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Theoretical Conformational Analysis of Saturated Heterocycles. Substituent Effects on Primary Ozonides

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Abstract: The theoretical conformational analysis of 12 substituted primary ozonides has been carried out. The results indicate that several conformers for each compound are approximately equal in stability and hence no conformer predominates. A study of $O-O-C^+-R$ zwitterion conformation shows that the R group will rotate into an anti zwitterion if the $O-O-C-R$ angle is greater than 90° ; analysis of $O-O-C-R$ angles in the primary ozonides indicates that all substituents will tend to form anti zwitterions upon ring fission. An analysis of the relative stability of various conformers indicates that, within the limitation of the investigation, lone-pair interactions are more important than substituent interactions in determining ring conformation.

Primary ozonides (1,2,3-trioxolanes) are intermediates in the reaction of ozone with olefins to produce final ozonides (1,2,4-trioxolanes) and a mixture of polymeric peroxides. A mechanism for this reaction was originally proposed by Criegee¹ and later modified by Bailey, *et al.*,² and more recently by Kuczkowski, *et al.*³ The Bailey, *et al.*, mechanism, shown in Figure 1, involves the initial formation of the primary ozonide, followed by its decomposition into a carbonyl moiety and a zwitterion. The zwitterion formed is postulated to be anti (from equatorial primary ozonide substituents) or syn (from axial substituents). The anti and syn zwitterion then react with carbonyl compounds to orient bulky groups *cis* or *trans*, respectively, in the final ozonides. This mechanism was proposed to account for much of the stereochemical data obtained from the ozonolysis of olefins, but not all. In particular ¹⁸O-labeling experiments indicate that the introduction of ¹⁸O-carbonyl moieties into the reaction produce final ozonides with ¹⁸O in the peroxide position and support an alternate mechanism proposed by Murray, *et al.*⁴⁻⁷ An alternate mechanism to explain the ¹⁸O data has been proposed⁸ and more recent studies of ¹⁸O-labeled final ozonides produced from phenylethylenes⁹ and small alkenes^{10,11} show no peroxide ¹⁸O. The recent

modification of the Criegee mechanism of Kuczkowski, *et al.*,³ postulates that the primary ozonide ring fission proceeds through a single conformer and is consistent with orbital symmetry arguments. Additional discussion of all but the last of these mechanisms can be found in the initial report of these theoretical studies.¹²

In order to determine the validity of the Bailey, *et al.*, proposal, two theoretical studies have been performed.¹²⁻¹⁴ These studies concentrated on determining the lowest energy conformer(s) of the primary ozonide intermediate to see if well-defined axial and equatorial substituents could be found for the most stable ring conformation. The conclusions reached can be summarized by stating that several conformers were found to be very close in energy and it is difficult to identify one as the predominant conformer in a reaction mixture. Among the lowest energy conformers are conformers with substituents which do not occupy axial or equatorial substituent positions.

The initial study was performed with the extended Hückel theory^{13,14} and did not include all conformers of the primary ozonide ring and used a crude approximation to the ring geometry. The second study¹² included all conformers with the crude geometry, along with a proposal for an improved geometry and was based on the CNDO/2 method. The results presented here conclude the semiempirical studies using the improved geometry and considering the effect of bulky groups (up to *tert*-butyl) on the conformations of the primary ozonide molecule. These results also provide information on the relative importance of lone-pair and substituent interactions about the ring.

The molecules studied here are: propene, 1-butene,

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- (2) N. L. Bauld, J. A. Thompson, C. E. Hudson, and P. S. Bailey, *J. Amer. Chem. Soc.*, **90**, 1822 (1968).
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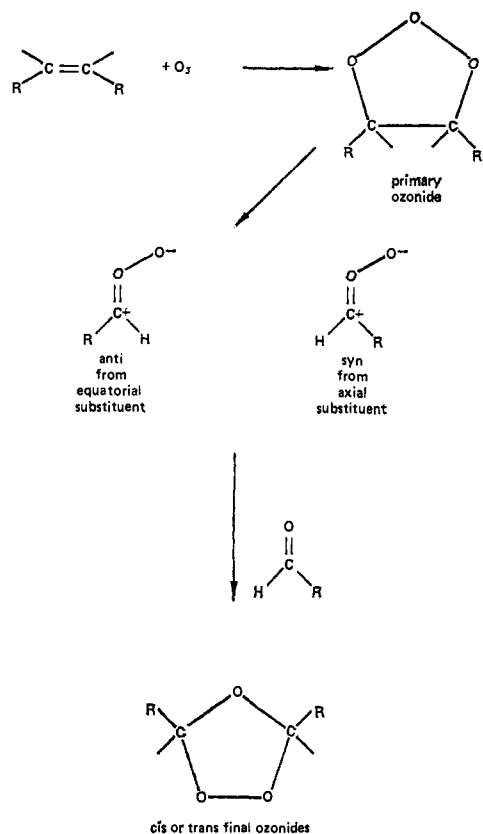


Figure 1. Proposed zwitterion mechanism for the ozonolysis of alkenes.

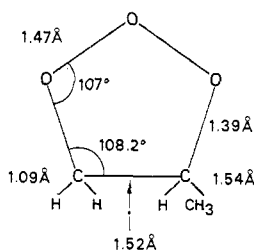


Figure 2. New geometry of the primary ozonide intermediate.

3-methyl-1-butene, and 3,3-dimethyl-1-butene primary ozonides, and *cis*- and *trans*-2-butene, 3-hexene, 2,5-dimethyl-3-hexene, and 2,2,5,5-tetramethyl-3-hexene primary ozonides. These correspond to methyl, ethyl, isopropyl, and *tert*-butyl substituents.

Choice of Theoretical Method and Ring Geometry

There are relatively few conformational studies on saturated heterocycles; most investigations of heterocyclic geometric and electronic structure with *ab initio* and semiempirical techniques have focused on planar unsaturated molecules; see ref 12 for a discussion of this study. The CNDO/2¹⁵ technique is chosen here on the basis of previous studies which demonstrated its successful prediction of the conformation of ethylene (final) ozonide and several substituted final ozonides;¹⁶ the EHT predicted the wrong structure in each case.

The improved primary ozonide ring geometry is shown in Figure 2. Instead of having all ring bond

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(16) R. A. Rouse, *Int. J. Quant. Chem.*, **7S**, 289 (1973).

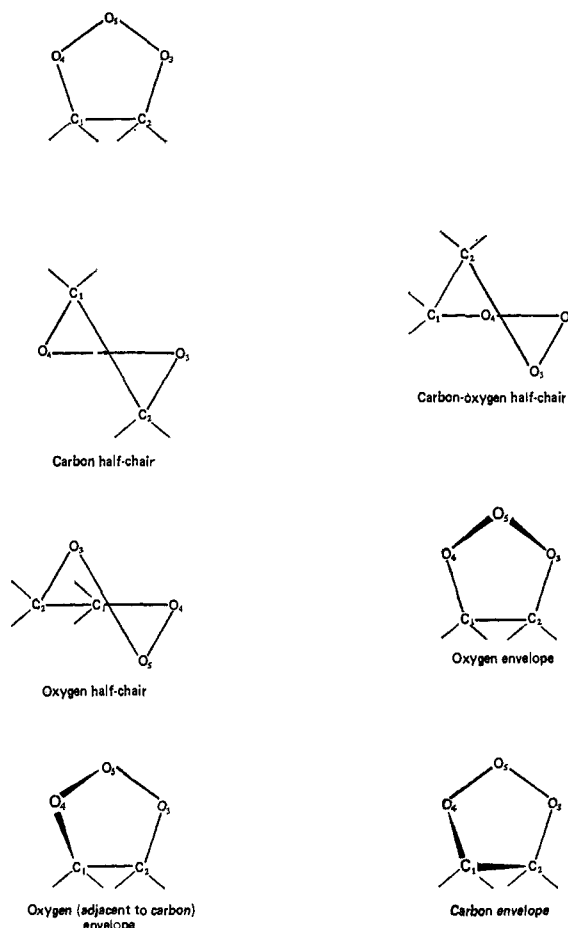


Figure 3. Conformers of the primary ozonides.

lengths identical, the new geometry is synthesized by considering a variety of four-, five-, and six-membered rings containing the appropriate bonds, including the ethylene ozonide geometry obtained by Kuczkowski and Gillies.^{10,17} The longer C-C bond should more accurately provide a description of substituent interactions. The O-O and C-O bond lengths are changed by smaller amounts. The C-O-O bond angle is chosen to yield O-C-C angles characteristic of other nonplanar five-membered ring molecules.

The primary ozonide ring can exhibit a total of 12 conformers, six half-chairs and six envelopes. The envelopes have one atom out of the plane of the remaining four ring atoms; the half-chairs have two atoms out of the plane of the remaining three atoms in the ring (see Figure 3). Of these 12 possible conformers, eight are considered here. The two oxygen envelopes were not considered on the basis of the earlier studies and their relatively minor effects on ring and substituent interactions. The energies of each conformer for each molecule considered were calculated at 5° twist angle increments. The twist angles are defined in Table I; the positive twist angles are shown in Figure 3.

By analyzing dihedral angles between substituents as a function of ring twist angle, the following order of interactions is found: substituent interactions are minimized most in the carbon half-chair, followed by the carbon-oxygen half-chair, carbon envelope, and

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Table I. Definition of Twist Angles for Conformers of Primary Ozonide

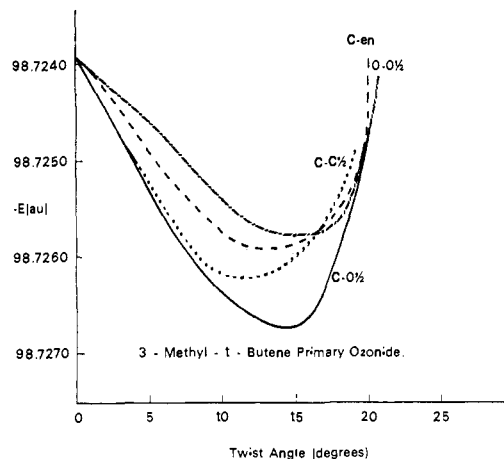
Conformer	Twist angle ^a
Carbon half-chair	C ₁ -C ₂ -O ₃ and C ₁ -C ₂ -O ₃
Carbon-oxygen half-chair	C ₂ -O ₃ -O ₄ and C ₂ -O ₃ -O ₃
Oxygen half-chair	O ₃ -O ₃ -C ₁ and O ₃ -O ₃ -O ₄
Carbon envelope ^b	C ₂ -O ₃ -O ₃ -O ₄ and C ₁ -C ₂ -O ₄

^a The twist angle is the dihedral angle between the planes indicated. See Figure 3 for atom numbering. ^b For comparison purposes please note that the carbon envelope twist angle is defined differently here and in ref 12.

the oxygen half-chair. If substituent interaction dictates ring conformation, the order of conformer stability should follow this sequence. If nonbonded, lone-pair interactions among themselves or with substituents are most important, the oxygen and carbon-oxygen half-chairs should be most stable. Furthermore, as substituents increase in size these factors should magnify themselves and provide insight into the relative importance of these factors. It should be noted that only the carbon half-chair conformer has clearly defined axial and equatorial substituent positions.

Results

The results for the monosubstituted primary ozonides are summarized in Table II. Since the substituent

**Figure 4.** Conformational energies for 3-methyl-1-butene primary ozonides.

in dictating ring conformation, followed by substituent-substituent interactions. The other point to note is that as the substituent size increases, the stability of the equatorial position decreases; this is the case for the *tert*-butyl group for each conformer; this will become more important for the disubstituted compounds. Typical results for 3-methyl-1-butene are shown in Figure 4.

Table II. Summary of Results for Monosubstituted Primary Ozonides^a

Substituents	Carbon half-chair		Carbon-oxygen half-chair ^b		Oxygen half-chair		Carbon envelope			
	Twist angle, deg	E, kcal/mol	Twist angle, deg	E, kcal/mol	Twist angle, deg	E, kcal/mol	Twist angle, deg	E, kcal/mol		
Methyl	a	nm ^b	1a	nm	15	<0.5	nm			
	e	10	0.6	1e	10	<0.5	15	0.8	10	0.6
				2a	nm		15	0.9	nm	
				2e	15	0.9	nm		10	<0.5
Ethyl	a	nm	1a	nm	15	<0.5	nm			
	e	10	1.0	1e	10	1.0	15	0.7	10	1.3
				2a	nm		15	0.9	nm	
				2e	15	1.8	nm		10	<0.5
Isopropyl	a	nm	1a	nm	15	0.7	nm			
	e	10	1.4	1e	10	0.9	15	<0.5	10	1.2
				2a	nm	nm	nm	nm	nm	
				2e	15	1.8	15	1.2	15	1.3
<i>tert</i> -Butyl	a	nm	1a	nm	15	<0.5	nm			
	e	10	<0.5	1e	10	<0.5	15	0.8	10	<0.5
				2a	nm		15	0.8	nm	
				2e	10	0.7	nm		10	<0.5

^a Energies in kcal/mol below planar conformations; nm = no minimum. ^b Conformers labeled a and e include pseudoaxial and pseudo-equatorial. See text.

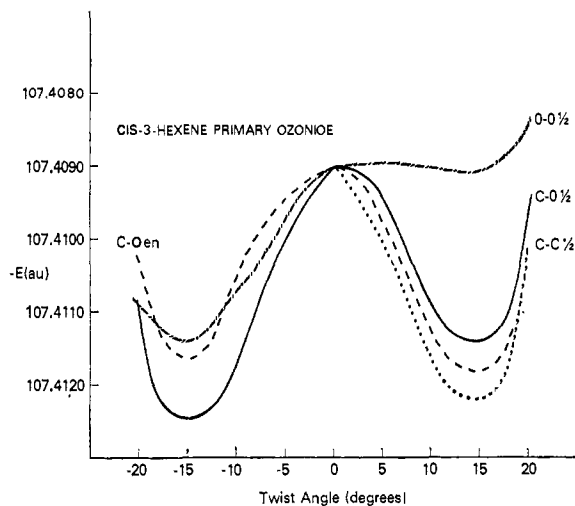
orientations on each carbon are in general different, there are four possible substituent positions; the carbon half-chair has two positions by symmetry. The conformers are distinguished by labeling the carbon atom and the (pseudo) axial or (pseudo) equatorial position. The pseudoaxial or pseudoequatorial positions are determined by measuring the movement of the group away from the center of the ring. For each compound either the carbon-oxygen half-chair or the oxygen half-chair is most stable, followed by the carbon half-chair and carbon envelope. The results indicate that substituent-lone pair interactions are most important

The disubstituted primary ozonide results are presented in Table III. These results show that the trends suggested in the monosubstituted compounds are accentuated in the disubstituted compounds. Again the axial and equatorial positions are only well defined for the carbon half-chair; the other axial and equatorial designations are only approximate. The *cis* configurations for methyl and ethyl substituents exhibit minima, but the isopropyl and *tert*-butyl do not. The steric interactions between isopropyl and *tert*-butyl groups with themselves in a *cis* position is so large as to render these conformers unstable. The results of *cis* methyl

Table III. Summary of Results for Disubstituted Primary Ozonides

Substituents	Carbon half-chair		Carbon-oxygen half-chair		Oxygen half-chair		Carbon envelope	
	Twist angle, deg	$E,^a$ kcal/mol	Twist angle, deg	$E,^a$ kcal/mol	Twist angle, deg	$E,^a$ kcal/mol	Twist angle, deg	$E,^a$ kcal/mol
Methyl								
cis ^b	15	1.8	15	1.3	15	<0.5 ^d	15	1.6
trans ^c (e,e)	15	1.6	-15	2.0	-15	1.7	-15	1.4
(a,a)	nm		15	1.3	15	0.9	15	<0.5
			nm		-15	<0.5	nm	
Ethyl								
cis	15	1.9	15	1.6	15	<0.5	15	1.8
trans (e,e)	10	1.4	-15	2.3	-15	1.3	15	1.3
(a,a)	nm		15	1.4	15	0.9	15	1.3
			nm		-15	<0.5	nm	
Isopropyl								
cis	nm		nm		nm		nm	
trans (e,e)	nm		nm	nm	nm		nm	
(a,a)	nm		-5	0.9	-15	1.5	-5	<0.5
<i>tert</i> -Butyl								
cis	nm		nm		nm		nm	
trans (e,e)	nm		nm		nm		nm	
(a,a)	-10	1.8	-10	1.9	-15	2.0	-10	1.8

^a Energies in kcal/mol below planar conformation; nm = no minimum found. ^b Positive cis angles have equatorial substituents on carbon 1 and axial substituents on carbon 2; negative angles have axial substituents on 1, equatorial on 2. See test for discussion of axial and equatorial designations. ^c Positive trans angles refers to (e,e) conformers; negative angles to (a,a). ^d The cis dimethyl primary ozonide results appear reversed here (compared to report in ref 12). This is due to more precise reporting of which C has equatorial substituent here. Both reports are the same.

Figure 5. CNDO/2 results of *cis*-3-hexene primary ozonide.

compounds indicated that the four conformers are very close in energy; all fall in a 0.4 kcal/mol range; the most stable conformers are the carbon and carbon-oxygen half-chairs. The *cis* diethyl conformers show a similar trend (see Figure 5).

The trans disubstituted primary ozonides are most interesting in that the stability of the compounds switches from (e,e) to (a,a) conformers as the substituents increase in size. There is also a clear trend toward the stability of the oxygen half-chair conformer as the substituents increase in size. Again the four conformers are close enough in energy that the molecule would not exist primarily in one conformation. The results for the trans disubstituted compounds are shown in Figure 6.

The disubstituted results also indicate that lone-pair interactions play a major role in dictating conformational stability. Only in the case of the *cis* diisopropyl and *tert*-butyl compounds were the substituent interactions predominant. In the other cases carbon-

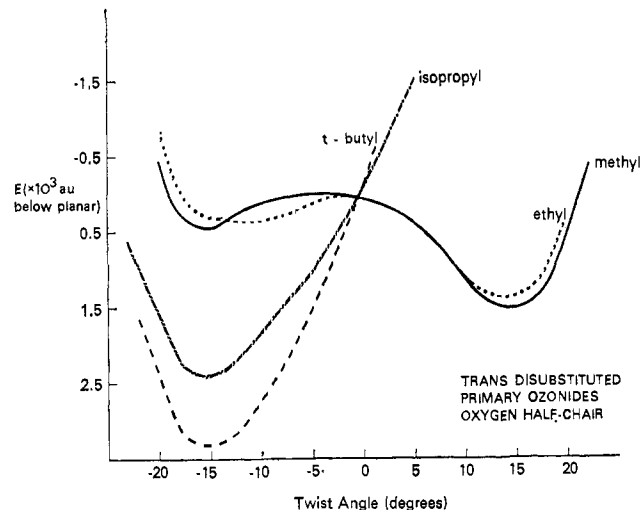


Figure 6. Energies of the trans disubstituted primary ozonides oxygen half-chair.

oxygen and oxygen half-chairs are favored indicating that lone-pair interactions are important and in the trans diaxial isopropyl and *tert*-butyl dominant.

In addition to the assertion of a preferred primary ozonide conformer by the Bailey, *et al.*, proposal, it is postulated that the zwitterion formed on ring fission will preferentially move to syn (from axial substituents) or anti (from equatorial substituents). Therefore after the zwitterion is formed, the substituent will be rotated into a syn or anti configuration. To check this assumption, two substituted zwitterions, methyl and *tert*-butyl, were studied by calculating their energy as a function O-O-C-R dihedral angle. These calculations, using bond lengths and bond angles from the ozonide ring to reflect O⁻-O-C⁺-R geometries, are summarized in Figure 7 and Table IV. They indicate that a substituent will move to an anti configuration if the initial O-O-C-R angle is greater than 90° and to a syn configuration if the angle is less than 90°. Now a study

Table IV. Summary of Results of Methyl and *tert*-Butyl Zwitterions. Energies in kcal/mol below 90° Dihedral Angle (O-O-C-R) Configurations

Minima, deg	Methyl	<i>tert</i> -Butyl
0	13.6	14.4
180	11.1	12.2

of the O-O-C-R angles in the primary ozonide conformers indicates that all the conformers will tend to form anti zwitterions regardless of axial or equatorial substituent positions. In other words *all* O-O-C-R dihedral angles are greater than 90° for all the conformers of the primary ozonide molecules studied here. The greater stability of the syn conformers strongly indicates hydrogen bonding.

The results presented thus far do not include consideration of the O-adjacent-to-carbon (O(adj-C)) envelope which has been suggested by Kuczkowski, *et al.*,³ as the possible transition state for the fission of the primary ozonide ring. In order to comment on this recent development, the O(adj-C) envelope conformer was studied for propylene and *cis*- and *trans*-2-butene primary ozonides. For propylene primary ozonide, the only O(adj-C) envelope showing energy less than planar was the one with an equatorial methyl group on the carbon next to the envelope oxygen; it was 0.9 kcal/mol below planar. For *cis*-2-butene primary ozonide the conformer with the equatorial methyl on the carbon next to the envelope oxygen (1.7 kcal/mol below planar) was most stable; the other *cis* conformer showed a small minimum (<0.5 kcal/mol). The diequatorial *trans*-2-butene primary ozonide was the stable O(adj-C) envelope conformer (1.1 kcal/mol below planar); the diaxial conformer showed no energy lower than planar. All of these conformers exhibited 15° twist angles (between the C₂-O₃-O₅-O₁ and O₅-O₄-C₁ planes) for the minimum energy. These results indicate that this envelope will be an important conformer and should be included in any further studies, but do not change the conclusions presented above. With respect to the Kuczkowski, *et al.*, mechanism, the results agree with their propylene and *cis*-2-butene conclusions, but not with their speculations of the greater stability of the diaxial *trans*-2-butene conformer. Also a study of O-O-C-R angles in this conformer implies that no syn zwitterions would be formed upon ring fissions.

Conclusion

A consideration of the 8 most important conformers of a series of 12 substituted primary ozonides using an improved geometry and the CNDO/2 method indicates that several conformers of the five-membered ring are close in energy. Hence a sample of a primary ozonide would be expected to be composed of a mixture of

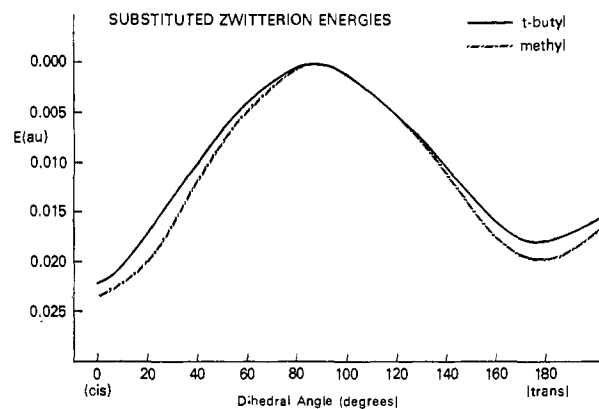


Figure 7. Zwitterion conformational energies.

several conformers, with no one conformer in the majority. Furthermore it is difficult to identify clear-cut axial and equatorial positions in many of the conformers present and it is difficult to apply the Bailey, *et al.*, rules unambiguously to these conformers. In addition the study of zwitterion conformational maps indicates that any substituent, axial, equatorial, or in between, will twist to form anti zwitterions upon ring fission, all ring O-O-C-R angles being greater than 90° in the most stable form of each conformer of each compound studied.

The evaluation of which ring interactions are most important in determining ring conformations leads to the order of lone-pair interactions being greater than substituent interactions. The greater stability of oxygen and carbon-oxygen half-chairs establishes this relation.

As Kuczkowski, *et al.*, have pointed out, the transition state for ring fission may not correspond to one of the low-energy conformers which have been identified by these calculations. In fact the potential surface on which the primary ozonide molecules move during pseudorotation is so flat that the fission probably occurs in a variety of conformations—some perhaps will be further from planar than the minimum energy conformers discussed above and yield preffission O-O-C-R angles within the ring that will lead to syn zwitterions. These other transition states will lead to ring fissions as consistent with orbital symmetry arguments as the oxygen-adjacent-to-carbon envelope and will not put the entropy constraints on the reaction that postulating a single conformational pathway for the reaction will.

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