Tetrahedron Vol. 43, No. 21, pp. 5089 to 5094, 1987
Printed in Great Britain.

0040-4020/87 $3.00+.00

EXPERIMENTAL EVIDENCE FOR AcO-7 NEIGHBORING GROUP PARTICIPATION‡

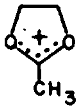
Samuel H. Wilen*, Luciano Delguzzo[1] and Richard Saferstein

The City University of New York, City College, Department of Chemistry
New York, N.Y., 10031, USA

(*Received in UK* 10 *April* 1987)

Abstract - The reaction of diol diacetates with anhydrous aluminium chloride at ca 100° leads to displacement of only one of the acetoxy groups by chlorine. An oxygen-18 label study has shown that these displacements take place via acetoxonium intermediates and has provided direct evidence for the intervention of a seven-membered ring acetoxonium ion in the displacement of acetate by chlorine in 1,4-butanediol diacetate.

Neighboring group participation by acetoxy groups is a well-established feature of heterolytic displacement reactions.[2] Participation involving five-membered ring (AcO-5) (I) or six-membered ring (AcO-6) (II) intermediates has been invoked in a variety of reactions on the basis of kinetic and stereochemical evidence and confirmed by O^{18}-labelling experiments[3] and by isolation of cyclic orthoesters[4] and of acetoxonium ion salts.[5]

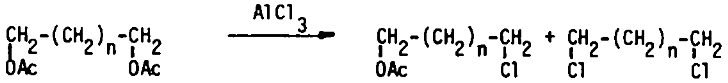

I


II


III

No experimental evidence in support of the intervention of seven-membered ring acetoxonium ions such as III has yet been presented to our knowledge. Nonetheless, participation by a seven-membered ring orthoester intermediate has been invoked to explain ester isomerization in diol monoesters.[6] It has been pointed out that the 7-exo-tet process leading to rings such as III is a favorable process.[7] In gas-phase electron-impact induced formation of $[M-X^+]$ ions (X = acyloxy) from diol diesters in which five- and six-membered ring acyloxonium ion formation is favored, the analogous seven-membered ring ion is a borderline case.[8] On the other hand, reaction of diol diacetates with $SbCl_5$ which yields stable five- and six-membered ring acetoxonium ions (nmr evidence) failed to yield analogous seven- and eight-membered ring ions.[9]

We now present direct evidence for appreciable AcO-7 participation in a displacement reaction occurring in 1,4-butanediol diacetate. Equation (1) describes a reaction which is rather sensitive to neighboring group effects and which we hoped would reveal the intervention of a seven-membered ring acetoxonium ion as an intermediate.



$$\underset{\text{OAc}}{CH_2}-(CH_2)_n-\underset{\text{OAc}}{CH_2} \xrightarrow{AlCl_3} \underset{\text{OAc}}{CH_2}-(CH_2)_n-\underset{\text{Cl}}{CH_2} + \underset{\text{Cl}}{CH_2}-(CH_2)_n-\underset{\text{Cl}}{CH_2} \qquad (1)$$

IV V VI

n = 0, 1, 2, 3, 4.

---

‡Dedicated to Professor Hans Wynberg on the occasion of his 65th birthday.

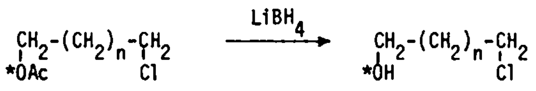
Table 1 summarizes results from several reactions which demonstrate that the reaction is slow but clean for diol diacetates IV, n = 2, 3, 4 with rates comparable to that for n-butyl acetate. On the other hand, diol diacetates IV, n = 0 and 1 react much faster. At 154°±4°, these two esters yield the corresponding chloroacetates V virtually quantitatively in one hour while these products react only slowly with $AlCl_3$ to form dichlorides VI. AcO-5 and AcO-6 participation in the reactions of I, n = 0 and 1, respectively, was suggested by the faster relative rates of reaction of these compounds.

Table 1. Reaction primary diol diacetates and n-butyl acetate with $AlCl_3$.

Ester	Mole ratio Ester: $AlCl_3$	Temp. °C	Time hr	Yield[a] V	VI	Recovered[a,c] IV
IV, n=0	2:1	104±2	0.5	51%[b]	-	20%
IV, n=1	2:1	106±1	1	56%	-	44%
IV, n=2	2:1	107±2	1	5%	-	87%
IV, n=3	2:1	108±2	1	5%	-	95%
IV, n=4	2:1	110±1	1	5%	-	93%
IV, n=4	2:1	154±4	1	29%	4%	41%
n-BuOAc	4:1	108±2	1	2.5%[d]	-	90%

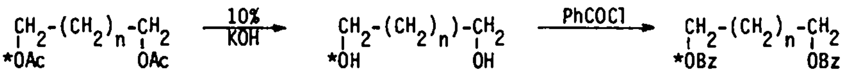
[a] Gas chromatographic analysis (assuming a stoichiometry of 2:1 which was independently confirmed); [b] Isolated; [c] Rearranged starting material was not found; [d] n-BuCl, 2%; sec-BuCl, 0.5%.

The actual intervention of acetoxonium ions for esters IV, n = 0, 1 and 2 was demonstrated by an oxygen-18 label study. The appropriate diacetates were synthesized by acetylation of the corresponding diols with acetyl chloride-O^{18} and subjected to reaction with $AlCl_3$. The reaction was stopped by hydrolysis of aluminium salts with water. Product and unreacted starting material were separated by distillation and treated as shown in equations (2) and (3).



$$\underset{*OAc}{CH_2}-(CH_2)_n-\underset{Cl}{CH_2} \xrightarrow{LiBH_4} \underset{*OH}{CH_2}-(CH_2)_n-\underset{Cl}{CH_2} \qquad (2)$$

VII



$$\underset{*OAc}{CH_2}-(CH_2)_n-\underset{OAc}{CH_2} \xrightarrow[KOH]{10\%} \underset{*OH}{CH_2}-(CH_2)_n)-\underset{OH}{CH_2} \xrightarrow{PhCOCl} \underset{*OBz}{CH_2}-(CH_2)_n-\underset{OBz}{CH_2} \qquad (3)$$

VIII

Labelled IV, VII, and VIII were combusted to CO_2 and analysed for O^{18} content.[10] The results are summarized in Table 2. Incorporation of O^{18} in the chlorohydrin VII directly yields the percentage of acetoxonium ion formation N(max). Thus, for IV, n = 0 and 1 virtually all of the product has been formed _via_ ions I and II, respectively. The alkyl O^{18} content of unreacted starting material measured as dibenzoate VIII shows that a slight amount of scrambling has occurred, this probably _via_ internal return from the symmetrical acetoxonium ion. N (min) is calculated on the basis of the simplifying assumption that scrambled product formation is concluded at the onset of reaction of IV with $AlCl_3$.

Table 2 O^{18} Analyses in reactions of labelled esters with $AlCl_3$.[a]

Starting ester IV		Product VII	Unreacted starting material as VIII	Temp. °C	N^b (max)	N^b (min)
n=0	1.17±0.2%	1.13±0.01%	0.159±0.08%	104±2[c]	96.6%	95.3%
n=1	0.660±0.001%	0.642±0.002%	-	106±2[d]	97.3%	-
n=2	0.585±0.05%	0.346±0.02%[e]	0.143±0.005%	107±2[f]	59.1%	20.1%

[a] Results are given in atom % excess (the values shown are the average of two or more determinations and the average deviations). [b] N = percent acetoxonium ion formation (calculated as described at the end of the Experimental Section); [c] 80% completion in 0.5 h; [d] 65% completion in 1.25 h; [e] Product V was converted to and analysed as tetrahydrofuran in the case of ester IV, n=2; [f] 20% conversion in 8 h.

The results for esters IV, n = 0 and 1 and the stability of product V (n = 2) in the presence of $AlCl_3$ (94°) encouraged us to look for acetoxonium ion formation in the IV, n = 2 homolog. The results for IV, n = 2 clearly demonstrate appreciable AcO-7 participation via the ion III. Unreacted starting material is considerably more scrambled than in the first case (48.9% O^{18} scrambling for n = 2 vs. 27.2% for n = 0) principally as a consequence of the long reaction time.

Scrambling via return from a symmetrical acetoxonium ion is less likely to occur in the case of ester IV, n = 2 than for esters IV, n = 0 and 1 since a seven-membered ring acetoxonium ion is expected to form less rapidly than the corresponding five- and six-membered rings. The scrambling observed must largely occur by straight displacement of acetate at a rate approaching that of acetate displacement by Cl in the limiting cases, e.g., IV, n = 3 or 4.[11] In view of this, N (min) for AcO-7 participation tends to underestimate the actual extent of formation of acetoxonium ion III. .

Experimental Section

Nuclear magnetic resonance (NMR) ^1H spectra were recorded on a Varian A-60 spectrometer at 60 MHz. Chemical shifts (δ) are expressed in parts per million (ppm) downfield from internal tetramethylsilane (δ = 0.0). Infrared spectra were determined on a Perkin-Elmer 137 Infracord spectrometer. Melting points were determined on a Thomas-Hoover apparatus and are corrected; boiling points are uncorrected. Elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn.

Gas chromatography (gc) was performed on a F & M Model 720 dual column instrument fitted with thermal conductivity detectors using helium as carrier gas. The column (10 ft. x 0.25 in. O.D.) was packed with 20% Carbowax 20M on 60/80 mesh Chromosorb W. Gas chromatographic peak areas were measured with a planimeter or with a Honeywell Disc Chart Integrator, Model 201-B and are uncorrected for thermal response.

Preparation of Acetyl Chloride-O^{18}. Acetyl chloride (52.2 g, 0.66 mole) was hydrolyzed with 10.0 g (0.55 mole) of water-O^{18} (5% or 3.84% O^{18} enrichment) at 0°. The reaction mixture was heated at 55° for 2 h, and allowed to cool gradually to room temperature. Thionyl chloride (65.0 g, 0.55 mole) was then slowly added to the stirred mixture over a period of 30 min, and the reaction mixture then heated at 40-45° for 2.5 h. Glacial acetic acid (1 ml) was added in order to insure the complete reaction of the thionyl chloride, and the heating continued for 1 h. Distillation yielded 38.5 g (89%) of acetyl chloride-O^{18}, b.p. 35-54°.

Preparation of 1,2-Ethanediol Diacetate-carbonyl-O^{18}. The reaction of 7.8 g (0.13 mole) of 1,2-ethanediol, 24.0 g (0.31 mole) of dry pyridine, and 23.0 g (0.30 mole) of acetyl chloride-O^{18} in 100 ml of chloroform yielded 11.5 g (63%) of a clear, colorless liquid: b.p. 78-80° (10 mm) (lit.[12] b.p. 188.8-190.3°). Gas chromatographic analysis (at 160°, 45 cc/min) showed the product to have a purity in excess of 99%. The infrared spectrum (liquid film) was identical to that of the corresponding unlabelled compound.

Preparation of 1,3-Propanediol Diacetate-carbonyl-O^{18}. 1,3-Propanediol (9.3 g, 0.12 mole) was acetylated with 24.0 g (0.31 mole) of acetyl chloride-O^{18} as described above. The yield was 27.0 g (64%) of clear, colorless product: b.p. 94-95° (11 mm) (lit.[13] b.p. 91-92 (10 mm)). Gas chromatographic analysis (at 170°, 45 cc/min) showed the product to have a purity in excess of 99%.

Preparation of 1,4-Butanediol Diacetate-carbonyl-O^{18}. 1,4-Butanediol (25 g, 0.277 mole) was acetylated in chloroform (250 ml) with acetyl chloride-O^{18} (47.5 g, 0.605 mole) in the presence of pyridine (46 g) as described above. The yield was 35.0 g (73%); b.p. 74° (1-2 mm) (lit.[14] b.p. 130-130.5° (14 mm)). The product was reacetylated to convert a small amount (5-6%) of 1-acetoxy-4-butanol contaminant to diester as demonstrated by gas chromatographic analysis (at 175°, 60 cc/min); ^{1}H-NMR ($CDCl_3$); = 1.7 (m, 4H), 2.0 (s, 6H), and 4.1 (m, 4H) ppm.

Reaction of Aluminium Chloride with 1,2-Ethanediol Diacetate-carbonyl-O^{18}. Anhydrous aluminium chloride (1.6 g, 12.2 mmoles) and 1,2-ethanediol diacetate-carbonyl-O^{18} (p. 50) (3.5 g, 24.0 mmoles) were heated and stirred together at 104±2° for 0.5 h. Gas chromatographic analysis (at 140°, 45 cc/min) indicated that the reaction had proceeded to 80% completion. The reaction was quenched by adding 15 ml of diethyl ether and 5 ml of water. The aqueous layer was washed with two 10 ml portions of ether and the combined ether extract was washed with 10 ml of 10% aqueous sodium bicarbonate. The ether was dried over magnesium sulfate, filtered and removed by distillation. A clear, colorless liquid, (1.3 g) was obtained by vacuum distillation: b.p. 49-50° (10 mm). The distillate consisted of 90% 2-chloroethyl acetate and 10% 1,2-ethanediol diacetate while the residue (0.5 g) a yellow oil, consisted of 85-90% 1,2-ethanediol diacetate and 5-10% 2-chloroethyl acetate (gc analysis).

Reduction of 2-Chloroethyl Acetate-O^{18}, 2-Chloroethanol-O^{18}. The distillate (above) was dissolved in 10 ml of anhydrous diethyl ether and slowly added to a solution of 0.25 g (11 mmoles) of lithium borohydride in 10 ml of anhydrous diethyl ether. The reaction mixture was stirred at room temperature for 3 h and hydrolyzed by addition of 1 ml of methanol and 1 ml of water. Ten ml of methylene chloride was added and the filtered reaction mixture was distilled in order to remove the solvent. The residue yielded 150 mg of a clear, colorless liquid by preparative gc (at 115°, 60 cc/min). Product purity was estimated to be higher than 99% by gc analysis. The infrared spectrum (liquid film) was identical to that of commercial 2-chloroethanol. The sample recovered by preparative gc was analysed for O^{18} content.

Hydrolysis of Recovered 1,2-Ethanediol Diacetate-O^{18} Conversion to 1,2-Ethanediol Dibenzoate-O^{18}. The yellow residue obtained (above) was added to a solution consisting of 1.6 g (29 mmoles) of potassium hydroxide dissolved in 100 ml of water. The mixtures was stirred at room temperature for 2 h. The flask was cooled to 0° and 0.7 g (5 mmoles) of benzoyl chloride was quickly added to the stirred reaction mixture. Rapid stirring was maintained for 10 min while a white solid precipitated. The solid product was filtered and recrystallized three times from *n*-hexane. Crystallization was induced each time by immersion of the *n*-hexane solution in a dry-ice acetone bath. The white, crystalline product (39 mg) had a m.p. of 70-71° (lit.[15] m.p. 70.5-71°). The infrared spectrum (KBr) was identical to that of standard 1,2-ethanediol dibenzoate. The product was analysed for O^{18} content.

Reaction of Aluminium Chloride with 1,3-Propanediol Diacetate-carbonyl-O^{18}. Anhydrous aluminium chloride (1.7 g, 13.0 mmoles) and 1,3-propanediol diacetate-carbonyl-O^{18} (4.3 g, 26.9 mmoles) were heated and stirred together at 106±2° for 1.25 h. Gas chromatographic analysis (at 175°, 45 cc/min) showed the reaction to have proceeded to 65% completion. The distillate was prepared for O^{18} analysis as described for the ethanediol diacetate case.

Reaction of Aluminium Chloride with 1,4-Butanediol Diacetate-carbonyl-O^{18}. Anhydrous aluminium chloride (11.6 g, 0.087 mole) and 1,4-butanediol diacetate-carbonyl-O^{18} (19.0 g, 0.167 mole) were heated and stirred together at 107±2° for 8 h and worked up as described for ethanediol diacetate-carbonyl-O^{18}. Vacuum distillation, b.p. 64-102° (9 mm) gave three fractions that were redistilled to separate the 4-chlorobutyl acetate product (4.9 g, 0.033 mole) from residual diester. This corresponds to a 20% conversion.

Saponification of the 4-Chlorobutyl Acetate Product. The product of the above reaction (4.3 g) was stirred at room temperature with 10% aqueous KOH (50 ml). The reaction mixture was salted out with NaCl and extracted with diethyl ether. Tetrahydrofuran product (0.38 g) was isolated by preparative gc (97°, 60 cc/min). The purity of the recovered tetrahydrofuran (18%) was estimated to be 99% by gc analysis. This tetrahydrofuran was analysed for O^{18} content.

A control reaction demonstrated that no scrambling of the oxygen label occurred during the formation of the tetrahydrofuran product: 1-acetoxy-4-chlorobutane-carbonyl-O^{18} (prepared by reaction of 4-chloro-1-butanol with acetyl chloride-O^{18} in hexane; 0.619 atom % excess O^{18}) was stirred with 10% aqueous KOH for 3 h at room temperature and the reaction mixture extracted with diethyl ether. The tetrahydrofuran was isolated by preparative gc (at 113°, 60 cc/min). Analysis for O^{18} showed that the tetrahydrofuran contained 0 atom % excess O^{18}.

Conversion of Residual 1,4-Butanediol Diacetate to 1,4-Butanediol Dibenzoate. Residual 1,4-butanediol diacetate from the reaction of O-18 labelled diester with $AlCl_3$ (2.0 g, 0.012 mole) was treated with 20% aqueous KOH (50 ml) and benzoyl chloride (5.0 g, 0.036 mole) at room temperature for 1.5 h. The solid product was recrystallized from hexane to yield crystals of 1,4-butanediol dibenzoate, m.p. 81.5-82° (lit.[16] 82°) that were analysed for O^{18} content; ^{1}H-NMR ($CDCl_3$); δ = 1.92 (m, 4H), 4.4 (m, 4H), 7.2-7.5 (m, 6H) and 8.0-8.1 (m, 4H) ppm.

Oxygen-18 Analyses. Oxygen-18 enriched un-normalized water (deuterium content exceeds natural abundance) was purchased from Bio-Rad Laboratories in 5%, and from Miles Laboratories, Inc., in 3.84% concentration. The appropriately labelled polyol acetates were prepared by acetylation of the corresponding polyol with acetyl chloride-O^{18}. The latter was prepared by hydrolysis of unlabelled acetyl chloride with 3.8-5% atom percent excess water-O^{18} followed by treatment with thionyl chloride to regenerate acetyl chloride. O-18 analyses were performed either by Isotopes Inc., Westwood, New Jersey or at Columbia University, College of Physicians and Surgeons. Analyses at Columbia University were carried out by Carter Cook and Richard B. Johnson, Jr.

All O-18 labelled compounds were subjected to combustion to carbon dioxide according to the modified procedure of Rittenberg and Ponticorvo (10) and analysed for O-18 content by isotope ratio-mass spectrometry. The percent excess O-18 was calculated by subtracting the O-18 abundance in natural carbon dioxide as calculated from a standard carbon dioxide spectrum. The results (average of two or more determinations) were assumed to have a maximum error of 3%.[17] The excess O-18 concentrations are given in Table 2.

Calculation of the Extent of Acetoxonium Ion Formation. The maximum percent of acetoxonium ion formation, 100 N', is given by the relationship N' = 4C/(A + B) where A equals the atom percent excess O^{18} in the diacetate labelled only at the carbonyl oxygen atom multiplied by the number of oxygens in the molecule; B equals the atom percent excess O^{18} in the diacetate labelled only at the alkyl oxygen multiplied by the number of oxygens in the molecule; and C equals the atom percent excess O^{18} of the alkyl oxygen of the final product multiplied by the number of oxygens in the molecule.

In order to correct for the extent to which scrambling had occurred in the starting material (by internal return), the reactions of labelled polyol were not run to completion. This permitted the recovery of some of the starting polyol acetate and the subsequent analysis of its alkyl oxygen for O^{18} content. The extent of scrambling was taken into account in the calculation of the minimum value of acetoxonium ion formation, 100 N, by assuming internal return to be an infinitely fast process. The following equation was applied in these calculations: $AN/4 + BN/4 + B(1-N)/2 = C$. The third term in this equation represents the percent of diacetate scrambled by internal return and undergoing direct displacement to give a labelled alkyl oxygen.

The percent acetoxonium ion formation is given in Table 2.

Acknowledgement. We thank Prof. J. Nasielski (Université Libre de Bruxelles, Brussels, Belgium) for valuable comments.

Reference and Notes

1. Undergraduate research participant.
2. B. Capon, Quart. Rev. (London), 18, 45 (1964); M. I. Page, Chem. Soc. Rev., 2, 195 (1973).
3. See for example, L. J. Dolby and M. J. Schwartz, J. Org. Chem., 30, 3581 (1965).
4. S. Winstein and R. E. Buckles, J. Amer. Chem. Soc., 65, 613 (1943).
5. (a) C. B. Anderson, E. C. Friedrich, and S. Winstein, Tetrahedron Lett., 2037 (1963); (b) G. Schneider and O. K. J. Kovacs, Chem. Comm., 202 (1965); (c) M. Haet and D. A. Tomalia, Tetrahedron Lett., 3383, 3389 (1966); (d) G. A. Olah and M. A. Bellinger, J. Amer. Chem. Soc., 89, 4744 (1967); (e) H. Paulsen and H. Meyborg, Tetrahedron Lett., 3973 (1972).
6. (a) M. Derbesy and M. Naudet, Bull. Soc. Chim. Fr., 4531 (1968); (b) M. Derbesy, M. Chicheportiche, and M. Naudet, ibid., 1789 (1971).
7. J. E. Baldwin, J. Chem. Soc. Chem. Commun., 734 (1976).
8. W. J. Baumann, A. J. Aasen, J. K. G. Kramer, and R. T. Holman, J. Org. Chem., 38, 3767 (1963).
9. H. Paulsen, H. Behre, and C. P. Herold, Topics in Current Chem., 14, 472 (1970) and references cited therein.
10. D. Rittenberg and L. Ponticorvo, Int. J. Appl. Radiat. Isotopes, 1, 208 (1956).
11. Displacement actually occurs on acetate complexed by $AlCl_3$ which yields a much better leaving group.
12. A. Streitwieser and J. R. Wolfe, J. Amer. Chem. Soc., 79, 903 (1957).
13. M. Jenkus, J. Amer. Chem. Soc., 68, 734 (1946).
14. I. M. Gverdtsiteli and S. G. Mikadze, Zh. Obshch. Khim., 22, 1401 (1952); Chem. Abstr., 47, 6338 (1952).
15. J. E. Millington and F. L. M. Pattison, Can. J. Chem., 34, 1532 (1956).
16. F. Fichter and A. Schnider, Helv. Chim. Acta, 14, 857 (1931).
17. J. W. Taylor and I-J. Chen, Anal. Chem., 42, 224 (1970).