Ozonation of Compounds of the type Ar-CH=CH-G.

Cis-trans Isomeric Ozonides from Methyl p-Methoxy

Cinnamates

I. Structure of the Ozonides

PER KOLSAKER

Universitetets Kjemiske Institutt, Blindern, Oslo 3, Norway

Ozonation of methyl *cis-p*-methoxy cinnamate and methyl *trans-p*-methoxy cinnamate in methylene chloride at —78°C gave both a pair of stereoisomeric ozonides which was separated by fractional crystallization. PMR data for the starting materials and the products are given and discussed. Assignment of configuration was made based on PMR, melting points, solubilities, R_F-values.

As a part of our studies on ozonation of compounds of the type Ar—CH=CH—G, where Ar represents various substituted phenyl groups and G represents groups like —COOH, —COOCH$_3$, —CH$_3$, the methyl ester of *trans* *p*-methoxy cinnamic acid was ozonized in methylene chloride at —78°C. The absorption of ozone was quantitative. Fractional crystallization of the ozonation product gave two isomeric ozonides, m.p. 62—62.5°C (A) and 38—39°C (B). Both compounds analyzed as $C_{11}H_{12}O_6$. By using intensity measurements of PMR signals it was found that the total yields were 53 % A and 47 % B. The same compounds were also found to be the products from ozonation of methyl *cis-p*-methoxy cinnamate. By the same technique as above yields of 45 % A and 55 % B were determined.

Properties such as melting points, solubilities, mobilities in thin-layer chromatography suggested that the two compounds were the *cis-trans* isomeric ozonides of methyl *trans-p*-methoxy cinnamate.

For the sake of simplicity the *trans* configuration was assigned to the higher melting and *cis* configuration to the lower melting compound. Arguments justifying this choice will be presented in the following.

Cis-trans isomeric ozonides have been isolated earlier from *cis* and *trans* di-tertiary butylethylene by Schröder[1] and from methyl oleate and methyl elaidate by Privett and Nickell[2] as well as by Riezebos, Grimmelikhuysen

and van Dorp.[3] In these cases the substituents at the double bond were alkyl groups or, as in the case of the fatty esters, the negative ester group was far removed from the double bond. This paper presents the first case where *cis-trans* isomeric ozonides have been isolated from an olefin where one of the substituents at the double bond is electron-withdrawing. The thermal stability of the present ozonides is rather high (left in open vessel at room temperature they are stable for a couple of days), which is remarkable, since the accepted structure of ozonides is that of 1,2,4-trioxalanes, which is thought to be stabilized by electron-donating and not by electron-withdrawing substituents. It is notable that while previous workers [1-3] had to use chromatography and/or the urea inclusion compounds [3] to separate the isomers, one could here use fractional crystallization. This could be due to the fact that the steric differences between the isomers are large which ought to result in large differences in dipole moments and other physical properties.

Infrared spectra of the two isomers showed only small differences. A band at 1360 cm^{-1} was found in the spectrum of the *trans* compound but not in the *cis* spectrum. The *cis* compound gave a small shoulder at 855 cm^{-1} absent in the *trans* compound. Similar differences were also found by the previous workers.[1-3] Medium strong bands in the *cis* spectrum were found at 685, 995, and 1015 cm^{-1}, absent in the *trans* spectrum. Small differences were also observed in the carbonyl region, but of questionable identification value.

High resolution proton magnetic resonance spectroscopy confirmed the assumption that the compounds were stereoisomers, since the number of resonance signals and their relative intensities were the same in both compounds. A survey of the chemical shifts and coupling constants for *cis* and *trans* methyl *p*-methoxy cinnamates and for the isomeric ozonides is given in Table 1. The proton symbols refer to Fig. 1.
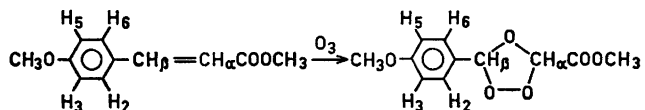

Fig. 1.

Table 1.

	$\tau_{H_\alpha}{}^a$	$\tau_{H_\beta}{}^a$	$J_{H_\alpha,H_\beta}{}^b$	$\tau_{H_2,H_6}{}^a$	$\tau_{H_3,H_5}{}^a$	$\tau_{ortho}{}^{b,c}$	$\tau_{CH_3}{}^a$
trans-Ester	3.80	2.37	17.1	2.51	3.15	9.3	6.18; 6.25
cis-Ester	4.18	3.15	13.5	2.11	3.07	8.5	6.15; 6.27
trans-Ozonide	4.38	3.80	—	2.57	3.11	9.0	6.18; 6.22
cis-Ozonide	4.33	4.09	—	2.40	3.12	9.0	6.18; 6.22

^{a} τ-values are given in ppm with tetramethylsilane as reference.
^{b} Coupling constants are given in cycles per sec.
^{c} Only *ortho* coupling constants could be determined here.

The assignment of the β-proton as the more unshielded proton in both the esters and the ozonides was based on PMR spectra of partially deuterated compounds. p-Methoxy benzaldehyde-d_1 in about 50 % isotopic purity, was made from anisole by the Gattermann reaction.[4] *Trans* p-methoxy cinnamic acid-β-d was then synthesized by the Knoevenagel method, esterified and ozonized. The PMR spectra of the ester showed that the intensity of the high field doublet had decreased and a 1:1:1 triplet located exactly in the middle of the doublet occurred with a coupling constant 2.5 cycles per second. This triplet is due to coupling between the α-proton and the β-deuteron in the deuterated molecule. In the *cis* and *trans* ozonide obtained from partially deuterated cinnamic ester the low field signal had decreased intensity, showing that the β-proton is the more unshielded one.

A couple of interesting conclusions can be drawn from the PMR spectra. There seems to be no spin-spin interaction between the two protons attached directly to the ozonide ring. This means that the true ozonide ring has not the same conjugative power as is found in epoxide rings [5,6] and as postulated for the initial ozonide (or adduct between ozone and olefinic double bonds).[7]

The change in chemical shift of the β-protons in the ozonides going from one isomer to the other enable us to determine the configuration of the isomers. Jackman and Wiley [8,9] have studied a number of *cis*- and *trans*-olefins and for compounds with ester groups at one side and hydrogen on the other side of the double bond they found a marked difference in chemical shift of the proton in β-position to the ester group going from *cis* to *trans* form. The *cis*-β-proton (*cis* to ester group) resonance signals always occurred at lower field, the difference being between 0.5 and 0.9 ppm. They attributed the effect to the long range shielding effect (due to magnetic anisotropy) of the ester carbonyl group on the β-proton *cis* to the ester group. Since this shielding effect is proportional to $1/R^3$, where R is the distance between the centre of the nucleus experiencing the shielding effect and the electrical centre of gravity of the cloud of electrons setting up the effect, Jackman and Wiley [8] postulated that R must be smaller than 3 Å in order that this long range shielding effect should come into play. In the p-methoxy cinnamic esters we have $\Delta\tau = 3.15 - 2.37 = 0.78$ ppm. By using molecular models (Stuart-Briegleb) R in the *trans* cinnamate was measured to be 2.2—2.3 Å. In the isomeric ozonides we have $\Delta\tau = 4.09 - 3.80 = 0.29$ ppm. Assuming that the other terms in the equation for the shielding constant (eqn. 1, Jackman and Wiley [8]) are the same in the cinnamic esters and the ozonides, we can calculate that R in the *trans* ozonide ought to be about 2.9—3.0 Å to give a shielding constant of 0.29 ppm. Molecular models of both the *cis* and *trans* ozonide can be made (using saturated 5-ring carbon atoms and ether oxygen atoms in building the ozonide ring). The ozonide ring in these models is not rigid but can be bent to give different angles between the ring atoms. Measurements of R in the *trans* ozonide will thus give values between 2.6 and 3.7 Å. Which would be the preferred conformation is difficult to say, but it seems to be safe to say that a distance (R) of about 2.9—3.0 Å is possible, thus allowing a small long range shielding effect to take place.

Turning now to the vinyl protons of the *cis* and *trans* cinnamic esters, the β-protons are the more unshielded ones, even though indications [10] are

cited that the α-protons may have the lowest electron density. Whatsoever, in the *trans* ester, which is coplanar, both vinyl protons are shifted downfield compared to methyl acrylate where the corresponding protons have τ-values of 3.80 ppm (α) and 3.62 ppm (β).[11] This could be attributed to ring current effects from the aromatic ring. A similar effect is found in the pair crotonic acid-*trans*-cinnamic acid.[11] In models of the *cis* ester, which is nonplanar, the vinyl protons are over and below the plane of ring; the ring current effect, if any, will cause an upfield shift of the protons.

In the models of both isomeric ozonides there seems to be no rotational restrictions for the bond between the two rings, thus causing the β-proton to be partly in, below or over the aromatic ring plane and any ring current effect, if any, ought to be small. The α-proton seems to be too far away to experience any effect. However, there seems to be some chemical evidence, that the α-proton in the case of these ozonides [12] is the more acidic one. This is not unexpected, since the ozonide ring is not transmitting any conjugative effects from the aromatic ring and hence the acidity of the ozonide ring protons will depend mostly on the inductive effects of the anisyl *vs.* the ester group. The nuclear deshielding of the β-proton can be explained by assuming that the aromatic ring prefers positions where the β-proton is *in* the plane of the ring.

The ring-proton spectra, contained in all cases two doublets. Under the present resolving conditions, coupling of spins of protons on opposite side of the benzene ring was not fully resolved. Only the *ortho* coupling constants could be determined to be 8.5—9.3 cps, which are of the right order of magnitude.

The assignment of the low field doublet signals to the aromatic protons in 2- and 6-position was based on arguments similar to those of Gronowitz and Hoffman.[13] Those resonance structures of the cinnamic esters that put charges on ring atoms were considered. The $+R$ effect of the methoxy group set up negative charges on the atoms in 3- and 5-position, and the $-R$ effect of the acrylic ester group set up positive charges on the atoms in the 2- and 6-position. Thus one would expect the resonance signals for the 2- and 6-protons to occur at lower field than for the 3- and 5-protons.

In the *cis* ester the ester carbonyl will be in near proximity of the 2- and 6-protons thus giving rise to a long range shielding effect causing the signals for these protons to occur at lower field than in the *trans* ester.

In the ozonides only the $+R$ effect from the methoxy group has to be considered, leading to the same results as for the cinnamic esters. The inductive effects of the substituents in both esters and ozonides are thought to be equally distributed throughout the aromatic ring atoms (Ref. 13 and references cited therein), thus causing no differences between the 2,6- and 3,5-proton resonance signals.

A small long range shielding effect of the ester carbonyl group on the 2- and 6-protons seems to be present in the *cis* ozonide, but not in the *trans* compound.

Riezebos *et al.*[3] did not find different resonance signals for the ozonide ring protons, nor did they get any differences in the spectra going from *cis*

to *trans* ozonide. This in consistent with the more symmetrical spatial distribution in their isomeric pairs.

In general *trans* isomers have higher melting points, lower solubilities, larger R_F-values in chromatography than *cis* isomers. This is what we find in our case. The above discussion of proton magnetic resonance spectra furnishes strong additional evidence that assignment of the high melting ozonide isomer as the *trans* compound is fairly safe in this case.

EXPERIMENTAL

General

The ozone source was a Welsbach T 23 Ozone Generator which gave a concentration of 4—6 % ozone in oxygen.

PMR spectra were recorded on a Varian Associate Dual Purpose Spectrometer operating at 60 Mc/sec. The high resolution spectra were taken in carbon tetrachloride solutions with tetramethyl silane as internal reference.

IR spectra were recorded on a Perkin Elmer Model 21 Double Beam Spectrophotometer in carbon disulphide (650—1400 cm⁻¹) and in carbon tetrachloride (0.1 mm cell, CaF prism, 1400—4000 cm⁻¹).

Melting points are not corrected.

Materials

Trans-p-*methoxy cinnamic acid* was prepared from anisaldehyde by the Knoevenagel reaction, m.p. 176—177°C. The acid was esterified with methanol and conc. sulphuric acid. Yields were good. M.p. 90.5—91°C.

Cis-p-*methoxy cinnamic acid* was synthesized according to Noyce and Avarbock.[14] The UV source was a 310 W Hanau Immersion Quartz lamp and irradiation time was 20 h. The crude *cis* isomer was dissolved in a small amount of ether and treated with diazomethane. The resulting ester was distilled, b.p.₀.₂₅ 99°C. By cooling in an icebox the ester crystallized and could be recrystallized by dissolving in pentane at room temperature and cooling to 0°C. M.p. 37.5—38°C. Total yield of ester 40 %.

Anisaldehyde-d₁ was synthesized in about 50 % isotopic purity (determined by PMR) by the Gattermann reaction.[4] Deuterium chloride was made from 99.7 % deuterium oxide and benzoyl chloride.[15] The yield was about 60 %.

Methyl trans p-*methoxy cinnamate-β-d* was synthesized from anisaldehyde-d₁ similarly to the corresponding undeuterated compound.

The solvents used were pure and anhydrous.

Ozonation of methyl *trans-p*-methoxy cinnamate

3.844 g (20 mmoles) ester was dissolved in 100 ml methylene chloride and cooled to —78°C in dry ice/acetone. 20 mmoles ozone was passed into the solution. The ozone absorption was quantitative. The solvent was evaporated leaving a colorless oil weighing 4.98 g. By fractional crystallization using mixtures of ether and pentane and cooling to —33°C, two compounds could be obtained. The compound (A) that precipitated first melted at 62—62.5°C. (Found: C 55.29; H 4.98; OCH₃ 25.84. Calc. for $C_{11}H_{12}O_6$: C 55.00; H 5.04; OCH₃ 25.86). The second compound (B) melted at 38—39°C. (Found: C 55.07; H. 5.08. Calc. for $C_{11}H_{12}O_6$: C 55.00; H 5.04). From a run on this scale 1.60 g A (6.6 mmoles — 33 %) and 0.54 g B (2.2 mmoles — 11 %) could be obtained in pure state. The rest was shown by thin layer chromatography to be mixtures of A and B. By comparing the intensities of proton resonance signals at 3.80 τ (A) and 4.09 τ (B) in the spectrum of freshly ozonized solutions of methyl *trans-p*-methoxy cinnamate one could estimate the total yield as 53 % A and 47 % B.

Ozonation of methyl *cis-p*-methoxy cinnamate

was carried out similarly to the *trans* ester. The products were not isolated but PMR of the freshly ozonized solution gave the same spectrum as for the ozonized *trans* ester. Comparison of intensities at 3.80 τ (A) and 4.09 τ (B) gave 45 % A and 55 % B.

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