C.—Crotyl *m*-tolyl sulfide (3.4 g) and 15.0 g of distilled quinoline was refluxed under nitrogen for 6 hr at 234°. The pyrolysate was taken up in ether, washed with aqueous hydrochloric acid, extracted with sodium hydroxide (10%), and dried over anhydrous magnesium sulfate. The base extracts were acidified and taken up in ether. The ether extracts were combined and dried over anhydrous magnesium sulfate. After filtering, the solvent was evaporated to give 0.24 g (7.1%) of *m*-tolyl mercaptan. Evaporation of the solvent from the original ether solution gave 2.81 g (82.1%) of an oil, which on distillation yielded 1.82 g of 4,7-dimethyl-1-thiachroman, bp 81–83° (0.8 mm), $n^{24.0}_{\mathrm{D}}$ 1.5716.

Anal. Calcd for $C_{11}H_{14}S$: C, 74.10; H, 7.91; S, 17.99. Found: C, 74.06; H, 7.72; S, 18.06.

The nmr spectrum for 4,7-dimethyl-1-thiachroman showed ten peaks split between τ 8.12 and 9.26 attributed to the C-4 methyl, a singlet at τ 7.86 for the C-7 methyl, 13 peaks split between τ 6.12 and 7.5 for the thiopyran ring, and finally the aromatic ring protons split between τ 3.01 and 3.44.

Synthesis of β-Methylallyl Phenyl Sulfide.—The reaction of thiophenol with β-methylallyl chloride was carried out according to the procedure of Cope, Morrison, and Field[26]: bp 89° (3.4 mm), $n^{23.5}_{\mathrm{D}}$ 1.5605.

The nmr spectrum (neat) showed one peak for methyl at τ 8.24, a singlet for methylene at τ 6.61, a singlet at τ 5.22 for the terminal $=CH_2$, and the aromatic ring protons split between τ 2.58 and 2.99.

Pyrolysis of β-Methylallyl Phenyl Sulfide.—β-Methylallyl phenyl sulfide (6.0 g) was heated in a Pyrex tube at 310° for 1.75 hr. The pyrolysate taken up in ether, extracted with sodium hydroxide (10%), and dried over anhydrous magnesium sulfate. These extracts were combined, acidified, and extracted with ether. The ether extracts were combined and dried over anhydrous magnesium sulfate and filtered, and the solvent was evaporated to yield 0.3 g (5.0%) of thiophenol. Table III shows results from several runs.

The solvent was evaporated from the original ether layer to give 5.5 g (91.4%) of a red oil, which on distillation yielded 3.1 g (51.0%) of 2,2-dimethyl-1-thiacoumaran, bp 102–105° (2.4 mm), $n^{26.0}_{\mathrm{D}}$ 1.5625.

Anal. Calcd for $C_{10}H_{12}S$: C, 73.10; H, 7.50; S, 19.50. Found: C, 72.93; H, 7.60; S, 19.25.

The nmr spectrum showed a singlet for one methyl group at τ 9.01, a singlet for the other methyl at τ 8.16, a methylene peak at τ 7.25, and the aromatic ring protons split between τ 2.67 and 2.90.

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Observations Regarding the Mechanism of Olefin Epoxidation with Per Acids

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A strong similarity is to be observed between the reactivity parameters and general kinetic characteristics of the two typical olefin reactions, epoxidation with per acids and adduct formation with 1,3-dipolar reagents. This comparison is made the basis for proposing an epoxidation mechanism involving 1,3-dipolar addition of a hydroxycarbonyl oxide reagent (derived from the per acid) to the olefinic dipolarophile. Direct experimental evidence which can be construed to support this proposal has been obtained in studies of cases where a carbonyl oxide, generated from a molozonide, can be displaced from its association with the indigenous carbonyl component by the (added) olefin. In such cases a good yield of epoxide can be realized. The epoxidizing activity of other agents (which do not form per acid under the reaction conditions) can also be reconciled with a carbonyl oxide intermediate. Other details of the proposed epoxidation mechanism are also discussed.

The "molecular" mechanism of epoxidation by per acids, first suggested by Bartlett[1] and developed by others,[2] has been a very useful guide for interpreting the course of many epoxidations reported in the literature of the last decade.[3] However, it must be recognized that very important advances in our understanding of the details of molecular mechanisms (in general) have recently developed from the elegant studies of Huisgen and his co-workers.[4] 1,3-Dipolar addition reactions[5] comprise one of the most typical classes of "molecular" reaction mechanisms. Furthermore, many of the reactivity parameters and general kinetic characteristics which have been identified by various groups of workers[2,3] in studies of the per acid epoxidation mechanism show strong parallelism to the related properties of 1,3-dipolar addition examples studied in the same depth.[4]

The relatively small negative value of the Hammett ρ constant (-0.8) has been interpreted by Lynch and Pausacker[2a] as supporting the Bartlett mechanism.[1] However, Criegee[6] has shown that the reaction of olefins with ozone, a reaction recognized as possessing a typical 1,3-dipolar mechanism, is also characterized by a relatively small (olefin) substituent effect.[6,7] The noted absence of general acid catalysis and neutral salt effects,[2] which was also construed by Lynch and Pausacker[2a] as support for the accepted molecular mechanism,[1] is quite in keeping, as well, with the concerted transition state of a 1,3-dipolar addition course.[4]

At first glance, the relatively low response of rate to solvent polarity, established by Huisgen and coworkers[4] for the general case of 1,3-dipolar addition and by others[8,9] for the case of molozonide formation

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(1) P. D. Bartlett, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **18**, 111 (1957).

(2) (a) B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.*, 1525 (1955); (b) see also N. N. Schwartz and J. H. Blumbergs, *J. Org. Chem.*, **29**, 1976 (1964); M. Vilkas, *Bull. Soc. Chim. France*, 1401 (1959).

(3) For reviews of the earlier literature and earlier interpretations attributing electrophilic character to the epoxidation mechanism, see D. Swern, *Org. Reactions*, **7**, 378 (1953); *J. Am. Chem. Soc.*, **69**, 1692 (1947); A. Robertson and W. A. Waters, *J. Chem. Soc.*, 1574 (1948).

(4) See, for a complete discussion, reviews by R. Huisgen: (a) *Angew. Chem.*, **72**, 359 (1960); (b) *Proc. Chem. Soc.*, 357 (1962); (c) *Ann.*, **658**, 169 (1962); (c) *Angew. Chem.*, **75**, 604 (1963); (e) *ibid.*, **75**, 742 (1963).

(5) L. I. Smith, *Chem. Rev.*, **23**, 193 (1938).

(6) For a thorough discussion of the mechanism of ozonolysis and references to the experimental basis of these conclusions, see (a) R. Criegee, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **18**, 111 (1957); (b) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

(7) T. Vrbaski and R. J. Cvetanović, *Can. J. Chem*, **38**, 1053 (1960).

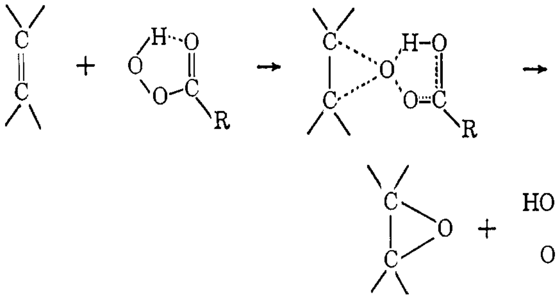
(8) F. L. J. Sixma, H. Boer, and J. P. Wibaut, *Rec. Trav. Chim.*, **70**, 1005 (1951).

(9) T. W. Nakagawa, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **82**, 269 (1960).

resulting from olefin reaction with ozone, appears to be inconsistent with analogous observations of solvent effects in epoxidation. Thus, in perbenzoic acid epoxidation Lynch and Pausacher[2a] have reported an approximately 30-fold rate advantage for the reaction of cyclohexene in solvent benzene *vs.* solvent ether. The explanation, however, lies in the fact that solvent nature exerts an important influence on the hydrogen bond in per acids. In benzene the intramolecular hydrogen bond is fostered and leads, consequently, to a greater equilibrium concentration of the only form of perbenzoic acid purported to be reactive in epoxidation (see Scheme I). In ether intramolecular hydrogen bonding competes poorly with the intermolecular bond to the basic oxygen center of the solvent ($RC(=O)OOH$----OEt_2) and thus diverts material from the essential equilibrium peroxidation reagent. Thus, the solvent effect in epoxidation is not related to a solvent influence in the transition state.

SCHEME I

BARTLETT'S MECHANISM OF PER ACID EPOXIDATION



Ordinarily, solvent striction effects, even in a transition state of low polarity, can be correlated with the occurrence of an increasingly negative entropy of activation of the reaction in the more polar solvents. In fact, the data of Lynch and Pausacker would suggest that the more polar solvent is associated with the (somewhat) less negative ΔS^*. The generally large negative values of ΔS^* ($-18 \rightarrow -25$ eu for all the cases reported by Lynch and Pausacker)[2] are readily accorded with the concerted transition state in the 1,3-dipolar reaction.

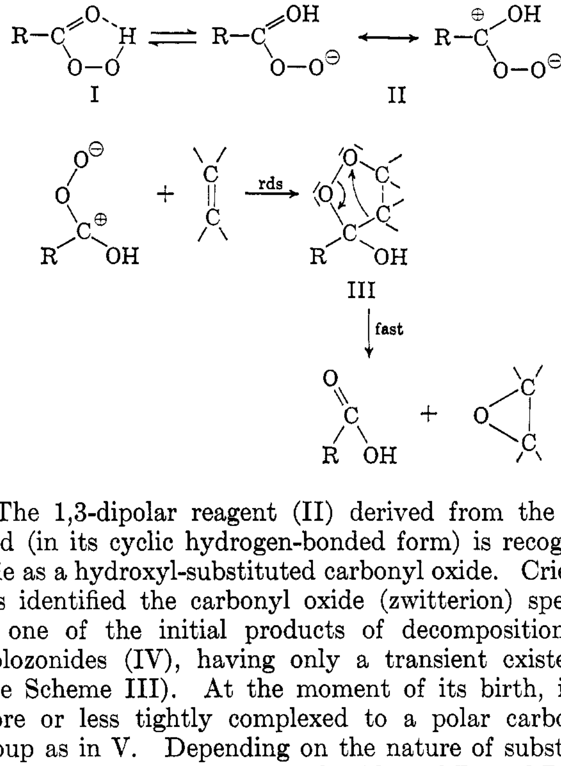
Finally, it has been emphasized by Swern in his very informative summary[3] that only in highly methylated double bonds is any significant acceleration of the epoxidation rate in solution to be noted. It is apparently no coincidence that this "methyl" effect is also characteristic of the ozonization reaction[7] assumed by Criegee[6] and Huisgen[4] to be a 1,3-dipolar addition. Huisgen,[4] in fact, has stressed that, among alkylated, acyclic, and cyclic olefins, the 1,3-dipolar addition reaction occurs most readily with the most strained dipolarophiles; the reaction has even attained the status of a diagnostic tool for double-bond strain in alicyclic and bicyclic systems. Analogously, it has been demonstrated[2] that the distorted double bond in *cis*-stilbene undergoes epoxidation more rapidly than its completely planar *trans* isomer.

Results and Discussion

The discussion above has presented only a very condensed inventory of the evidence that establishes a close parallel of the per acid epoxidation and the reaction of a 1,3-dipolar reagent with an olefinic dipolarophile. These considerations lead to the suspicion that per acids (or easily formed derivatives thereof) are capable of 1,3-dipolar activity and, consequently, the mechanism of epoxidation has a characteristic 1,3-dipolar transition state. In this report we wish to describe such a per acid epoxidation mechanism (Scheme II) and to present certain lines of experimental evidence that are in consonance with and afford a measure of plausibility to it (as follows).

SCHEME II

PROPOSED 1,3-DIPOLAR MECHANISM OF OLEFIN EPOXIDATION



The 1,3-dipolar reagent (II) derived from the per acid (in its cyclic hydrogen-bonded form) is recognizable as a hydroxyl-substituted carbonyl oxide. Criegee has identified the carbonyl oxide (zwitterion) species as one of the initial products of decomposition of molozonides (IV), having only a transient existence (see Scheme III). At the moment of its birth, it is more or less tightly complexed to a polar carbonyl group as in V. Depending on the nature of substitution R_1 and R_2 on the carbonyl oxide and R_3 and R_4 on the complexing carbonyl center, either or both of two types of covalent products can be formed, the isozonide VI or dimeric polymeric peroxides VII.

The existence of molozonide IV at −78° was confirmed by Criegee and Schröder[10] in the case of *trans*-di-*t*-butylethylene and by Greenwood[11] using several other olefins. It is not possible to consider all the data obtained by these and other workers confirming the path of molozonide formation through reaction with various reducing agents and leading to the inference of a carbonyl oxide complex V. However, two items of their evidence can be stressed. Firstly, in the *trans*-di-*t*-butylethylene-derived complex V, the carbonyl component can be replaced by another (externally added) carbonyl compound, suggesting the indicated equilibrium between IV and V (see Scheme III), or some form of solvent cage encompassing the two moieties and restricting their freedom of action (recently evaluated[12] by means of cross-ozonide experiments). However, the replacement of $R_3R_4C{=}O$

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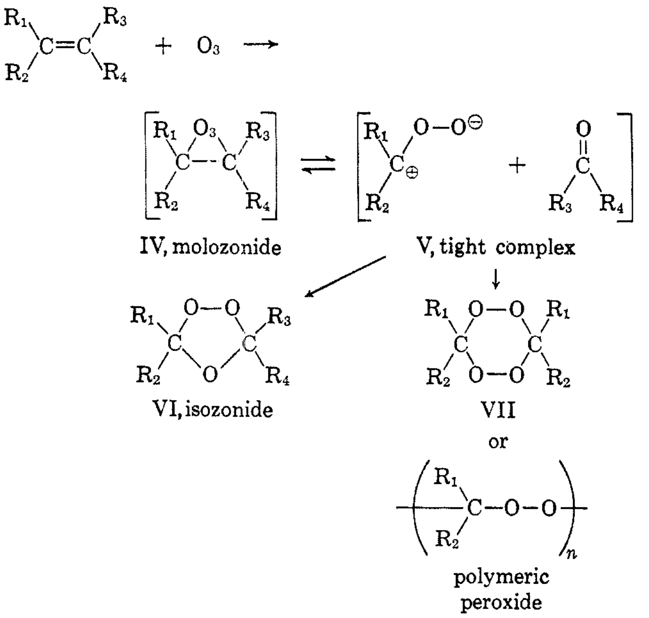
[10] R. Criegee and G. Schroder, *Chem. Ber.*, **93**, 689 (1960).

[11] F. L. Greenwood, *J. Org. Chem.*, **29**, 1321 (1964).

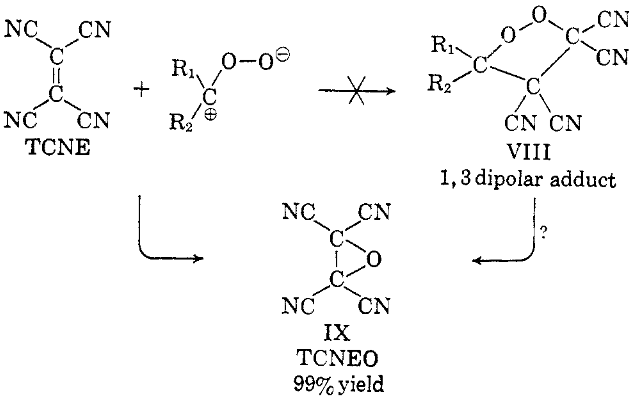
[12] L. D. Loan, R. W. Murray, and P. R. Story, *J. Am. Chem. Soc.*, **87**, 737, 3025 (1965).

Scheme III

Criegee Ozonization Mechanism



Scheme IV



in V by an olefin donor such as $R_3R_4C{=}CH_2$ apparently does not occur readily, since ozonizations in the presence of excess of olefin have not reported the products to be anticipated from such a metathetical displacement. Apparently, under ordinary circumstances, olefin donors cannot displace a carbonyl component from its cage interaction[12] with the zwitterion reagent. Furthermore, Greenwood's work[11] confirms that not all molozonides are so stable at $-78°$ as in the *trans*-di-*t*-butylethylene case, and, moreover, the molozonides of *cis* olefins are considerably less stable than those of *trans* olefins.

Seeking proof that the transition of molozonide IV to isozonide VI actually proceeded through the carbonyl oxide V (and that the carbonyl oxide, indeed, is a 1,3-dipolar reagent), Criegee and Gunther[13] ozonized several olefins at $-78°$ in the presence of TCNE (tetracyanoethylene). Since TCNE is not attacked by ozone under these conditions, they expressed[13] the hope of trapping the product of addition of the 1,3-dipolar carbonyl oxide to the excellent dipolarophile, TCNE, as the adduct VIII. The only product of reaction, however, in addition to the carbonyl compounds expected from the decomposition of the molozonide, was tetracyanoethylene oxide (TCNEO) formed in near quantitative yield. Whether the TCNEO arose from the direct oxidative attack of the molozonide on the TCNE (a reaction that can be carried out with other oxidants as well) or from the actual formation of the adduct VIII followed by breakdown to the carbonyl product, $R_1R_2C{=}O$, and TCNEO was not determined. (See Scheme IV.)

The experimental work being reported here was in progress for about 1 year when Criegee's experiments[13] on the reaction of molozonide with TCNE were first disclosed. Our original plan was to generate a series of carbonyl oxides $R_1R_2\overset{\oplus}{C}{-}O{-}O^{\ominus}$ possessing various substituents, R_1 and R_2. It was assumed[14] that the complex (V) of the zwitterion species and carbonyl compound could be separated into its components (prior to recombination with formation of VI and VII) only if R_1 and R_2 conferred sufficient stability of the 1,3-dipolar moiety and if the substituents of the carbonyl component, R_3 and R_4 in V, reduced its complexing ability. The most recent data[12] would appear to indicate that the degree of interaction between the components of V depends upon the polar nature and the bulk of all the groups R_1, R_2, R_3, and R_4. In other words, if the carbonyl oxide were sufficiently stabilized against dimerization or polymerization, and if the complex V was extensively dissociated, some olefin capable of dipolarophilic activity, when added to the molozonide, could conceivably trap it by conversion to the 1,3-dipolar adduct precursor of oxide (according to Scheme II).

In this article we propose to discuss only our results with two olefinic dipolarophiles representing the widest range of activity within which we could anticipate measurable differences in behavior. The weaker dipolarophile used was norbornene having a strained double bond previously diagnosed[4b] as very active toward phenyl azide in 1,3-dipolar addition. The strongest dipolarophile used was TCNE which owes its great activity to its widely recognized[15] abilities as an acceptor agent in formation of molecular complexes. If any olefinic reagent was capable of intercepting the unstable carbonyl oxide before it could undergo irreversible dimerization and polymerization, TCNE gave greatest promise of achieving this.

The data listed in Table I were obtained by passing a stream of ozone through a solution containing olefin substrate to be converted to molozonide at Dry Ice (or lower) temperature. When an aliquot of ozone had been absorbed, an excess of the olefinic dipolarophile was added, after which the entire mixture was permitted to warm slowly to room temperature. The solution was then analyzed by various means for the presence of the oxide. When norbornene served as the dipolarophile, vapor phase chromatography afforded an excellent method for determining the extent (of theory) to which it had been converted to oxide (compared with an appropriate control run). When TCNE functioned as the added dipolarophile, the reaction mixture was analyzed for TCNEO by a combination of gravimetric and titrimetric methods which are commonly used for these substances. All the in-

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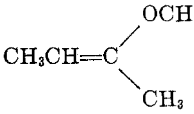
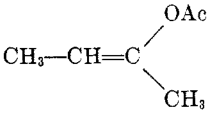
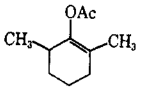
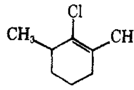
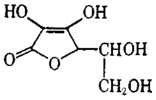
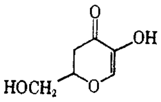
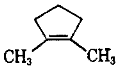
[13] R. Criegee and P. Gunther, *Chem. Ber.*, **96**, 1564 (1963).

[14] As convincingly shown earlier by R. Criegee, G. Blust, and H. Zinke, *ibid.*, **87**, 766 (1954).

[15] R. E. Merrifield and W. D. Phillips, *J. Am. Chem. Soc.*, **80**, 2778 (1958).

TABLE I

EPOXIDATION *via* CARBONYL OXIDES

Olefin source of the molozonide precursor	% conversion[a] to epoxide of the dipolarophile					
	TCNE	Solvent[b]	Temp, °C	Norbornene	Solvent[b]	Temp, °C
$(CH_3)_2C{=}CHCH_3$	. . .	. . .	. . .	0	A, D	−78
 $CH_3CH{=}C(OCH_3)(CH_3)$	. . .	. . .	. . .	0	(B)	−78
 $CH_3{-}CH{=}C(OAc)(CH_3)$	60	E	−78	0	A, B, C. D	−78
Norbornene	. . .	. . .	. . .	0	B	−78
	70	E	−78	0	C	−78
	53	E	−78	0	C, D	−78
	. . .	. . .	. . .	30–35[c]	D	−78
	. . .	. . .	. . .	5[c]	D	−78
$CH_3COCH_2COCH_3$	75	E	−78	12–15[c]	C	−78
$(CH_3)_2C{=}C(CH_3)_2$	98[d]	E	−78	0	B	−115
$CH_3(CH_2)_3CH{=}CH_2$	. . .	. . .	. . .	0	B	−115
	89[d]	E	−78	. . .	. . .	. . .
$C_6H_5{-}CH{=}CHC_6H_5$	85[d]	E	−78	. . .	. . .	. . .
	86[d]	E	−78	. . .	. . .	. . .

[a] Zero per cent is experimentally less than 1%. [b] Solvent: A, heptane; B, pentane; C, methylene chloride; D, dimethylformamide; and E, ethyl acetate. [c] These are apparently low figures since complete epoxidation cannot be achieved with norbornene for several reasons. First, the enolic olefin cannot be ozonized in the presence of norbornene, thus giving the molozonide time to decompose partially even at −78° (see ref 11 and 16). Second, the norbornene had to be added to the DMF solutions in suspension owing to its lack of solubility in this solvent at the low temperatures. [d] Results of Criegee in ref 13.

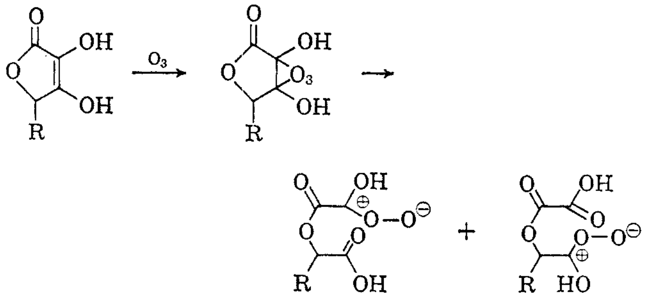
stances of formation of TCNEO in the experiments described by Criegee[13] have been included in Table I for comparison with our results. These are to be regarded (in his interpretation) as direct evidence for the occurrence of the molozonide intermediate in ozonization of the respective olefins.

The data listed in Table I demonstrate conclusively that only enols or substances which readily tautomerize into enols form carbonyl oxides which can epoxidize norbornene. The greatest amount of norbornene oxide is formed when ascorbic acid is ozonized in DMF at −78°. Lesser amounts of epoxidation are observed in the cases of acetyl acetone and kojic acid. Apparently, the formation of norbornene oxide can be correlated only with the opportunity to form a hydroxy-substituted zwitterion species, $\mathrm{RH\overset{\oplus}{O}C{-}O{-}O^{\ominus}}$. This, it will be seen, is the substance proposed (Scheme II) to be the active agent in epoxidation with peroxy acids. Ascorbic acid molozonide has no choice but to form hydroxylcarbonyl oxide and, consequently, the highest yields of norbornene oxide are associated with this unidirectional cleavage (see Scheme V). The molozonides of acetyl acetone and kojic acid can be transformed to carbonyl oxide in two alternative ways, only one of which results in a hydroxy-substituted zwitterion capable of epoxidizing norbornene.

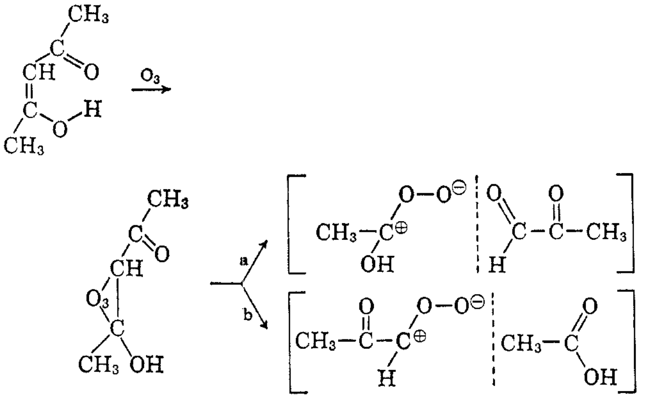
It cannot be said with certainty that cleavage path a (Scheme VI) for the molozonide would be preferable to path b because of the greater stability of its hydroxycarbonyl oxide. However, recent evidence would suggest that the two alternative cleavage modes are manifest even in the case of simple olefins.[12]

The failure of all other functionally substituted carbonyl oxides (listed in Table I, such as OAc, OCH_3, Cl, and C_6H_5,) to produce epoxidation of norbornene might be attributed to several (not unrelated) causes. In all cases except that of the hydroxyl substituent, the carbonyl oxide is too tightly caged with the conjugate carbonyl component. Norbornene represents a much weaker complexing agent in competition with the indigenous carbonyl. The hydroxycarbonyl oxide appears to possess a special element of stability that frees it from the embrace of the counter-carbonyl compound. This stability may originate from both

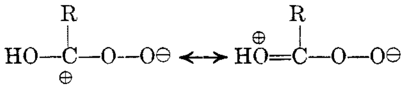
SCHEME V



SCHEME VI



the unusually high electron release of the hydroxyl function, as in



$$HO-\overset{R}{\underset{\oplus}{C}}-O-O^{\ominus} \longleftrightarrow H\overset{\oplus}{O}=\overset{R}{C}-O-O^{\ominus}$$

and/or it may be the consequence of the internal hydrogen-bond stabilization to which reference has been made in Scheme I.

On the basis of the very instructive work of Greenwood,[11,16] it must be considered highly possible that many of the failures to epoxidize norbornene noted in Table I can be correlated with the premature decomposition of the molozonide (*i.e.*, before addition of norbornene). That this may *be partly but not entirely* the case, however, is to be perceived from the following illustration.

When 1-methoxy-2,6-dimethylcyclohexane and 1-chloro-2,6-dimethylcyclohexene were ozonized at −78° in methylene chloride solvent, the reaction was warmed to room temperature, and TCNE was then added (as a solution in CH_2Cl_2), there was no TCNEO to be found. On the other hand, when the same ozonolyses were carried out at −78° in ethyl acetate, and the TCNE in ethyl acetate was added in the cold (−78°) prior to warming to room temperature, 25–40% of the theoretical amount of TCNEO could be isolated. When the TCNE was present during the ozonolysis, yields of more than 70% TCNEO were found (although the 99% yields obtained under similar circumstances by Criegee[13] with cyclohexene itself were never realized). Thus, as much as 40% of the necessary molozonide persisted in solution after the ozonolysis was effected at −78° and could react with the TCNE. Since the addition of norbornene under these identical conditions gave no oxide, it must be judged incapable or far less capable than TCNE of displacing the carbonyl moiety of the molozonide complex V, the event postulated to be the prelude to oxide formation (Scheme II).

A further indication that the carbonyl oxides derived from the nonenolic olefins (we have examined) are incapable of epoxidizing ordinary olefinic dipolarophiles is the lack of self-epoxidation. Thus, when olefins such as norbornene or tetramethylethylene (which are readily epoxidized with per acids) are subjected to partial ozonization at −78°, it is not possible to detect any oxide formation. The use of temperatures as low as −115°, where most molozonides possess a measureable lifetime, does not alter these results (see Table I).

Finally, some comment on the ease of decomposition of the proposed 1,3-dipolar adduct (III) in Scheme II seems to be in order. A good parallel may be drawn here to the instability of peroxy acids, contrasting in this respect with their corresponding peroxy esters.[17–19] A number of authors,[20–22] pointing to the evidence of strong, intramolecular (cyclic) hydrogen bonding in the per acids, have suggested that the instability is indicative of the weakness of the O–O bond caused by the chelation. Dipole moment measurements[20,23] have established that the development of this five-membered ring interaction has twisted the O–O bond out of its stable skew configuration of nonbonding p orbitals; *i.e.*, the resulting twist results in great repulsions on bringing the lone-pair orbitals of the two (bonded) peroxy oxygen atoms face to face. It will be seen, analogously, that the cyclic peroxide adduct III possesses this element of instability to an even greater degree since the -O-O- bond is incorporated in a five-membered ring with even shorter bonding distances and a stronger tendency to planarity. The tendency to planarity even in six-membered cyclic peroxides (such as diphthaloyl peroxide[24]) may also be invoked to account for the observed "explosive" instability.

Conclusions and Applications

Consideration of all the points elicited in the discussion above provides a basis for revision of the currently accepted mechanism of per acid epoxidation. The mechanism herein postulated, requiring the 1,3-dipolar addition of a carbonyl oxide reagent and an olefinic dipolarophile, has been found to be entirely consistent with all the available facts. The variation in stability of the (1,3-dipolar) carbonyl oxide reagent with features of substitution and the dipolarophilic activity of the olefin reagent appear to be the most important factors governing the ease of the molecular reaction by which olefins can be converted to epoxides.

It must be anticipated that other sources of carbonyl oxide reagent are to be found than per acids and molozonides. In fact, whenever olefins are

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[16] F. L. Greenwood and B. J. Haske, *Tetrahedron Letters*, 631 (1965).

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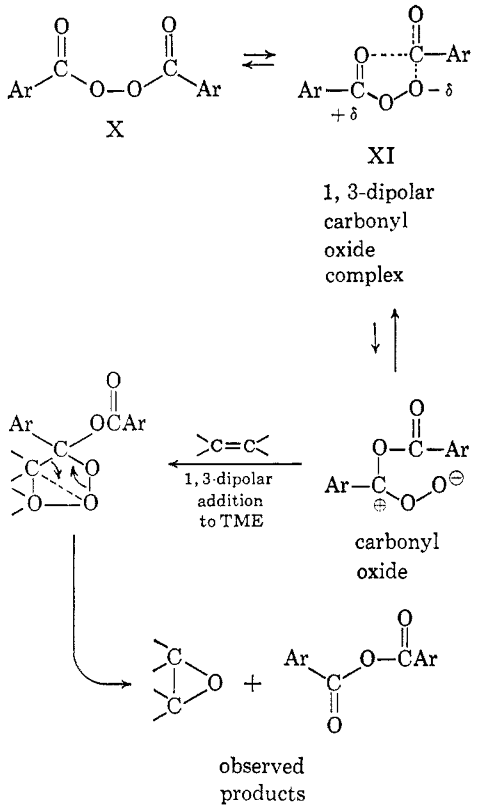
epoxidized through the agency of an unusual reagent, we may look for a carbonyl oxide intermediate formed at some juncture in the course of reaction. A case in point can be reconstructed from the observations of Greene and Adams[25] that highly susceptible (to epoxidation) olefins may be directly epoxidized by specific diaroyl peroxides (X). In our estimation, the specific activity of these peroxides can be very plausibly reconciled with the 1,3-dipolar addition mechanism of epoxidation on the assumption of an intramolecular pseudo-ester type of intermediate (XI). In this instance Greene and Adams[25] have shown that tetramethylethylene in benzene solution at 45° affords the oxide on reaction with *m,m'*-dibromobenzoyl peroxide. They have also recognized that in this reaction contributions of free-radical chain processes are negligible. This reaction may be characterized by means of the mechanistic scheme (VII), which we find to be in good agreement with both the oxygen-labeling results and all the kinetic data disclosed by Greene and Adams.[25]

SCHEME VII



Experimental Section

Infrared spectra were determined with a Perkin-Elmer Infracord. Gas chromatography was performed on an F and M Corp. Model 500 thermal-detection or Model 700 flame-ionization instrument. Ozonolyses were carried out using a Welsback Model T-25 ozonator, and nmr spectra were taken on a Varian Model A-60 or A-60A spectrometer.

2-Methoxybutene-2.—The preparation was carried out according to Kistiakowsky, *et al.*,[26] by treatment of either *cis*- or *trans*-butene-2 in methyl alcohol with solid iodine at a reaction temperature of −15°. The resulting 2-methoxy-3-iodobutane was then treated with methanolic potassium hydroxide to produce the enol ether. *trans*-Butene-2 gave a product with bp 68–70°, n^{25}D 1.4034, with two approximately equal unsaturation peaks at 1670 and 1690 cm. The product obtained with *cis*-butene-2 (bp 74–75°, n^{25}D 1.4046) had only one unsaturation band at 1700 cm^{-1}. On standing for several months, the infrared spectra changed to that of the product obtained from *trans*-butene-2.

2-Acetoxybutene-2 was prepared according to the method of Hagemeyer and Hull[27] from methyl ethyl ketone and isopropenyl acetate.

1-Methoxy-2,6-dimethylcyclohexene.—The dimethyl ketal of 2,6 dimethylcyclohexanone,[28] prepared from the ketone and methyl orthoformate, was heated in the presence of a crystal of *p*-toluenesulfonic acid, and the methanol evolved by distillation through a short column. When the theoretical amount of methanol was collected (4–5 hr), 1 g of sodium acetate was added and high vacuum distillation was applied to the residue. A small amount of unreacted ketone came over in the first fraction. The fraction boiling between 65 and 67° at 15 mm was the pure enol ether in 68% yield, n^{25}D 1.4587. The infrared spectrum displayed a single unsaturation peak at 1680 cm^{-1}. The nmr spectrum showed a singlet near 3.40 ppm, a doublet near 0.99 ppm, and a singlet near 1.57 ppm superimposed on the typical cyclohexene pattern. Integration of the peaks gave results which were very close to theoretical.

1-Chloro-2,6-dimethylcyclohexene.—A solution of 20 g of 2,6-dimethylcyclohexanone[28] in 40 ml of dry benzene was added to a refluxing solution of 100 ml of benzene containing 40 g of PCl_5, over a period of 1 hr. This solution was refluxed for an additional 3 hr. The benzene and most of the PCl_3 formed in the reaction were flashed off and the resulting oil was poured into ice-water and allowed to stand for 1 hr. The water-insoluble layer was extracted twice into pentane and dried over $MgSO_4$, and the pentane was removed by flash evaporation. The infrared spectrum of the crude material contained only a trace of carbonyl impurity and no unsaturation bands. Prolonged reflux (48 hr.) of this material with potassium *t*-butoxide in *t*-butyl alcohol gave nearly complete conversion to 1-chloro-2,6-dimethylcyclohexene: yield 15 g (66%), bp 65–67° (15 mm), n^{25}D 1.4831. The nmr spectrum showed a doublet at 1.12 ppm and a singlet (1.74 ppm) superimposed over a typical methylene chain pattern. The results on integration of the nmr peaks were very close to theoretical for the structure assumed.

Tetramethylethylene was prepared by treatment of pinacolyl alcohol with amalgamated zinc and HCl[29]: bp 72–73.5°, n^{20}D 1.4091.

Ozonolysis Procedure.—From 1 to 3 mmoles of olefin, dissolved in 1 ml of solvent and cooled in a Dry Ice–acetone bath, was ozonized by passing a slow stream of ozone (precooled by passing through a coiled Dry Ice trap) through the mixture until saturation occurred. The excess ozone was removed by flushing the solution with a slow stream of nitrogen for several minutes. A previously cooled (−78°) solution of 10–20 mmoles of norbornene in 1 ml of solvent was then added in one portion and the contents of the flask were mixed with a stream of nitrogen. The flask was raised just above the Dry Ice bath and allowed to warm slowly to room temperature. The volume of the solution was measured and a sample was analyzed by vpc for norbornene oxide content using either a Silicone Oil 200 (10 ft) or a Ucon Polar (10 ft) column.

Low-temperature (−115°) ozonolyses were carried out in pentane by keeping the solution at as low temperature as possible without solidification, using a liquid nitrogen bath. In the instances where the ozonolysis solvent was dimethylformamide, the addition of norbornene was in the form of a suspension owing to its low solubility in this solvent at Dry Ice temperatures.

In the ozonolyses involving tetracyanoethylene (TCNE), the determination of tetracyanoethylene oxide (TCNEO) was performed by titration of the iodine formed in the following reactions. Following ozonolysis, the solvent was removed under

$$\text{TCNEO} + H_2SO_4 + \text{NaI} \longrightarrow 4\text{CNI} + I^-$$

$$\big\downarrow H^+$$

$$2(CN)_2 + 2I_2$$

vacuum and the remaining solid was washed several times with small quantities of hexane to remove any ozonide formed.

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The combined hexane washings were placed in a centrifuge tube and cooled in Dry Ice. The tube was then quickly centrifuged and the liquid was poured off. The solid in the tube was twice washed with hexane, cooled, and centrifuged. The combined solids were dissolved in a small amount of isopropyl alcohol, 10% sodium iodide solution was added, and the iodine was liberated by the addition of 0.1 *N* H_2SO_4. The amount of iodine thus formed was estimated in the usual fashion by standard thiosulfate titration.

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Cycloheximide Transformations. I. Kinetics and Mechanisms in Aqueous Acid[1,2]

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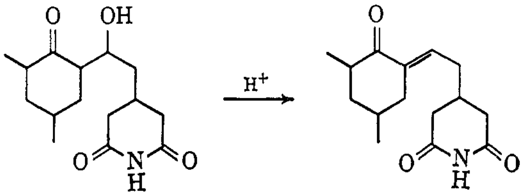
The antibiotic, cycloheximide, undergoes hydrogen ion catalyzed dehydration to anhydrocycloheximide. The mechanism is through dehydration with stereospecific rehydration. The isolated major product of rehydration is a new stereoisomer of cycloheximide and may be either α-epi-Naramycin B or α-epicycloheximide with the former assignment preferred. Hydrolyses of the imides of each of the reaction components occur simultaneously with the above mechanism but at a much slower rate. The rate-determining step in the solvolytic sequence is the hydrolysis to the acid amide. The complex equilibria among the imide, acid amide, and dicarboxylic acid forms of these three components have been quantified as functions of temperature and acidity so that the concentration of any component can be defined as a function of time with the aid of the analog computer.

The antifungal antibiotic cycloheximide (I) is unstable in acid[4] and alkali[5-8] and mild structural changes markedly alter the biological activity.[9] However, the kinetics and mechanisms of such chemical changes have not been quantified. The possible chemical transformations in aqueous solution are dehydration to anhydrocycloheximide (II), imide hydrolysis, dealdolization, and oxidation.[5] In addition, the possibility of stereochemical changes increases the complexity of the system.[6] This paper reports on a complete investigation of the kinetics and mechanisms of the transformations of cycloheximide in aqueous acid.

Results

Spectral Transformations of Cycloheximide in Acidic Solutions.—The absorbance at 245 mμ, due to the formation of the α,β-unsaturated ketone II from the dehydration of cycloheximide (I), increased as a function of time and approached a maximum (Figure 1, upper right). The average yield of anhydrocycloheximide, at this maximum, for the various temperatures was 68%, 40.0°; 70%, 50.0°; 71%, 61.8°; 72%, 70.0°; and 73%, 74.6°. The per cent yields for various hydrochloric acid concentrations were not significantly different at a given temperature. Analysis of the variance showed that this increase of yield with temperature is statistically significant ($P > 0.99$). Subsequently, the absorbance decreased at a slower rate to a minimum value.



I II (1)

First-order plots for the rate of approach to the maximum absorbance obtained at 245 mμ, A_m, were linear for two to three half-lives. Typical plots are given in Figure 2. The apparent first-order rate constants (Table I) were calculated from the slopes based on eq. 2, where A_t is the absorbance at time, *t*.

$$\ln(A_m - A_t) = -kt + \ln A_m \qquad (2)$$

The apparent first-order rate constants were directly proportional to hydrogen ion activity in agreement

$$k = k_{H^+}(a_{H^+}) \qquad (3)$$

with eq. 3, where the activities of the hydrogen ion, a_{H^+}, were calculated from the HCl concentrations (Table I) and the activity coefficients, *f*, in the literature where $a_{H^+} = f[\text{HCl}]$.[10] The catalytic rate constants, k_{H^+}, were calculated from the slopes of the plots of *k vs.* f[HCl] (Figure 3 and Table II). An Arrhenius plot of the hydrogen ion catalytic rate constants is given in Figure 4 where

$$\log k_{H^+} = -\Delta H_a/2.303RT + \log A \qquad (4)$$

The value of ΔH_a is 19.0 kcal./mole and log *A* is 13.4.

Apparent first-order rate constants for the subsequent loss of the absorbance, A_t, at 245 mμ (Figure 1, upper), were calculated from the slopes based on eq. 5,

$$\ln(A_t - A_\infty) = -k't + \text{constant} \qquad (5)$$

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[2] Abstracted in part from a thesis submitted by R. E. Notari in partial fulfillment of the requirements of Doctor of Philosophy at the University of Florida, Aug. 1964.

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