone (**11**), in which the bicyclo(3,1,0) system adopts the boat conformation as demonstrated by NMR-analysis,[8,9] also gave the corresponding *cis*-epoxide (**12**) (relative to isopropyl group) *via* the overlap-stabilized intermediate.

Based on these data, it may be generalized that in the epoxidation of endocyclic double bond involved in pinane skeleton, the isomer with the oxirane ring *trans* relative to geminal dimethyl groups is formed exclusively, and in other terpene ketones, the oxirane ring is stereospecifically introduced to the double bond so as to enable sterically the most favored intermediate conformation to be



Scheme III

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6) R. T. Gray and H. E. Smith, *Tetrahedron*, **23**, 4229 (1967).

7) H. E. Richard and C. S. James, *J. Am. Chem. Soc.*, **76**, 4118 (1954).

8) M. S. Bergqvist and T. Norin, *Arkiv for Kemi*, **22**, 137 (1964).

9) K. Tori, *Chem. Pharm. Bull. (Tokyo)*, **12** 1439, (1964).

stabilized by an effective and concomitant orbital-overlap stabilization.

When this generalization is applied to some endocyclic α,β-unsaturated terpene ketones, (1R)-3(4)-menthen-2-one (**13**) and (1R)-4(5)-menthen-3-one (**14**), the following configurations of the exclusive epoxide products may be predicted, experimental verification of which will be the subject of future publications.

Although available data for the epoxidation of exocyclic double bonds are scarce in literature, the epoxidation of (+)-(1R)-pulegone[10] (**15**), (+)-(1S : 5R)-pinocarvone[11] (**16**), (+)-(1R : 4S)-isopropylidenecamphor[12] (**17**) and (+)-(1S : 2S)-piperitenone oxide[10] (**18**) clearly shows that a mixture of diastereomeric epoxides is always obtained in a definite isomer ratio except in the last example, the sterically more favored and therefore the more stable isomer being dominant in every case. Since the exocyclic double bonds are not locked in a rigid cyclic skeleton and consequently the rotation around the single bond connecting the carbanionic sp^2-carbon (α) with the β-carbon carrying the hydroperoxy group is quite free, the hydroperoxy group is capable of fulfilling the stereoelectronic requirements for the maximum orbital overlap at both sides of the carbanionic sp^2-carbon and consequently to undergo nucleophilic displacement to form oxirane ring in two ways—one with axial oxirane-oxygen and equatorial carbon, and the other with the reversed conformational orientation of oxirane ring. The energy difference between these two diastereomeric transition states is thus purely steric in origin and is not so great as in the endocyclic counterparts, so that the stereoselectivity of epoxidation is dependent on the relative conformational stability of these two conformers, as was actually observed in product distribution.

TABLE 1

Starting material	Product isomers	Yield %
(+)-Pulegone	(−)-(1R:4R)-*trans*-**19**	64.5
	(+)-(1R:4S)-*cis*-**20**	35.5
(+)-Pinocarvone	(−)-(1R:2S:5R)-*trans*-**21**	35.5
	(+)-(1R:2R:5R)-*cis*-**22**	64.5
(+)-Isopropylidenecamphor	(−)-(1R:3S:4S)-*trans*-**23**	67
	(+)-(1R:SR:4S)-*cis*-**24**	33
(+)-Piperitenone oxide	(−)-(1S:2S:4S)-*cis*-**25**	

In pulegone oxide, the *trans* epoxide (**19**) (relative to $C_{(7)}$ and $C_{(10)}$) with the conformation involving both isopropyl and methyl groups in equatorial position is preferred to the *cis*-**20** with an axial methyl. The red shift in CD found for diastereomeric pinocarvone oxides showed the axial orientation of the oxirane-oxygen atom in both *trans*-**21** (relative to $C_{(6)}$ bridge carrying geminal dimethyl and $C_{(10)}$ methyl group) and *cis*-products (**22**) and on the basis of such conformations, the non-bonded interactions between the oxirane-oxygen and the $C_{(6)}$-dimethyl grouping favor the *cis*-**22** more than the *trans* epoxide (**21**), thus the former being the major product of epoxidation. The oxirane ring, O–$C_{(3)}$–$C_{(11)}$, in isomeric isopropylidenecamphor oxides is so situated as to be bisected by the carbonyl group and then the isomers differ in the non-bonded interactions between $C_{(7)}$-geminal dimethyl and isopropyl moiety of oxirane. Model inspection reveals that the the *trans* isomer (**23**) (relative to $C_{(7)}$ and $C_{(11)}$) is sterically more favored and stable than the *cis* **24**, in accordance with the result of product analysis. In the case of piperitenone oxide, the sole dioxide isolated (42%) was (−)-(1S : 2S : 4S)-diastereomer[10] (**25**) which has sterically the more favored conformation with both isopropyl moiety of oxirane and $C_{(1)}$-methyl group disposed equatorially. Although another diastereomeric *trans*-dioxide product was missing, the failure of its isolation may probably be due to experimental difficulties; this highly strained system containing two sensitive epoxide functions in an unfavorable conformation and a carbonyl group in a single C_{10}-molecule would supposedly be too labile to permit successful separation without any decay.

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10) J. Katsuhara, *J. Org. Chem.*, **32**, 797 (1967).
11) J. Katsuhara, This Bulletin, **41**, 2700 (1968).
12) J. Katsuhara, *ibid.*, **42**, No. 9 (1969), in press.