A Stereochemical Test for Ether-Oxygen Participation and Oxonium Ion Formation in the Acetolysis of 3-Tetrahydropyranyl Brosylate

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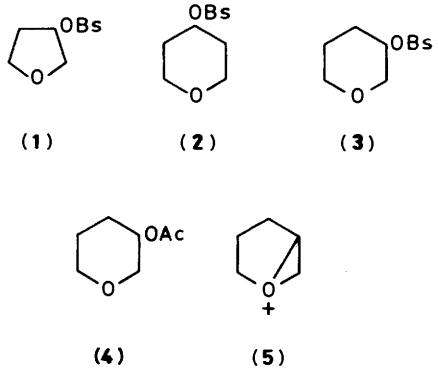
Optically active tetrahydropyran-3-ol was obtained by the horse liver alcohol dehydrogenase (HLADH)-catalysed reduction of tetrahydropyran-3-one, and the corresponding brosylate was prepared. Acetolysis of the optically active brosylate gave racemic 3-tetrahydropyranyl acetate as well as varying amounts of racemic tetrahydropyran-3-ol. Within experimental error, the polarimetric rate of acetolysis was the same as the previously measured titrimetric rate. The results provide no support for the intermediacy of a bicyclic oxonium ion in the acetolysis of 3-tetrahydropyranyl brosylate.

In 1969, Tarbell and Hazen studied the acetolysis of some simple heterocyclic sulphonate esters.[1] As expected, the reaction rates for the oxygen heterocycles (**1**) and (**2**) were slower than those of the corresponding carbocycles, owing to the unfavourable interaction between the C–O dipoles and the incipient carbenium ion centres. It was found, however, that 3-tetrahydropyranyl brosylate (**3**) was solvolysed faster than expected to yield (**4**), the observed rate being about the same as that for cyclohexyl brosylate. The absence of the expected rate-retardation for (**3**) was attributed to the operation of R_2O-3 neighbouring group participation, leading to an intermediate oxonium ion (**5**). Such anchimerically assisted R_2O-3 pathways have subsequently been established for more highly strained oxygen-bridged bicyclic brosylates,[2] and the consequences for reaction-rates and product stereochemistry in these cases are well understood.

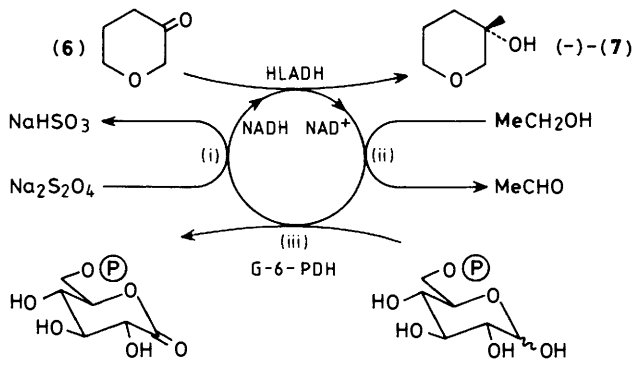


It has always seemed that the intermediacy of oxonium ion (**5**) in the acetolysis of (**3**) has not been satisfactorily established, the evidence in its favour being merely the absence of an expected rate-retardation. For this reason, we sought to apply a stereochemical test for the involvement of (**5**) in the acetolysis of (**3**), and this paper reports our preparation of an optically active sample of (**3**) and the results of our studies of its solvolysis.

Results

Preparation of Optically Active (**3**).—Racemic tetrahydropyran-3-ol (**7**) was conveniently prepared from the commercially available 2,3-dihydropyran.[3] Resolution of compound (**7**) was attempted by converting it into its phthalate half-ester, followed by fractional crystallization of the (−)-cinchonidine salt,[2] but only small optical rotations were achieved. Similar attempts to resolve compound (**7**) *via* its succinate and maleate half-esters met with no greater success.

Optically active compound (**7**) was eventually obtained by an enzymic method. Jones recently reported highly stereoselective reductions of 2-substituted tetrahydropyran-4-ones, catalysed by horse liver alcohol dehydrogenase (HLADH);[4] so that it was expected that a similar reduction of tetrahydropyran-3-one (**6**) would yield optically active (**7**). The pyranone (**6**) was prepared from racemic compound (**7**) by oxidation,[5] and a study was then made of its HLADH-catalysed reduction. Standard spectrophotometric methods[6] were used to show that (**6**) was reduced at 7.6% of the rate of the reference substrate, cyclohexanone. Fortunately, this is considered to be above the minimum necessary for a viable preparative scale reduction.[7] For small-scale reactions (up to 100 mmol), the consumption of the coenzyme, nicotinamide adenine dinucleotide (reduced form NADH; oxidized form NAD^+), required in stoicheiometric amounts, is a cost which may be tolerated. Nevertheless, if the coenzyme is regenerated *in situ*, only catalytic amounts are required. Accordingly, three methods of coenzyme recycling were investigated. Recycling by oxidation of sodium dithionite or ethanol [Scheme 1, (i) and (ii) respectively] produced no isolable yield of the alcohol. However, coenzyme recycling by means of the coupled enzyme, glucose-6-phosphate dehydrogenase, proved successful.[8] By this means [Scheme 1, (iii)],



Scheme 1.

(−)-(**7**) was prepared from (**6**) in *ca.* 70% yield. The enantiomeric excess (e.e.) of the sample of (**7**) was determined by converting it into its ester with (−)-α-methoxy-α-trifluoromethyl-α-phenylacetic acid, followed by 250 MHz ^1H n.m.r.

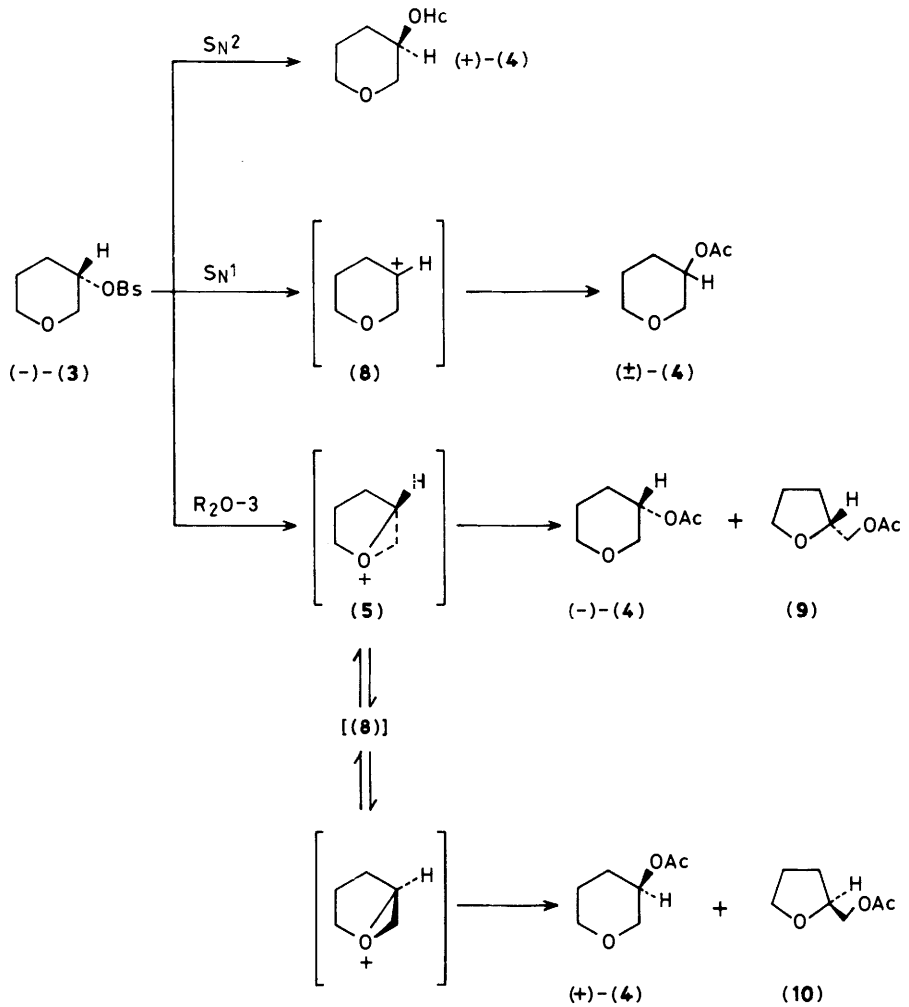
examination in the presence of $[Eu(fod)_3]$.[9] The e.e. determined in this way was 49%. No effort was made to decide the absolute configuration of the predominant enantiomer. Treatment of the partially resolved alcohol with brosyl chloride and pyridine afforded (−)-(**3**), while the corresponding laevorotatory acetate was similarly obtained by treatment of (−)-(**7**) with acetic anhydride and pyridine.

Acetolysis of Compound (−)-(**3**).—Solvolysis of compound (−)-(**3**) in buffered acetic acid at 90 °C in a sealed tube for a time greater than 10 half-lives led to the isolation of a mixture of a racemic 3-tetrahydropyranyl acetate (**4**) and the racemic alcohol (**7**). The yield of the latter could be reduced by excluding moisture from the system, but was never made negligible. There was no evidence for additional, rearranged products. The optically active acetate (−)-(**4**) was found to be stable under the same conditions; so that racemization is a direct consequence of acetolysis and not a secondary reaction.

Rates of acetolysis of compound (−)-(**3**) were determined polarimetrically at four temperatures between 79 and 90 °C. The first-order plots (ln(α) *vs.* time) often showed a slight initial curvature but soon settled down to good linear behaviour. The curvature was such that the initial rate was slightly enhanced, and we attribute this to traces of water in the system, which were quickly removed by reaction. It is possible that a hydrogen-bonded complex of water and compound (−)-(**3**) solvolyses faster than the uncomplexed brosylate, yielding the observed alcohol product. In view of the lack of rearranged products, the curvature could not reasonably be attributed to the formation of a rearranged brosylate of lower reactivity than compound (**3**). Polarimetric rate constants, taken from the linear portions of the plots, are given in Table 2, where it can also be seen that, within experimental error, the polarimetric rate of acetolysis of compound (−)-(**3**) is the same as the previously determined titrimetric rate.[1]

Discussion

There are three obvious mechanisms by which the acetolysis of compound (−)-(**3**) might proceed (Scheme 2). The first is an S_N2 displacement of the brosylate anion, which would invert the configuration and give (+)-(**4**). Besides being inherently unlikely, this is clearly ruled out by the formation of racemic acetate as the product. The second possible mechanism is a simple S_N1 process, yielding the achiral carbenium ion (**8**) and ultimately the racemic acetate (±)-(**4**). The third is an S_N1 process involving R_2O-3 participation, yielding the intermediate oxonium ion (**5**). In the most straightforward case, (**5**) would react with HOAc to give the acetate with retained stereochemistry [(−)-(**4**)] and possibly the isomeric (**9**). Since the observed product is racemic, this simple mechanism cannot operate, but racemization of the oxonium ion (**5**) could occur



Scheme 2.

Table 1. HLAD-Catalysed reduction of tetrahydropyran-3-one (**6**): relative rate determination

Assay mixture	Vol. used (cm^3)	Conc. in assay (mM)
1. 0.1 M-KH_2PO_4 adjusted to pH 7.0 with NaOH	2.5	86
2. (a) 96 mM Cyclohexanone	0.1	3.31
(b) 97 mM Tetrahydropyran-3-one (**6**)	0.1	3.34
3. mM NAD^+	0.1	0.17
4. HLADH (3.78 mg in 10 cm^3 of 50 mM tris–HCl at pH 7.0)	0.1	

Table 2. Polarimetric first-order rate constants for acetolysis of (−)-(**3**) compared with the titrimetric rate constant

	Temp. (°C)	$10^5k/s^{-1}$
Polarimetric	79.3	1.41
	81.4	1.73
	82.1	1.73
	89.9	7.86
	84.9	3.2[a]
Titrimetric	84.9	2.47[b]

[a] Data obtained by Arrhenius interpolation. [b] Data from ref. 1.

via the carbenium ion (**8**), as shown. The product stereochemistry, therefore, does not unambiguously discriminate between the assisted and unassisted S_N1 pathways. An experimental observation which would strongly support the R_2O-3 mechanism would, of course, be the isolation of ring-contracted acetates (**9**) and (**10**), but no evidence for their formation has been obtained. Such ring-contractions have been reported for well-established cases of R_3N-3 participation,[10] R_2S-3 participation,[11] and even R_2O-3 participation in pyranosides,[12] and are therefore to be expected in similar reactions.

The stereochemical results and product distribution, therefore, provide no support for the existence of the bicyclic oxonium ion intermediate (**5**). At most, if (**5**) is formed at all from (−)-(**3**), it must be very rapidly equilibrated with its enantiomer, presumably *via* the achiral monocyclic carbenium ion (**8**). This behaviour is in complete contrast to that of the tricyclic oxonium ion formed in the solvolysis of *endo*-8-oxabicyclo[3.2.1]octan-2-yl brosylate,[2] where the exclusive retention of *endo* stereochemistry in the product acetate and the fact that the *exo* epimer solvolyses by a completely different, rearrangement pathway argue strongly against the intervention of a bicyclic carbenium ion analogous to (**8**).

In conclusion, it should be emphasized that the stereochemical evidence is in complete accord with the simple S_N1 mechanism, leading directly from (−)-(**3**) to the carbenium ion (**8**). Only the unexpectedly high rate of solvolysis of (**3**) seems to suggest an R_2O-3 assisted pathway, and the possibility remains that this is due to peculiarities of solvation or some other effect.

Experimental

General.—I.r. spectra were recorded on a Perkin-Elmer model 397 spectrophotometer, and ^1H n.m.r. spectra on Perkin-Elmer R32 (90 MHz) and Bruker WM 250 (250 MHz) instruments. U.v. measurements were made using a Pye-Unicam SP 8000 spectrophotometer, and optical rotations with a Perkin-Elmer model 241 polarimeter equipped with a jacketted, 10 cm pathlength cell and a constant temperature bath.

HLAD-*Catalysed Reduction of Tetrahydropyran*-3-*one* (**6**): *Relative Rate Determination.*—Solutions 1, 2a or 2b, and 3 (Table 2) were incubated at 25 °C for 5 min in a cuvette. The reaction was started by addition of solution 4, and the rate of change of absorbance at 340 nm was measured. The rate of reduction of (**6**) was found to be 7.6% of that of cyclohexanone.

Preparative Scale HLADH-*Catalysed Reduction of Tetrahydropyran*-3-*one* (**6**).—The barium salt of glucose-6-phosphate heptahydrate (11.6 g, 20 mmol) was stirred vigorously in 0.18 M-sulphuric acid (111 cm^3) for 45 min. The bulk of the precipitated $BaSO_4$ was removed by centrifugation, and the solution was carified by filtration and neutralized with sodium hydroxide. To this solution of glucose-6-phosphate (185 cm^3), which was de-aerated by passage of N_2, was added tetrahydropyran-3-one (2.0 g, 20 mmol), $MgSO_4$ (76.8 mg, 0.4 mmol), NAD^+ (12.6 mg, 18.3 μmol), HLADH (56.6 mg), and glucose-6-phosphate dehydrogenase (0.36 mg, 22.4 u). The pH was maintained automatically at 7.0—7.4 by addition of 4M-aqueous KOH. The reaction was conducted under nitrogen with stirring, and its progress was followed by g.l.c. and by enzymic assay of glucose-6-phosphate concentration. After 24 h, further portions of NAD^+ (4.04 mg, 5.9 μmol) and $MgSO_4$ (17.6 mg, 91 μmol) were added. The reaction was complete after 4.5 days. The mixture was centrifuged to remove a light precipitate, and the supernatant liquor was saturated with NaCl and extracted continuously with ether (250 cm^3) for 3.5 days. After drying ($MgSO_4$) and removal of the solvent under reduced pressure, Kugelrohr distillation of the residue gave optically active tetrahydropyran-3-ol (−)-(**7**) as a clear, colourless liquid (1.49 g, 68%), with spectra corresponding to those of racemic (**7**); $[\alpha]_D^{24.5}$ −8.7 ± 1.4°; $[\alpha]_{365}^{29.25}$ −23.7 ± 1.4° (*c* 3.39 in $CHCl_3$).

Determination of the Enantiomeric Excess of Compound (−)-(**7**).—(−)-α-Methoxy-α-trifluoromethyl-α-phenylacetic acid chloride [(−)-MTPA-Cl] was prepared from the acid by the published method;[9] $[\alpha]_D^{18.5}$ −129.2° (*c* 4.76 in CCl_4). Compound (−)-(**7**) (20.8 mg, 0.2 mmol) and (−)-MTPA-Cl (51.9 mg, 0.2 mmol) were mixed in 5 drops of CCl_4, pyridine (5 drops) was added, and a white precipitate formed immediately. The mixture was shaken at room temperature overnight, then water (1 cm^3) was added and the mixture was extracted with ether. The organic phase was washed with 0.1 M-HCl (5 cm^3) saturated $NaHCO_3$ (2 cm^3), and water (2 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure to yield the ester, which was not further purified. The racemic alcohol was treated in the same way, yielding the corresponding ester, which was used for comparison. The enantiomeric excess of (−)-(**7**) was determined by 250 MHz ^1H n.m.r. examination of the diastereoisomeric methoxy protons of the ester in $CDCl_3$ solution in the presence of [Eu(fod)$_3$] shift reagent. Integration of the signals indicated an enantiomeric excess of 49%.

Optically Active 3-*Tetrahydropyranyl Brosylate* (−)-(**3**) *and Acetate* (−)-(**4**).—The optically active alcohol (−)-(**7**) was converted by standard procedures into the corresponding brosylate (−)-(**3**), m.p. 71—73 °C (Found: C, 40.8; H, 4.0. Calc. for $C_{11}H_{13}BrO_4S$: C, 41.1; H, 4.1%); $[\alpha]_{365}^{25.5}$ −10.3° (*c* 2.46 in $CHCl_3$). Compound (−)-(**7**) was also converted into the corresponding acetate (−)-(**4**), and obtained as a colourless liquid; $[\alpha]_{365}^{25.5}$ −24.7° (*c* 1.64 in $CHCl_3$).

Acetolysis of (−)-(**3**)*: Polarimetric Rates.*—Anhydrous acetic acid was prepared by heating a solution of acetic anhydride (5% v/v) and CrO_3 (1% w/v) under reflux overnight, followed by distillation in a dry atmosphere. Sodium acetate was dried in an oven at 200 °C for 2 h, allowed to cool in a dessicator, then dissolved in anhydrous acetic acid to give a 0.0384 M solution, as determined by titration with perchloric acid.

Solutions of (−)-(**3**) (*ca.* 10 mg) in the buffered acetic acid (1 cm^3) were transferred to a heated polarimeter tube and allowed to come to thermal equilibrium over at least 5 min. The solutions were maintained at constant temperature and optical rotations at 365 nm were measured at suitable intervals. The data obtained were used to derive first-order rate plots [ln(α) *vs.* time]. These are discussed in the Results section above and the first-order rate constants are given in Table 2.

Acetolysis of (−)-(**3**)*. Identification of the Products.*—(−)-(**3**) (90 mg, 0.28 mmol) was dissolved in buffered acetic acid (9 cm^3) and heated in a sealed tube at 105 °C for 22 h. The cooled solution was diluted with water (25 cm^3) and extracted with ether (3 × 25 cm^3). The combined extracts were then washed with saturated $NaHCO_3$ solution until neutral, dried ($NaSO_4$), and concentrated under reduced pressure. Polarimetric examination of the product indicated no measurable optical rotation, and g.l.c. analysis showed the presence of two compounds with retention times corresponding to those of the acetate (**4**) and the alcohol (**7**). The identity of the two products was confirmed by g.l.c. and mass spectroscopy and comparison with authentic samples.

Stability of (−)-(**4**) *to Solvolysis Conditions.*—A solution of the optically active acetate [−]-[**4**] in buffered acetic acid, with initial optical rotation at 365 nm of −0.275°, was heated in a sealed tube at 105 °C for 18h. After cooling, the measured optical rotation at 365 nm was −0.264°.

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