Formation of *cis* and *trans* Ozonides from Cinnamic Esters

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Formation of several *cis* and *trans* ozonides from *p*-substituted methyl cinnamates is described. No cross ozonides have been observed. The configurations were established using ¹H NMR spectroscopy. The yields of isomers were solvent dependent, the ratio approaching unity in the more polar solvents. Slight variations in isomer ratio with substituents were also observed. The isomer variations are well accomodated within the theory of *syn* and *anti* zwitterions being intermediates in ozonide formations.
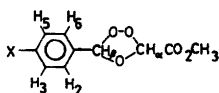
Since the discovery of *cis-trans* isomerism in ozonide formation in 1962[1] and the discovery of cross ozonides and their configurational isomerism,[2,3] the isomer distribution has been studied by several groups.[4] In a previous paper *cis* and *trans* ozonides from methyl *p*-methoxycinnamate were described.[5] The present paper deals with formation of ozonide pairs from some other methyl cinnamates. Most groups have used olefins with only alkyl substituents in their studies. Our choice of cinnamic esters as substrates was based on the fact that the stereoisomeric ozonides were crystalline compounds which fairly easily could be separated by fractional crystallization. Furthermore, changes in the electronic properties of the substrates and the ozonides could be brought about by merely changing the substituents in the *para* position of the aromatic ring, without the introduction of new steric parameters hampering the ozonide formation.

CONFIGURATION OF THE OZONIDES

Only normal ozonides were formed from the cinnamates in quantitative yields. Based on physical properties (¹H NMR, melting points,

Table 1. ¹H NMR data [a] and melting points [b] of

| X | cis | | | | | trans | | | | |
	M.p. °C	H_2+H_6 [e]	H_3+H_5 [e]	H_α	H_β	M.p. °C	H_2+H_6 [e]	H_3+H_5 [e]	H_α	H_β
NO_2	97	7.92	8.30	5.83	6.15	97	7.70	8.30	5.83	6.53
CN	[d]	7.73	7.87	5.97	6.10	77	7.60	7.78	5.82	6.48
CO_2Me	81	7.75	8.03	5.73	6.00	52	7.57	8.08	5.75	6.42
Br	74	7.58	7.58	5.80	6.02	34	7.40	7.57	5.77	6.35
Cl	60	7.65	7.43	5.80	6.03	29	7.40	7.40	5.77	6.35
H [c]	—	—	—	5.80	6.03	—	—	—	5.77	6.35
Me [c]	—	7.50	7.18	5.60	5.85	—	7.35	7.17	5.60	6.22
MeO [f]	37	7.60	6.88	5.65	5.92	64	7.42	6.90	5.62	6.20

[a] δ (CDCl$_3$). [b] M.p.'s not corrected. [c] Isomer separation not possible, see Experimental. [d] Not obtained in pure state. [e] Shifts obtained by treating the AA¹XX¹ (AA¹BB¹) pattern as AX (AB) spectra. [f] Ref. 5.
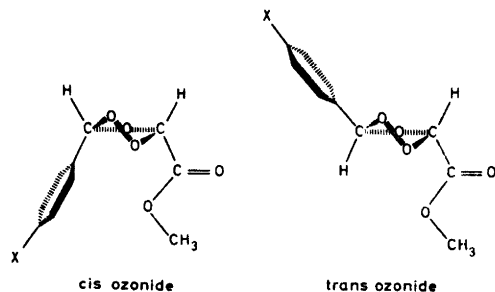
Fig. 1.

Fig. 2.

retention times in chromatography) an assignment of configuration was given for the ozonides from methyl p-methoxycinnamates,[5] later on confirmed by X-ray diffraction studies.[6] By analogy the configurations of the other *cis-trans* pairs were determined by ^{1}H NMR spectroscopy (Table 1).

The observed deshielding of the β-protons in the *trans* ozonides is probably due to the anisotropy of the carbonyl group of the ester group. A similar deshielding of the aromatic protons in the 2- and 6-positions in the *cis* ozonides (compared to the *trans* ozonides) is probably caused by the same carbonyl group [5] (Fig. 1).

MECHANISM OF THE OZONOLYSIS

There seems to be little disagreement about the first step in an ozonolysis being an 1,3-dipolar addition of ozone to the double bond. The intermediate *primary ozonide* from *cis* 1,2-di-t-butylethylene was isolated at low temperature by Bailey et al.[7]

The cleavage of this unstable primary ozonide *1* may now take two different courses, forming the zwitterion on the aromatic or the aliphatic side of the double bond (Fig. 2).

Based on the following observations we arrive at the conclusion that the zwitterion is formed predominantly on the aromatic side:

A. Only normal ozonides were observed. This should exclude the formation of both zwitterions *2* and *5* at the same time, since *5* ought to react with *3* in preference to *4*. This is in accordance with the fact that in ozonide formation aldehydes react faster than ketones, and that aldehydes with α-oxo functions react faster than aldehydes without such groups.[8] Even at conditions normally expected to favor statis-
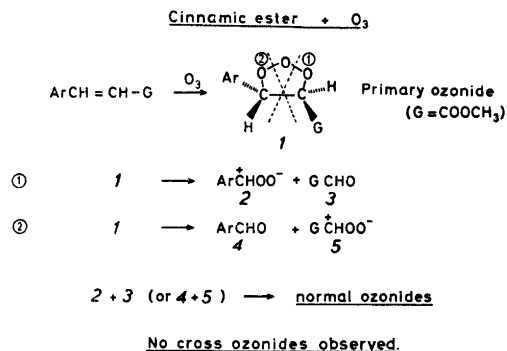
tical distribution of normal and cross ozonides, *viz.* ozonolysis at high concentration (> 5 M), at high temperature ($+ 5$ °C) and in polar aprotic solvents (acetone, acetonitrile) only normal ozonides were formed. Thus, most likely, either zwitterion *2* or *5* was formed.

B. "Foreign" ozonide formation was not observed when methyl p-methoxycinnamate was ozonized in presence of p-nitrobenzaldehyde using high temperature and relatively polar solvents. Since this aldehyde should be more reactive than p-methoxybenzaldehyde in ozonide formation using the same arguments as in A, aldehyde *4* is most likely not formed. Only when a large excess of trichloroacetaldehyde was added foreign ozonides were formed in small yields since this aldehyde may compete to some extent with methyl glyoxylate (*3*) for *2*.

These experimental results are reasonable from the point that zwitterion *5* ought to be destabilized by the ester group while *2* will be stabilized by resonance.

cis − *trans* RATIO IN OZONIDE FORMATION

Statistically one would expect to find a *cis* − *trans* ratio of one when olefins are ozonized, and also the same isomer distribution whether *cis* or *trans* olefins are ozonized. However, the experimental facts are different. Thus it is observed that in most cases *trans* olefins have a preference for formation of *trans* ozonides and *vice versa*.[1−5]

To explain the different *cis*/*trans* ratio in general Bailey et al.[4] worked out a theory which based on stereochemical consideration

Table 2. Solvent dependence in cis/trans ratios from ozonolyses of

$$X-\langle\bigcirc\rangle-CH\text{=}CHCO_2CH_3 \text{(trans)}$$
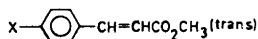
Solvent	ε^{a}	X					
		CN	COOCH₃	Br	H	MeO	MeO [b]
CCl₄	2.3	0.57	0.58	0.66	0.60	0.65	1.25
Et₂O	5.4	0.94	1.02	1.06	–	0.86	1.02
CHCl₃	5.7	–	–	0.65	0.68	0.69	–
MeOAc	7.8	–	–	–	–	0.93	–
BuCl	8.9	0.69	0.72	0.75	0.79	0.72	–
CH₂Cl₂	11.3	0.74	0.74	–	–	0.83	–
(CH₂Cl)₂	13.9	0.76	0.80	0.83	0.86	0.82	1.08
Me₂CO	26.5	–	–	–	–	1.00	–

[a] Dielectric constant at − 25 °C. [b] Ozonolyses of cis ester.

of the initial ozonide and on a proposal by Criegee [9] that the zwitterion may exist in syn and anti forms (Fig. 3).
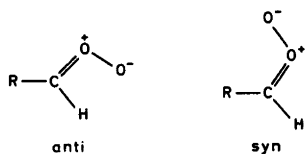

Fig. 3.   anti   syn

According to Bailey's theory syn zwitterions should always give trans ozonides and vice versa. Ozonolysis of trans olefins would normally lead to a predominance of syn zwitterions. Only with small substituents on the double bond anti zwitterions are predominantly formed giving excess cis ozonides from trans olefins. From cis olefins a predominance of anti zwitterions is always obtained.

Our results, summarized in Table 2, show a predominant "retention" of configuration upon ozonolysis. A trend towards equalization is observed with increasing solvent polarity and/or increasing electron-donating ability of the substituents. These variations could be well adapted to the theory of syn and anti zwitterions. Both increasing solvent polarity and/or increasing electron-donating power of substituents will allow a longer lifetime of the zwitterions and thus equilibration of their configurations is possible. Solvents having ether oxygen (ethers, esters) give almost equal amounts of cis and trans ozonides, probably through their ability to form oxonium ions on solvation.

EXPERIMENTAL

General. The ozone source was a Welsbach T23 ozone generator which gives a concentration of 4 − 6 % ozone in oxygen. ¹H NMR spectra were recorded on a Varian A 60 A spectrometer using deuteriochloroform as solvent and tetramethylsilane as internal standard.

Materials. The cinnamic acids were prepared from the corresponding aldehydes by the Knoevenagel reaction, and the acids were esterified with methanol and concentrated sulfuric acid.

Ozonolyses. Solutions (0.05 M) of the cinnamic esters in aprotic solvents (Table 2) were ozonized at − 25 °C. Ozone was quantitatively absorbed. The solvent was stripped off and the ozonide mixtures examined by ¹H NMR. Only normal ozonides were observed (Table 1). Repetitive integration scans at slow speed (1 Hz s⁻¹) across the ozonide ring proton region allowed a determination of the cis/trans ratio with an accuracy of approximately 2 % (Table 2). Due to thermal instability quantitative estimation by GLC was impossible. Separation of the isomers could in most cases be achieved by fractional crystallization from ether/pentane at − 35 °C. Where such separation was unsuccessful the ¹H NMR data were taken from the isomer mixtures and assignments of resonance signals done by analogy (Table 1). The IR spectra showed the expected absorption bands for the substituents for all ozonides, ¹H NMR data and melting points are given in Table 1. Elemental analyses (C, H) were satisfactory for all ozonides isolated in pure state.

Ozonolysis in the presence of p-nitrobenzaldehyde. Methyl trans p-methoxycinnamate (10 mM) was dissolved in dichloromethane (20 ml) and p-nitrobenzaldehyde (10 mM) was added. The solution was ozonized at +5 °C. The solvent was stripped off and the residue dissolved

in deuteriochloroform. Examination by ^{1}H NMR spectroscopy showed only peaks from normal ozonides together with peaks from *p*-nitrobenzaldehyde.

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