"Plasmalogen-type" cyclic acetals: formation and conformation of the 1,3-dioxanes and 1,3-dioxolanes from 1-*O*-*cis*-alk-1′-enyl-*sn*-glycerols

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Abstract Acid-catalyzed cyclization of 1-*O*-*cis*-alk-1′-enyl-*sn*-glycerol produced four structurally and geometrically isomeric long-chain cyclic acetals of glycerol. The isomers were isolated by adsorption and gas–liquid chromatography and were identified as *cis*-2-alkyl-5-hydroxy-1,3-dioxane (Ia), *trans*-2-alkyl-5-hydroxy-1,3-dioxane (IIa), *cis*-2-alkyl-4-hydroxymethyl-1,3-dioxolane (IIIa), and *trans*-2-alkyl-4-hydroxymethyl-1,3-dioxolane (IVa). The structure of each isomer was established by chemical and spectroscopic methods. Cyclization with *p*-toluenesulfonic acid in boiling benzene led to a thermodynamically equilibrated mixture of isomers Ia–IVa in which the *cis* isomers predominated. Cyclization in acetic acid was found to be kinetically controlled, and formation of the *trans* isomers was relatively favored. Rearrangement of the cyclic acetal isomers did not occur in acetic acid; hence, optically active five-membered ring acetals were prepared.

Supplementary key words cyclization · *p*-toluenesulfonic acid catalysis · acetic acid catalysis · thermodynamic equilibration · glycerol acetals · 1,2-alkylidene-*sn*-glycerols · 1,3-alkylidene-glycerols · mass spectrometry · nuclear magnetic resonance spectrometry

The "PLASMALOGENS" first isolated by Feulgen and Bersin (1) and by Thannhauser, Boncoddo, and Schmidt (2) from the lipids of mammalian muscle and brain were considered to occur as phosphorylamines of cyclic glycerol acetals. Later, Klenk and Debuch (3, 4) suggested a number of other structures, while Rapport and coworkers (5–7) demonstrated that the natural form of these aldehydogenic lipids was that of an alk-1-enyl acyl glycerophosphatide. Secondary formation of cyclic acetals from a native type of plasmalogen was first suggested by Anchel and Waelsch (8) and was extensively studied later by other investigators. Pietruszko and Gray (9) concluded from the rates of liberation of aldehyde from choline plasmalogen, lysoplasmalogen, cyclic acetals, and dimethyl acetals that probably two components are formed from choline plasmalogen on saponification with alkali: alk-1-enyl lyso compounds at a fast rate, and cyclic isomers at a slower rate. They isolated cyclic isomers after alkaline or enzymatic removal of the 2-acyl group and subsequent treatment of the hydrolysis products with 90% or glacial acetic acid (10). Davenport and Dawson (11) showed that cyclic acetals can be formed during acid-catalyzed hydrolysis of 1-alk-1′-enyl 2-acyl phosphatidylethanolamine and that cyclization of 2-lysoplasmalogens usually occurs in acidic medium, although cyclic acetal formation in alkaline medium appears possible at the moment of deacylation (12). Surprisingly, most of the questions concerning the formation and structure of cyclic glycerol acetals (13), as they are produced from plasmalogen-type compounds, have not been answered since.

There exists some evidence that cyclic glycerol acetals may occur as native lipid constituents, e.g., in the sea anemone (*Anthopleura elegantissima*) (14) and possibly in certain other marine species (15), but some of these findings have been contradicted (16). Studies of the lipids of starfish (*Asterias forbesi*) (17) suggested that in this organism long-chain cyclic glycerol acetals are natural constituents of both phosphatides and neutral

Abbreviations: I–IV refers to the ring structures given in Fig. 2; Ia–IVa designates the hydroxy compounds; Ib–IVb refers to acetyl derivatives. GLC, gas–liquid chromatography; TLC, thin-layer chromatography.

lipids and that fatty aldehydes and alcohols appear to be efficient precursors in the biosynthesis of glycerol acetals. More recently, smooth muscle contracting activities were ascribed to cyclic glycerol acetal phospholipids (18).

In a previous study we have established the configurations of the two pairs of isomeric 1,3-dioxanes and 1,3-dioxolanes as they were prepared by acid-catalyzed condensation of glycerol and long-chain aldehyde (19). In the present work we set about to study the formation of the four structural and geometrical isomers of cyclic glycerol acetals from 1-*O*-*cis*-alk-1′-enyl-*sn*-glycerols, the enol ether having the natural configuration. We also describe the complete separation of the four acetal isomers and establish the conformation of the 1,3-dioxanes and the configuration of the 1,3-dioxolanes as they are produced from optically active alk-1-enyl glycerol ether through acid-catalyzed cyclization or through rearrangement.

MATERIALS AND METHODS

Materials

1-*O*-*cis*-Alk-1′-enyl-*sn*-glycerol, $[\alpha]^{25}_{546.1}$ −2.9°, was prepared by lithium aluminum hydride reduction of the total phospholipids of pig heart followed by adsorption chromatography. All methods used in this preparation were described previously (20). The composition of the alk-1-enyl ether side chain was determined by GLC of the aldehydes that were obtained upon hydrolysis of the enol ether in 12 N HCl-saturated diethyl ether at room temperature for 20 min (21). Major constituent aldehydes were hexadecanal (68.5%), octadecanal (19.3%), and *cis*-9-octadecenal (8.4%). Long-chain aldehydes used as standards were prepared from the corresponding alkyl methanesulfonates (22) by oxidation with dimethyl sulfoxide (23).

Methods

Melting points were determined on a Kofler hot stage and are corrected. Infrared spectra were recorded with a Perkin-Elmer model 21 spectrophotometer. Carbon disulfide served as solvent, except in the ranges 2400–2000 and 1650–1400 cm^{-1}, where tetrachloroethylene was used. Relative intensities of IR absorption bands are reported as weak (w), medium (m), strong (s), or shoulder (sh). Absorption bands associated with vibrations of the aliphatic chains are not listed. Mass spectra were taken on a Hitachi Perkin-Elmer single-focusing instrument, RMU-6D, at 70 ev. Abundances of ions are given as percentages relative to the base peak. NMR spectra were recorded on Varian A-60A and HA-100 spectrometers, using deuterochloroform as solvent. NMR absorptions are given in parts per million (ppm) downfield from tetramethylsilane. Optical rotations, $[\alpha]^{25}$, were measured in chloroform solution with the Bendix automatic polarimeter 1169 at 546.1 nm.

Analytical adsorption chromatography was carried out on layers, 0.3 mm thick, of silica gel G (E. Merck A.G., Darmstadt, Germany) (24). Chromatoplates were developed in tanks lined with filter paper, using mixtures of hexane and anhydrous diethyl ether as developing solvents. Lipid fractions were made visible by spraying the plates with a saturated solution of potassium dichromate in 70% sulfuric acid and subsequent charring at 180°C. Aldehydogenic lipid fractions were detected by spraying the chromatoplates with a 0.4% solution of 2,4-dinitrophenylhydrazine in ethanol–concentrated sulfuric acid 10:1 (v/v).

Preparative adsorption chromatography was done on layers, 0.5 or 2 mm thick, of silica gel H (Merck) (25). After chromatography the lipid fractions were usually visible as opalescent bands without the use of an indicator; otherwise the fractions were made visible in UV light by spraying the layers with a 0.2% solution of 2′, 7′-dichlorofluorescein in ethanol. Bands of adsorbent were scraped off, the fractions were eluted with moist diethyl ether, the solvent was evaporated, and the products were freeze-dried in vacuo and stored in hexane solution in the cold.

GLC was done on a Hewlett-Packard 5750 instrument equipped with flame ionization and thermal conductivity detectors. The aluminum column, 180 cm × 0.4 cm I.D., was packed with 18% ethylene glycol succinate (HI-EFF-2BP) on Gas-Chrom P, 80–100 mesh (Applied Science Laboratories Inc., State College, Pa.). The column was operated at 215°C. Helium served as carrier gas at a flow rate of 20 ml/min. For preparative purposes, samples were collected in glass tubes fitted with ground joints to the heated outlet tube of the thermal conductivity detector.

Acid-catalyzed cyclization of 1-*O*-*cis*-alk-1′-enyl-*sn*-glycerol was brought about under the following conditions.

Procedure A: with p-toluenesulfonic acid. 250 mg of 1-alk-1′-enyl glycerol ether, 100 ml of absolute benzene, and 25 mg of *p*-toluenesulfonic acid were placed in a 250-ml three-necked flask equipped with distillation head and condenser, inlet tube for dry nitrogen, and stirrer. The mixture was kept at boiling temperature for 2 hr while solvent was continuously distilled off. After cooling, the reaction mixture was poured into 100 ml of ice-cold 1% aqueous potassium carbonate, and the products were extracted three times with a total of 250 ml of diethyl ether. The organic phase was washed twice with a total of 100 ml of water, dried over anhydrous sodium sulfate, and concentrated in vacuo, yielding 242 mg of glycerol acetals Ia–IVa.

TLC (developing solvent, hexane–diethyl ether 40:60 [v/v]) showed three major fractions with R_F values of 0.49 (Ia), 0.62 (IIa), and 0.56 (IIIa plus IVa). Most of the product was immediately acetylated as described below.

Procedure B: with acetic acid. 250 mg of 1-alk-1′-enyl glycerol ether and 5 ml of glacial acetic acid were reacted under nitrogen in a sealed ampoule for 2 hr at 50°C (10). Upon cooling, the mixture was poured into an excess of ice-cold, 5% aqueous potassium carbonate solution, and the reaction products were extracted as described above. After evaporation of the solvent in high vacuum, 238 mg of glycerol acetals Ia–IVa were obtained, which migrated as three fractions in TLC (see procedure A).

Procedure C: with trichloroacetic acid. 50 mg of 1-alk-1′-enyl glycerol ether, 1 ml of chloroform–isobutanol 1:1, and 1 ml of 10% aqueous solution of trichloroacetic acid were reacted as described by Piantadosi et al. (26). Purification of the reaction products by preparative TLC (developing solvent, hexane–diethyl ether 40:60 [v/v]) yielded 18 mg of glycerol acetals Ia–IVa and two major fractions consisting of long-chain aldehydes and the 1,3,5-trioxanes derived from them.

Acetylation of glycerol acetals was done in a 100-fold excess (w/v) of acetic anhydride–pyridine 10:1 (v/v) for 2 hr at 80°C. Thereafter, most of the acetic anhydride was removed under reduced pressure. The cold residue was poured into an excess of ice-cold, 5% aqueous potassium carbonate solution and extracted twice with hexane. The extract was washed with water, dried over anhydrous potassium carbonate, and concentrated in vacuo. The yields of acetal acetates Ib–IVb prepared by procedures A and B were essentially quantitative.

TLC (developing solvent, hexane–diethyl ether 70:30 [v/v]) showed three major fractions: Ib, IIb, and IIIb plus IVb (for R_F values, see Table 1). The three fractions were isolated by preparative TLC. A single fractionation by preparative GLC was sufficient to prepare pure C_{16} acetal acetates from the mixtures of homologs Ib and from IIb in 70–80% yield. Isolation of the individual C_{16} isomers IIIb and IVb from the mixture of both, and of their longer-chain homologs, required double fractionation by GLC. Individual fractions were finally purified by TLC. The physical characteristics of isomers Ib–IVb are given in Table 1.

TABLE 1. Acetates of C_{16} cyclic acetals of glycerol

Characteristics	Ib *cis*	IIb *trans*	IIIb[a] *cis*	IVb[a] *trans*
R_F value[b]	0.35	0.68	0.46	0.46
R_T, min[c]	47	33	36	40
mp, °C[d]	91–92	66–67	45–45.5	50.5–51
$[\alpha]^{25}_{546.1}$[e]			−3.7 (c = 0.19)	−4.8 (c = 0.31)

[a] Isomeric 1,2-hexadecylidene-*sn*-glycerol acetates.
[b] R_F values in TLC on silica gel G; developing solvent, hexane–diethyl ether 70:30 (v/v).
[c] Retention times in GLC on ethylene glycol succinate at 215°C.
[d] Melting points after recrystallization from hexane.
[e] Specific optical rotations in chloroform (c = g/100 ml; d = 0.2 dm).

Isomerization studies were carried out with *cis*-2-alkyl-5-hydroxy-1,3-dioxane (Ia), which was prepared by lithium aluminum hydride reduction (19) of its acetate Ib, under conditions similar to those used for the cyclization of enol ethers.

With p-toluenesulfonic acid. 50 mg of *cis*-2-alkyl-5-hydroxy-1,3-dioxane (Ia), 100 ml of absolute benzene, and 25 mg of *p*-toluenesulfonic acid were reacted for 2 hr while solvent was continuously distilled off. Reaction conditions, extraction, and acetylation were as described above (procedure A). TLC of the hydroxy compounds and acetates after isomerization and acetylation, respectively, showed three fractions corresponding to I, II, and III plus IV. GLC analyses of the acetates Ib–IVb are given in Table 2. No reaction products other than the acetal isomers were detected.

With acetic acid. 50 mg of *cis*-2-alkyl-5-hydroxy-1,3-dioxane (Ia) and 1 ml of glacial acetic acid were kept under nitrogen in a sealed ampoule for 2 hr at 50°C. Reaction conditions, extraction, and acetylation were as described above (procedure B). TLC of the hydroxy compounds, and of their acetates, showed one fraction only corresponding to I. GLC confirmed that no isomerization of the starting product had occurred.

RESULTS

1-*O*-*cis*-Alk-1′-enyl-*sn*-glycerol used in the present study was prepared from pig heart phospholipids (20). Its cyclization was brought about under conditions customarily employed for the condensation of aldehyde with polyhydric alcohols (19, 27) or for the cyclization of lysoplasmalogens (10) or alk-1-enyl glycerol ethers (26). The products formed from alk-1-enyl ether of glycerol in the presence of *p*-toluenesulfonic acid in boiling benzene, in glacial acetic acid, or with trichloroacetic acid as catalyst showed identical migration rates by TLC, although they were formed in significantly different proportions (Table 2). Adsorption chromatography of the reaction products on thin silicic acid layers (developing solvent, hexane–diethyl ether 40:60 [v/v]) showed only the three acetal fractions (R_F values 0.49, 0.56, and 0.62) when cyclization was catalyzed with *p*-toluenesulfonic acid or acetic acid. Trichloroacetic acid catalysis (26) gave only a small amount of these acetals, but led to a large amount of long-chain alde-

TABLE 2. Formation of long-chain cyclic acetals of glycerol

From:	Catalyst	Percentages of Cyclic Isomers[a]			
		Ib *cis*	IIb *trans*	IIIb *cis*	IVb *trans*
		%			
1-*O*-Alk-1′-enyl-*sn*-glycerol	TosOH[b]	46.8	18.7	20.6	13.9
cis-2-Alkyl-5-hydroxy-1,3-dioxane (Ia)	TosOH[b]	47.3	17.3	21.0	14.4
Hexadecanal and glycerol	TosOH[b]	46.4	17.2	22.8	13.6
1-*O*-Alk-1′-enyl-*sn*-glycerol	CH_3COOH[c]	11.0	6.0	34.8	48.3
cis-2-Alkyl-5-hydroxy-1,3-dioxane (Ia)	CH_3COOH[c]	100.0			
1-*O*-Alk-1′-enyl-*sn*-glycerol	CCl_3COOH[d]	11.2	8.9	31.9	48.0

[a] As determined by GLC of the acetates Ib–IVb.
[b] *p*-Toluenesulfonic acid in boiling benzene, 2 hr.
[c] In glacial acetic acid at 50°C, 2 hr (10).
[d] In 10% aqueous solution of trichloroacetic acid and the same volume of chloroform–isobutanol 1:1 (v/v) at 37°C for 1 hr and at 25°C for 17 hr (26).

hydes and 1,3,5-trioxanes. In order to facilitate fractionations, further characterization, and structural analyses, the isomer mixture was acetylated. The acetates were resolved by TLC into *three* fractions (for R_F values see Table 1). GLC of the acetates on a polar liquid phase revealed *four* major fractions, Ib–IVb (see Fig. 1), associated with C_{16} acetal isomers (for retention times see Table 1), and a number of poorly resolved smaller peaks corresponding to longer-chain homologs. Consecutive fractionation of the acetates by preparative TLC and GLC yielded the four individual C_{16} acetal acetates of glycerol, Ib–IVb, in pure form. Although the proportion of individual isomers formed depended greatly on cyclization conditions (procedures A–C), corresponding C_{16} isomers from all preparations showed identical or very similar physical characteristics, i.e., R_F values, retention times, infrared absorptions, and mass spectral fragmentation patterns. These characteristics were also in good agreement with those of the glycerol acetal acetates we have prepared by condensation of glycerol and hexadecanal (19). We could show that the most polar acetal acetate fraction (R_F 0.35) and the least polar one (R_F 0.68) yielded exclusively 2-alkyl glycerol ether upon deacetylation with lithium aluminum hydride, alkylation with long-chain alkyl methanesulfonate, and acidic hydrolysis, demonstrating that acetals I and II have six-membered ring structures. Identical treatment of the fraction of medium mobility (R_F 0.46) led to 1-alkyl glycerol ether, i.e., acetals III and IV are the five-membered ring isomers (see Fig. 2).

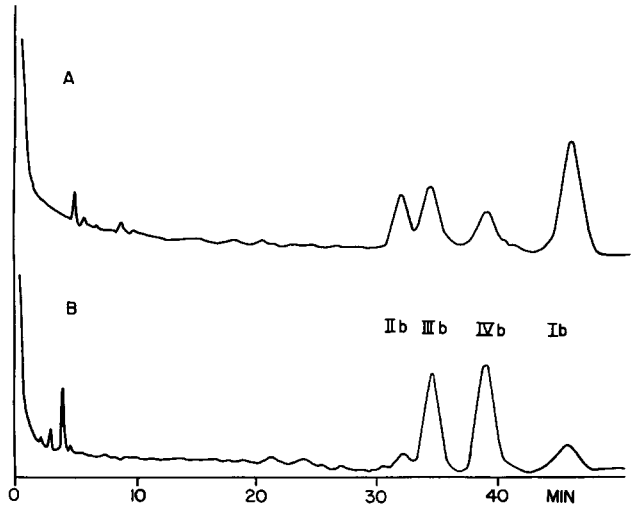
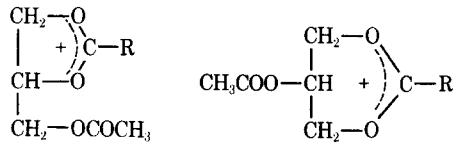


FIG. 1. GLC of the acetates of the isomeric long-chain glycerol acetals as obtained by catalytic cyclization of 1-*O*-*cis*-alk-1′-enyl-*sn*-glycerol with *p*-toluenesulfonic acid (*A*) or glacial acetic acid (*B*). The fractions represent *trans*-2-pentadecyl-5-acetoxy-1,3-dioxane (IIb), *cis*-2-pentadecyl-4-acetoxymethyl-1,3-dioxolane (IIIb), *trans*-2-pentadecyl-4-acetoxymethyl-1,3-dioxolane (IVb), and *cis*-2-pentadecyl-5-acetoxy-1,3-dioxane (Ib).

The mass spectra of the four isomeric glycerol acetal acetates Ib–IVb (Figs. 3 and 4) show the expected parent ion peak at *m/e* 356. A stronger signal is observed for $[M-1]^+$ at *m/e* 355 which is due to loss of the C-2 acetal proton. This was confirmed by specific C-2 deuteration. The most prominent peak in the spectra of isomers Ib–IVb occurs at *m/e* 145, which is caused by ion $[M-C_{15}H_{31}]^+$. Formation of *m/e* 145 from dioxolanes IIIb and IVb is more pronounced than it is from dioxanes Ib and IIb. Both types of fragmentation ions, $[M-H]^+$ and $[M-C_{15}H_{31}]^+$, have resonance-stabilized cyclic structures.



R = H: *m/e* 145

R = $C_{15}H_{31}$: *m/e* 355

A most significant difference between the five- and six-membered ring acetals is found in the abundances of the rearranged ions $[M-C_{15}H_{31}CO]^+$ at *m/e* 117. Due to the relatively higher stability of the dioxolanes under

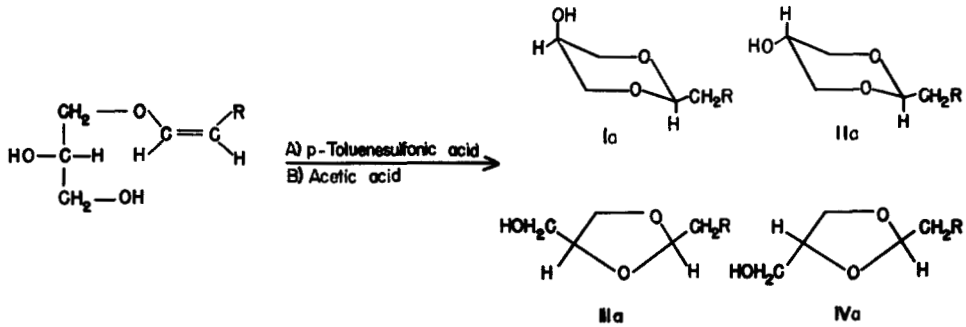
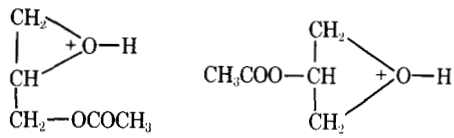


FIG. 2. Acid-catalyzed cyclization of 1-*O*-*cis*-alk-1′-enyl-*sn*-glycerol leading to *cis*-2-alkyl-5-hydroxy-1,3-dioxane (Ia), *trans*-2-alkyl-5-hydroxy-1,3-dioxane (IIa), *cis*-2-alkyl-4-hydroxymethyl-1,3-dioxolane (IIIa), and *trans*-2-alkyl-4-hydroxymethyl-1,3-dioxolane (IVa).

electron impact and/or due to favored formation of *m/e* 117 with a four-membered over a three-membered ring structure, ion *m/e* 117 is produced in five to six times higher abundance from the six-membered ring acetals.



m/e 117

Interestingly, *m/e* 117 does not retain the C-2 proton, as was shown by specific C-2 deuteration. The prominent signal at *m/e* 43 is due to the acetyl ion. Loss of the acetyloxy group gives rise to ion *m/e* 86. $[M-CH_3COO]^+$ is produced in considerably higher abundances from the 1,3-dioxanes (Fig. 3) than it is from the 1,3-dioxolanes (Fig. 4).

The conformation of the six-membered ring acetal isomers Ib and IIb can be established by NMR spectrometry either on the basis of differential shielding that occurs with axial and equatorial substituents arising

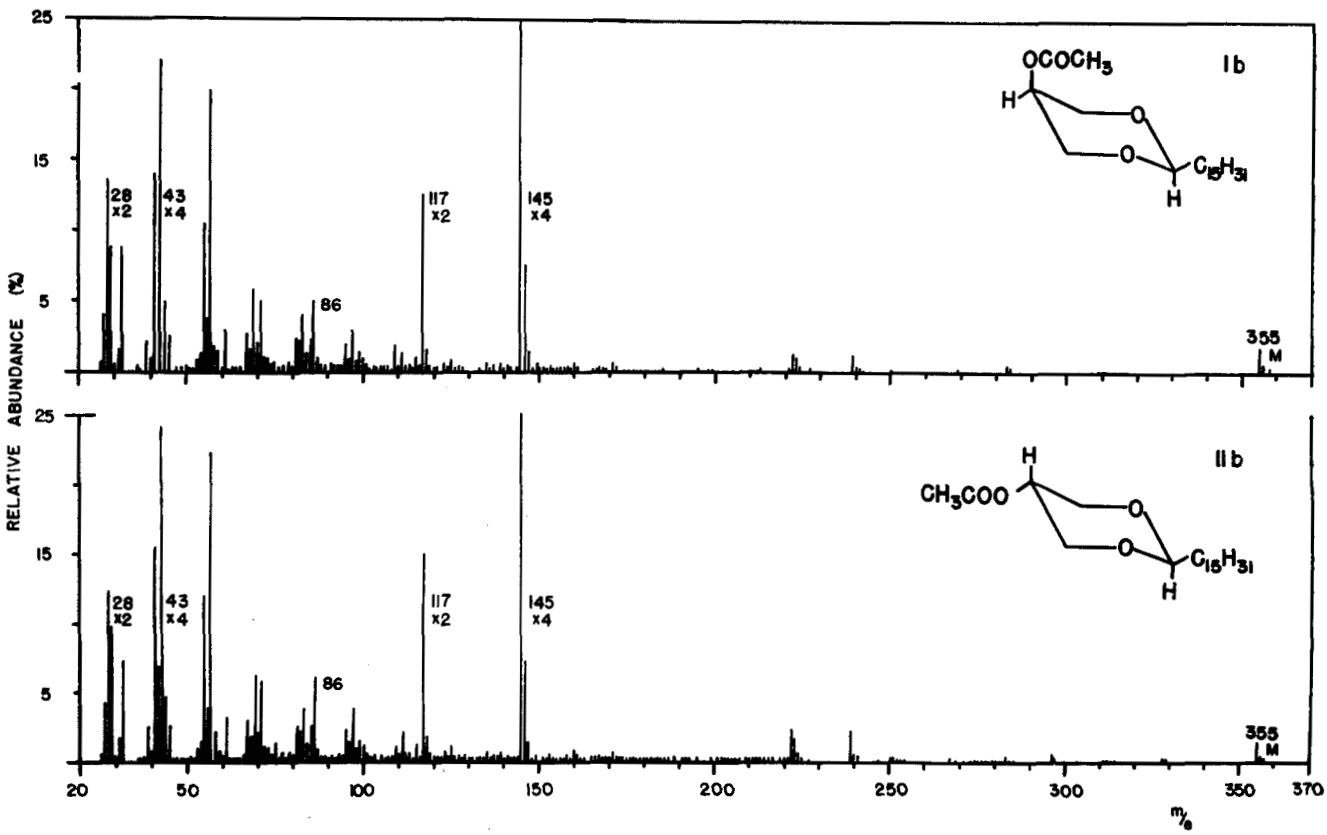


FIG. 3. Mass spectra of *cis*- (Ib) and *trans*-2-pentadecyl-5-acetoxy-1,3-dioxanes (IIb) recorded at an ionization potential of 70 ev.

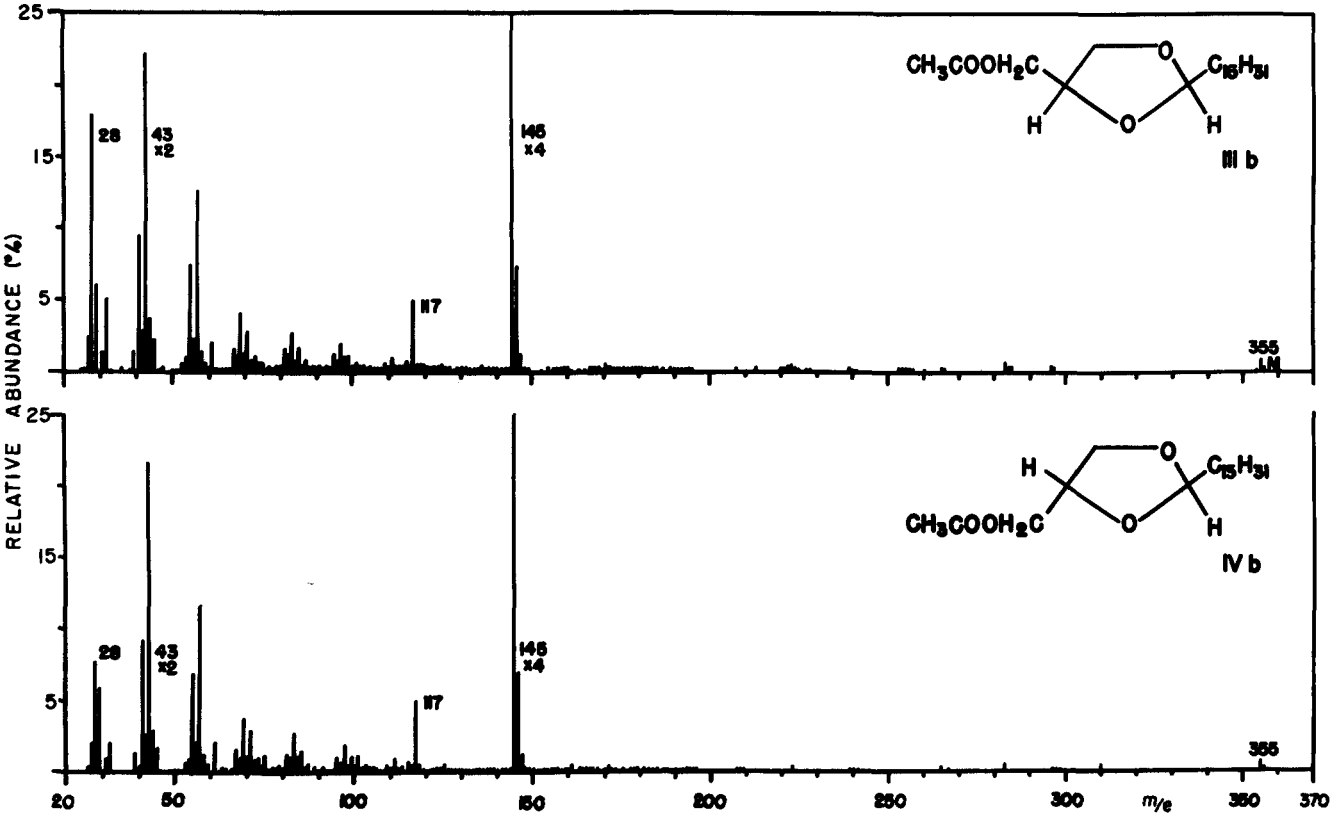


FIG. 4. Mass spectra of *cis*- (IIIb) and *trans*-2-pentadecyl-4-acetoxymethyl-1,3-dioxolanes (IVb) recorded at an ionization potential of 70 ev.

from the magnetic anisotropy of the ring and other substituents or based on the magnitude of the vicinal coupling constants in relation to the dihedral angle between coupling protons in such saturated systems. The NMR spectra of dioxanes Ib and IIb are shown in Fig. 5. The triplet at δ = 4.46 ppm (J = 5.0 Hz) in the 100-MHz spectrum of IIb (*bottom left*) and the partially embedded signal near 4.54 ppm (J = 5.0 Hz) in the spectrum of Ib (*top left*) are caused by the acetal hydrogens at C-2, as these signals are not present in the spectra of the specifically 2-deuterated isomers (Fig. 5, *right*). On the basis of the coupling constants (J = 5.0 Hz) and the chemical shifts, axial orientation can be assigned to H-2 of isomers Ib and IIb. For an equatorial proton in such cyclohexane-type systems, a chemical shift to lower fields would be expected (28). Such a shift to δ = 4.8 ppm has recently been observed also for 1,3-dioxanes (29). The spectrum of acetate IIb (Fig. 5, *bottom*) shows a characteristic "septuplet" near δ = 4.89 ppm, 5.1 Hz, due to an axial H-5, geminal to an acetoxy group. This superimposed "triplet of triplets" is caused by two diaxial splittings to H_a-4 and H_a-6 (J = 10.2 Hz) which are twice the axial–equatorial splittings to H_e-4 and H_e-6. The spectrum of acetate Ib (Fig. 5, *top*) does not exhibit this signal. Instead, Ib produces a quintuplet at δ = 4.60 ppm (J = 1.5 Hz) which is partially hidden in the H-2 triplet but is quite apparent in the spectrum of the C-2 deuterated isomer (Fig. 5, *top right*). The signal at 4.60 ppm must be assigned to an equatorial hydrogen at C-5. Obviously, in these dioxanes H_e-5 absorbs at higher field than H_a-5. This appears to be a consequence of shielding by the ring oxygens, as in other cyclohexane systems axial protons absorb at higher field strength (28). The four-line pattern of IIb near 4.25 ppm can be assigned to H_e-4 and H_e-6, whereas H_a-4 and H_a-6 produce the triplet at 3.47 ppm. The spectrum of Ib shows a pair of doublets centered at δ = 4.12 and 3.93 ppm for H_e-4,6 and H_a-4,6, respectively. The spectra thus show clearly that dioxanes I and II differ in the orientation of their substituents at C-5, while the 2-pentadecyl groups remain anchored in equatorial conformation. Dioxane I possesses *cis* configuration; dioxane II occurs as the *trans* stereoisomer.

The complete 60-MHz spectrum of dioxolanes IIIb plus IVb and the partial 100-MHz spectra of the pure isomers are shown in Fig. 6. The triplets at δ = 4.88 ppm (J = 4.5 Hz) in the spectrum of IIIb (*top insert*) and at 4.99 ppm (J = 4.5 Hz) of IVb (*lower insert*) were unequivocally correlated to the hydrogen at C-2, as these signals were lost upon C-2 deuteration. The configura-

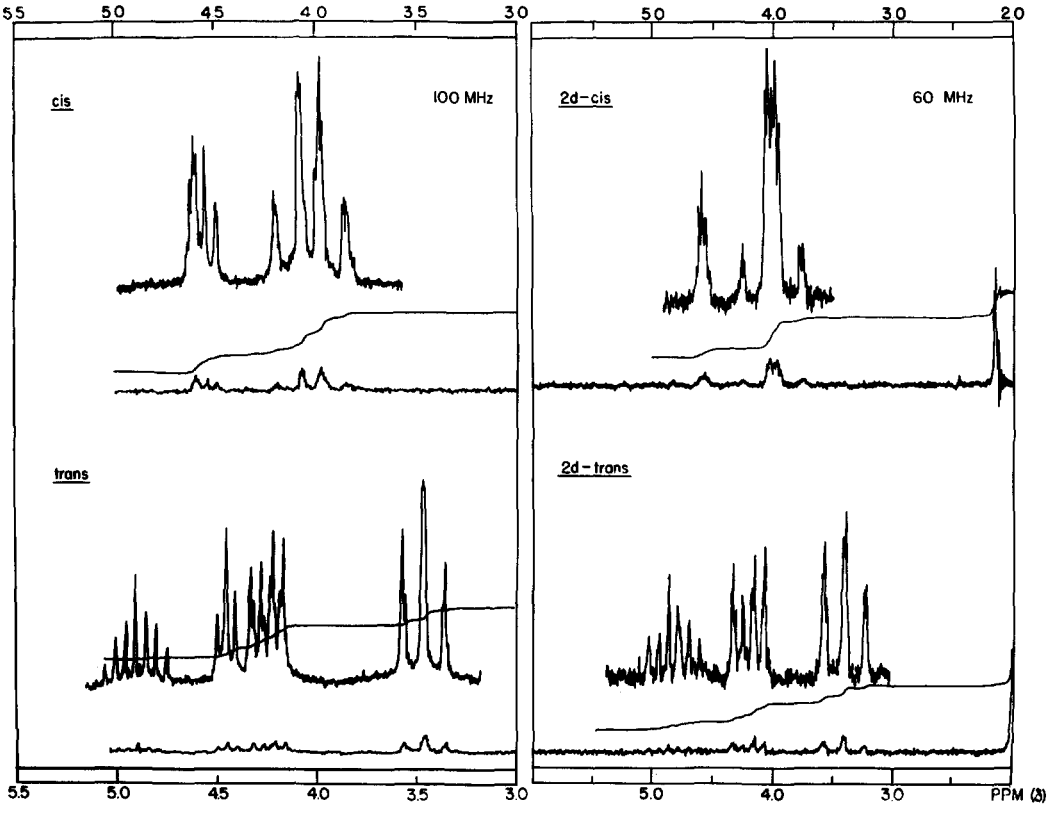


FIG. 5. 100-MHz NMR spectra of *cis*- (Ib) and *trans*-2-alkyl-5-acetoxy-1,3-dioxanes (IIb) (*left*) and 60-MHz spectra of their 2-deuterated analogs (*right*).

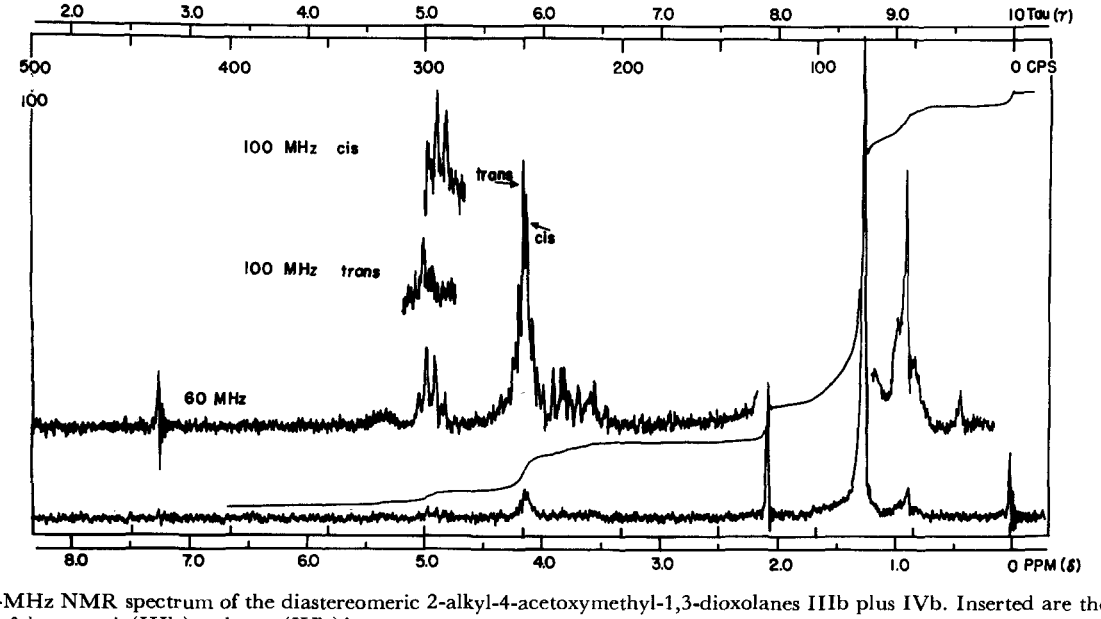


FIG. 6. 60-MHz NMR spectrum of the diastereomeric 2-alkyl-4-acetoxymethyl-1,3-dioxolanes IIIb plus IVb. Inserted are the 100-MHz H-2 signals of the pure *cis* (IIIb) and *trans* (IVb) isomers.

tions of the diastereomeric dioxolanes IIIb and IVb can be established on the basis of the chemical shifts observed for the H-2 protons. The closer proximity of the 4-acetoxymethyl group and H-2 in the *trans* isomer leads to mutual deshielding and thus to a shift of the H-2 signal to lower field strength. Therefore, isomer IV must possess *trans* configuration and isomer III, *cis* configuration. The poorly resolved signals between 3.4 and

4.4 ppm (Fig. 6) are due to H-4,5. The methylene protons next to the acetoxy group give rise to the signals at δ = 4.13 (*cis*) and 4.17 ppm (*trans*).

Additional signals in the spectra of both 1,3-dioxanes Ib and IIb and 1,3-dioxolanes IIIb and IVb are the singlet near 2.1 ppm for the acetyl protons, broad bands near 1.5–1.6 ppm for the C-1′ methylene protons and at 1.28 ppm for the internal methylene protons of the aliphatic chain, and an asymmetrical triplet centered at δ = 0.89 ppm (J = 6.0 Hz) characteristic of the terminal methyl group.

The IR spectral data of the isomeric dioxanes Ib and IIb and the isomeric dioxolanes IIIb and IVb agree well with the correlations based on NMR data. The spectrum of the *cis*-isomeric acetate Ib is characteristically different from that of the *trans* isomer IIb (see Fig. 7), which may be the consequence of an "oxygen bonding" effect between the acetyl group and the ring heteroatoms in the *cis* isomer. The diastereoisomer Ib (Fig. 7, *top*) gives rise to characteristic bands at 1151(s), 1103 (m), and 1009(m) cm^{-1} which are probably associated with ring vibrations. The spectrum of the *trans* isomer IIb (Fig. 7, *bottom*) exhibits characteristic absorptions at 1151(s) and 1115(m) and a very intensive band at 1049(s) cm^{-1}.

Prominent bands in the spectra of isomers IIIb *and* IVb (Fig. 8) characteristic of 1,3-dioxolanes (30) include the symmetrical ring stretching vibration at 1041 cm^{-1}, the asymmetrical ring stretching at 1140 cm^{-1}, and the ring C—O vibration at 1123 cm^{-1}. The spectrum of the *cis*-1,3-dioxolane IIIb (Fig. 8, *top*) shows the characteristic ring breathing band near 980 cm^{-1}, whereas for the *trans* isomer IVb (Fig. 8, *bottom*) the band is more intense at 951 cm^{-1}. Similar ring breathing vibrations have been reported for the diastereomeric 2,4-dimethyl-1,3-dioxolanes and other five-membered ring acetals (31).

The proportion of individual isomers I–IV formed from alk-1-enyl glycerol ether depends greatly on cyclization conditions. The compositions of the acetal mixtures obtained and as determined by GLC of acetates Ib–IVb are given in Table 2. Interestingly, the four isomers are formed either from alk-1-enyl glycerol ethers or from aldehyde and glycerol in very similar proportions when *p*-toluenesulfonic acid and boiling benzene serve as reaction medium, suggesting that a thermodynamically equilibrated mixture of cyclic acetals is obtained.

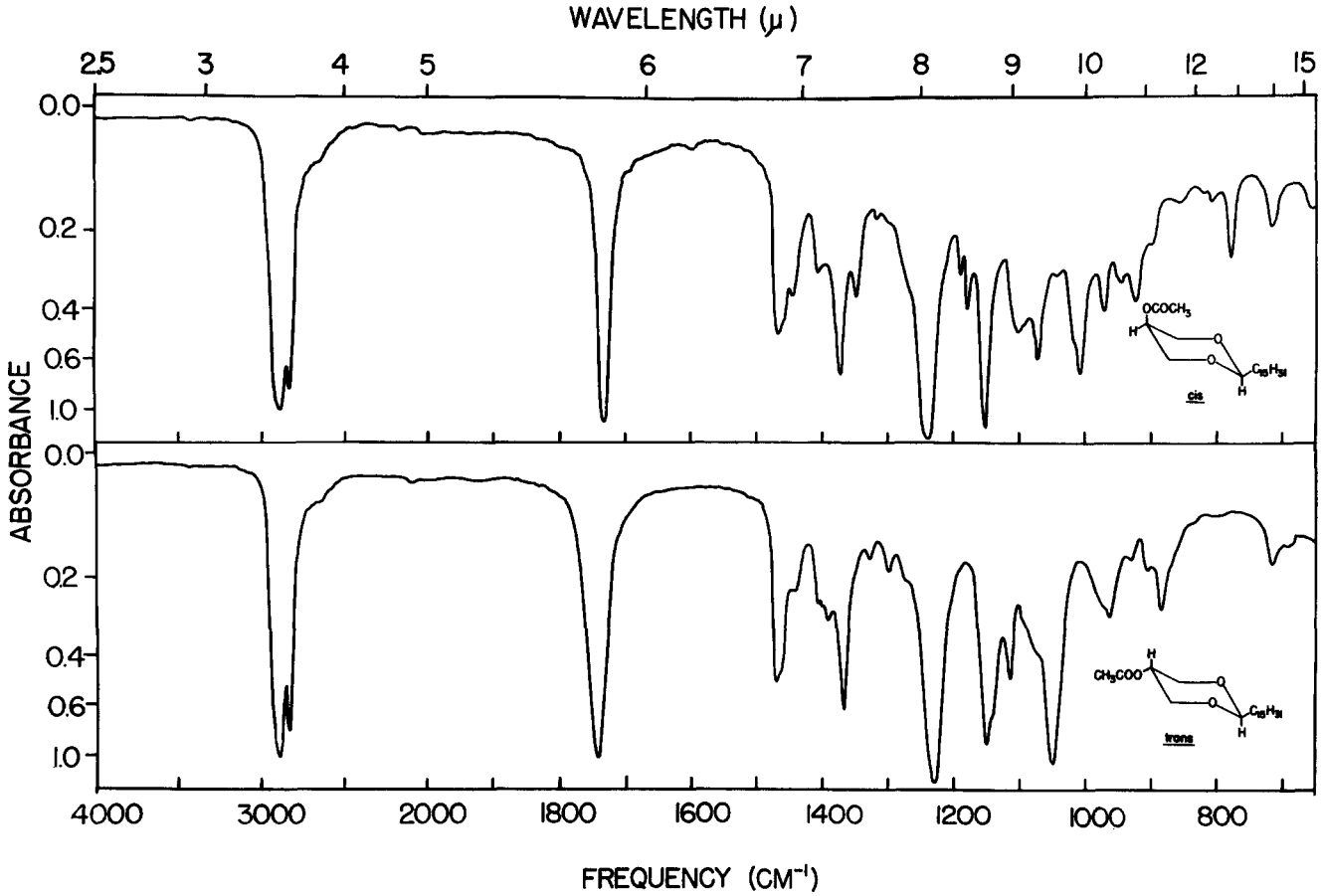


FIG. 7. IR spectra of *cis*- (Ib) and *trans*-2-alkyl-5-acetoxy-1,3-dioxanes (IIb).

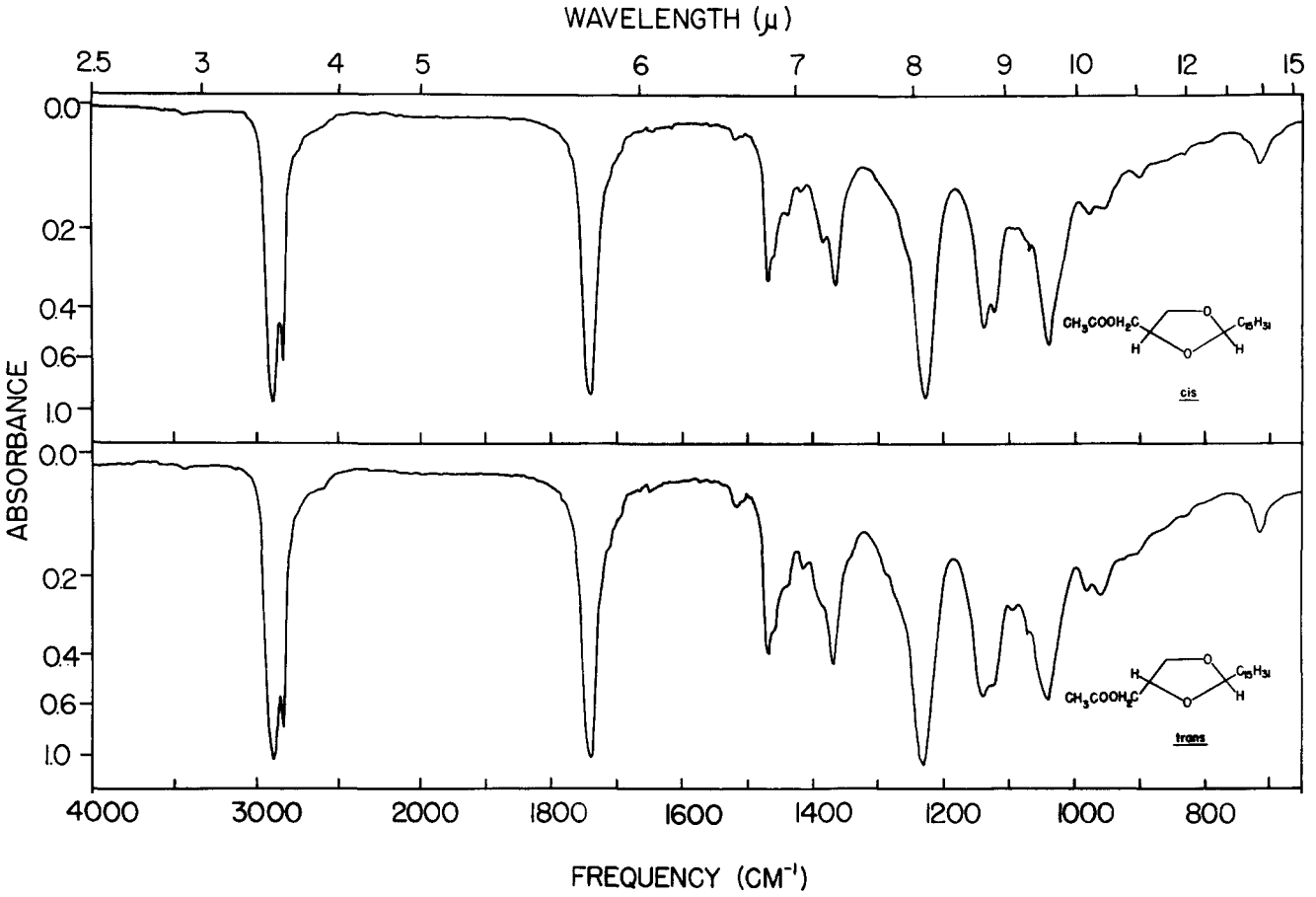


FIG. 8. IR spectra of *cis*- (IIIb) and *trans*-2-alkyl-4-acetoxymethyl-1,3-dioxolanes (IVb).

Formation of the *cis*-2-alkyl-5-hydroxy-1,3-dioxane (I) is clearly favored, and only small amounts of the *trans* isomer II are produced. *p*-Toluenesulfonic acid-catalyzed condensation also favors formation of the *cis* dioxolane III over that of its *trans* isomer IV. In contrast, acetic acid and trichloroacetic acid catalyses produce high percentages of the *trans*- and *cis*-dioxolanes IV and III and smaller amounts of the dioxanes I and II.

If *p*-toluenesulfonic acid-catalyzed cyclization proceeds under thermodynamically controlled conditions, an identical mixture of acetals should be formed from one of the isomers subjected to such conditions. This was confirmed, indeed, by rearranging pure *cis*-2-alkyl-5-hydroxy-1,3-dioxane (Ia) in the presence of *p*-toluenesulfonic acid. GLC analyses of the acetates of the rearranged acetal mixture agreed very well with those of the cyclization products (Table 2), i.e., cyclization in the presence of *p*-toluenesulfonic acid leads to a *thermodynamically equilibrated mixture* of glycerol acetals. When *cis*-2-alkyl-5-hydroxy-1,3-dioxane (Ia) was subjected to "cyclization conditions" in the acetic acid medium, TLC and GLC of the reaction product showed only the presence of the starting material. Evidently, glacial acetic acid is unable to protonate the acetal ring and does not lead to any isomerization of acetals. The proportions of isomers formed is thus exclusively due to the rapidity of their formation, i.e., cyclization of alk-1-enyl glycerol ether in acetic acid is *kinetically controlled.*

The latter finding enabled us to prepare optically active cyclic acetals from 1-*cis*-alk-1′-enyl-*sn*-glycerol having the optical and geometrical configuration of natural plasmalogens. There are altogether four stereomeric dioxolanes and two dioxanes. The *cis*- and *trans*-dioxolanes can each occur as 1,2- or 2,3-alkylidene-*sn*-glycerols. Due to the plane of symmetry in both *cis*- and *trans*-dioxanes, optical six-membered ring isomers do not exist. With 1-*O*-*cis*-alk-1′-enyl-*sn*-glycerol ([α] −2.9°) as starting material, only the *cis*- and *trans*-1,2-alkylidene-*sn*-glycerols and the two six-membered ring isomers can be expected. Indeed, only the *cis*- and *trans*-dioxolanes IIIb ([α]−3.7°) and IVb ([α] −4.8°), respectively, produced by acetic acid-catalyzed cyclization showed optical activity, and both were levorotatory.

DISCUSSION

A previous investigation reported by Piantadosi et al. (26) on the cyclization of alk-1-enyl glycerol ethers catalyzed by trichloroacetic acid must be considered inconclusive after it was shown (32) that mixtures of 1-alk-1′-enyl and 2-alk-1′-enyl glycerol ethers (33, 34) in *cis* and *trans* configuration were used in this work. Furthermore, under the reaction conditions chosen (26) we found that most of the enol ether was hydrolyzed rather than converted to glycerol acetals. Exclusive formation of α-monoglyceride upon acylation of the cyclization products followed by acidic hydrolysis was then taken as evidence (26) for the exclusive presence of five-membered ring acetals (26, 35), although the α-monoglyceride could have been formed by acyl migration as well. The view that only five-membered ring acetals are formed when trichloroacetic acid is used as catalyst (26) and that the *cis*-1,3-dioxolane predominates (36) with acetic acid as reaction medium has now been proved wrong.

The present study has also led to the conclusion that the thermodynamically more stable isomers are dioxanes I and dioxolanes III, i.e., those having *cis* configuration. Their formation from alk-1-enyl glycerol ether is especially favored when *p*-toluenesulfonic acid in boiling benzene serves as catalyst. Predominance of the *cis* isomer in the equilibrated mixture appears to be a consequence of intramolecular hydrogen bonding. The fact that, for example, 2-alkyl-5-hydroxy-1,3-dioxane is more stable in its *cis* configuration is quite in contrast with what is known for cyclohexane derivatives, where formation of the *trans*-1,4-disubstituted isomer is favored.

In contrast, acetic acid-catalyzed cyclization leads to relatively higher percentages of the kinetically favored isomers, which appear to be the *trans* compounds. The effect is most pronounced for the five-membered ring acetals, as more *trans*-dioxolane is produced than its *cis* isomer. Steric reasons should be responsible for accelerated formation of *trans* compounds.

Another interesting phenomenon is the significantly higher polarity of the *cis*-dioxane acetate Ib relative to its *trans* isomer IIb, as can be concluded from their migration rates in adsorption TLC. The difference in polarities of the geometrically isomeric dioxolanes is much less pronounced and here the *trans* isomer is slightly more polar. The unusually high polarity of *cis*-dioxane Ib is probably due to the polarizing effect of the ring oxygens on the carbonyl bond of the adjacent acetyl, giving rise to "oxygen-bonded" cyclic structures. This view is supported by spectroscopic data: the infrared absorption of the carbonyl group of the *trans* isomer IIb is found at 1742 cm^{-1}, but it is indeed shifted by 11 cm^{-1} to lower wave number for the *cis* isomer; similarly, the differences in ring absorptions found in the infrared spectra of Ib and IIb can be explained by "oxygen bonding" in the *cis* isomer. Furthermore, the NMR signal of the *cis*-acetyl protons occurs at lower field strength (δ = 2.15 ppm vs. 2.05 ppm), indicating deshielding due to increased polarization of the carbonyl bond. As a consequence of the relatively planar structure of the dioxolanes, "oxygen bonding" is not specifically favored for either isomer.

The results of the present investigation on the formation, separation, and structures of cyclic glycerol acetals constitute the basis for further, more biologically oriented, studies. The question of whether cyclic glycerol acetals play a role in the biosynthesis or metabolism of plasmalogens is still subject to speculation. Current work in our laboratory is directed towards studying the feasibility of such mechanisms.

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