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Control of Stereochemistry of Cyclisation by Orbital Overlap: Conversion of $\gamma\delta$ -Unsaturated Aldehydes into Cyclopentanones†

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Summary In the cyclisation of 4-methyldec-4-enal (**2**) to 3-methyl-2-pentylcyclopentanone (**3**), catalysed by stannic chloride, the *Z*-aldehyde (**2-Z**) forms the *cis*-ketone (**3-c**) and the *E*-aldehyde (**2-E**) the *trans*-ketone (**3-t**); this is an example of a geometrical factor of general importance.

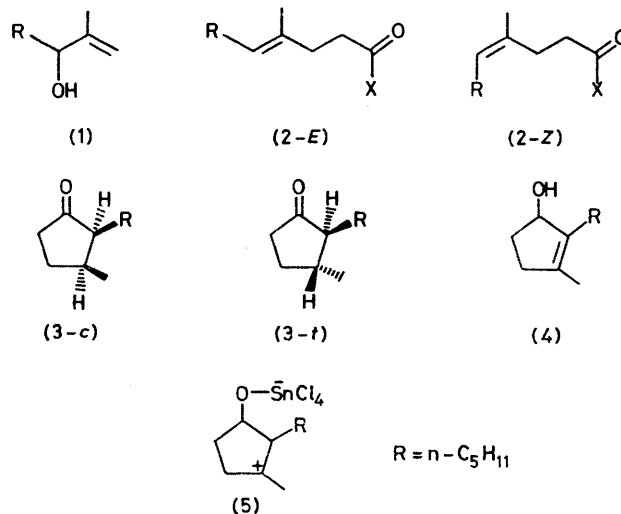
THE significance of orbital overlap in controlling the facility of ring closure has recently been emphasized.^{1,2} We now point out that the same geometrical factors³ may also control the stereochemistry of the cyclised products.

Thus there are numerous examples⁴ of cyclisation of 5,6- and 6,7-unsaturated aldehydes to cyclohexenols and cycloheptenols, often under very mild conditions, but similar cyclisation of 4,5-unsaturated aldehydes to cyclopentane derivatives‡ is almost unknown.⁵

Reaction of the allyl alcohol (**1**), made by addition of *n*-pentylmagnesium bromide to methacrolein (80% yield), with isobutyl vinyl ether catalysed by mercuric acetate, followed by Claisen rearrangement, gave the 4,5-unsaturated aldehyde (**2**, X = H) (54%) as a mixture of *Z*- (13 ± 2%) and *E*-isomers (87 ± 2%). Condensation of the allyl alcohol (**1**) with triethyl orthoacetate⁶ produced the corresponding ester (**2**, X = OEt) (91%), containing 98% *E*-isomer with only 2% *Z*-isomer.

Addition of the aldehyde (**2**, X = H) in methylene chloride to stannic chloride (1 mol) in methylene chloride at 0 °C caused cyclisation to the cyclopentanone (**3**) (60%). Three mechanisms were considered for the reaction: (i) cyclisation followed by shift of the double bond through

the allylic alcohol (**4**) or its SnCl₄ complex; (ii) cyclisation to the carbonium ion (**5**) followed by a 1,3-hydride shift; or (iii) cyclisation to (**5**) followed by two successive 1,2-hydride shifts.



Possibility (i) was excluded by subjecting the alcohol (**4**) (made by reducing the ketone with LiAlH₄) to the conditions of the reaction and finding that no ketone (**3**) was

† No reprints available.

‡ By an extension of earlier nomenclature^{1,2} this could be called a 5-*endo-trigonal*, *exo-trigonal* cyclisation, the former component making it a relatively disfavoured process (see J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R. C. Thomas, *J.C.S. Chem. Comm.*, 1976, 736).

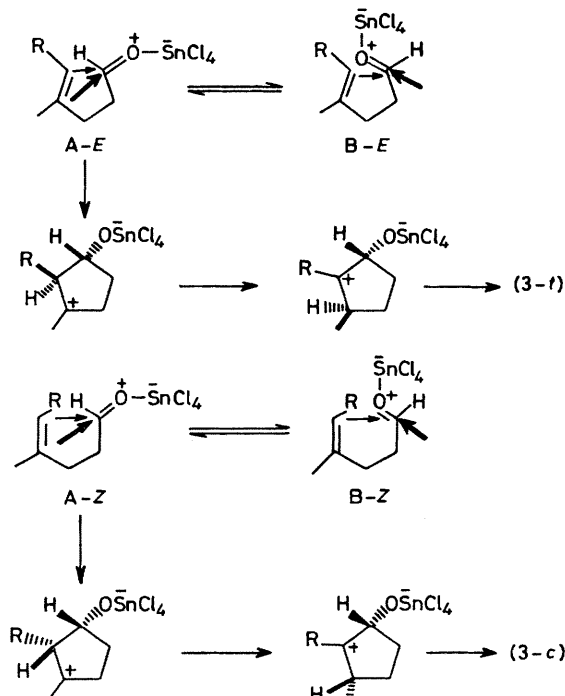
produced. A decision between the two remaining alternatives was reached by labelling the H atom on C-1 of the aldehyde (**2**, X = H).

Reduction of the ester (**2**, X = OEt) with LiAlD₄ and oxidation of the resulting alcohol with chromic oxide-pyridine in methylene chloride⁷ gave the 1-deuterio-aldehyde (**2**, X = D). Cyclisation of that aldehyde gave a cyclopentanone (59%), the mass spectrum of which showed > 99% retention of deuterium. The ¹H n.m.r. spectrum still contained the doublet (*J* = 7 Hz) at δ 1.15 from the 3-methyl group, showing that deuterium was not at C-3. The deuterium was removed by alkali in aqueous ethanol at room temperature, which indicated that it was attached to a carbon atom next to the CO group, presumably C-2. Complete proof of its position was provided by the ¹³C n.m.r. spectrum.

The signal (56.6 p.p.m.) with the largest chemical shift after that from the CO carbon atom, which appeared as a doublet in the off-resonance spectrum, can be assigned to C-2. This signal disappeared entirely in the spectrum of the deuteriated sample. However, when a delay of 3 s was introduced between irradiation and acquisition of the spectrum the signal reappeared as a 1:1:1 triplet (because of the longer relaxation time of ¹³C-D than of ¹³C-H). The deuterium atom is thus proved to be on C-2 and the reaction to proceed by two successive 1,2-hydride shifts.

The ketone (**3**) produced by cyclisation of the *E*-aldehyde (**2-E**, X = H) containing 2% *Z*-isomer was the *trans*-isomer (**3-t**), being stable to base. Cyclisation of the sample of aldehyde consisting of 87 ± 2% *E*- and 13 ± 2% *Z*-isomer gave the ketone as a mixture of 89 ± 2% *trans*-isomer and 11 ± 2% *cis*-isomer. The *cis*-ketone (separated by g.l.c.) isomerised to the *trans*-ketone on treatment with alkali in aqueous ethanol at room temperature.

Thus the *Z*-aldehyde (**2-Z**, X = H) cyclises mainly or entirely to the *cis*-ketone (**3-c**) and the *E*-aldehyde (**2-E**, X = H) to the *trans*-ketone (**3-t**). If only the overlap between the *p*-orbitals of C-1 and C-5 were important in the transition state for cyclisation both the *Z*- and *E*-aldehydes would be expected to give predominantly the *trans*-ketone, in order to minimise repulsion between the pentyl chain and



SCHEME

the complexed carbonyl oxygen atom. Clearly some other factor must control the orientation of the aldehyde group during cyclisation.

The Scheme shows in projection the alternative conformations for cyclisation, with the direction of bonding of the nucleophilic C-5 to the C-1 carbonyl group shown by a light arrow and the preferred direction³ of attack on the carbonyl group by a heavy arrow. Obviously conformation A is better than conformation B, so that A-E after two hydride shifts gives the *trans*-ketone (**3-t**) and A-Z the *cis*-ketone (**3-c**).

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¹ L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta*, 1970, **53**, 2059.

² J. E. Baldwin, *J.C.S. Chem. Comm.*, 1976, 734.

³ J. E. Baldwin, *J.C.S. Chem. Comm.*, 1976, 738.

⁴ Aldehydes: Y. R. Naves and P. Ochsner, *Helv. Chim. Acta*, 1964, **47**, 51; R. E. Ireland, M. I. Dawson, J. Bordner, and R. E. Dickerson, *J. Amer. Chem. Soc.*, 1970, **92**, 2568; N. H. Anderson, H. S. Uh, S. E. Smith, and P. G. M. Wuts, *J.C.S. Chem. Comm.*, 1972, 956; E. J. Corey and D. L. Boger, *Tetrahedron Letters*, 1978, 2461 and refs. given there. Acetals: W. S. Johnson, *Accounts Chem. Res.*, 1968, **1**, 1; A. van der Gen, K. Wiedhaup, J. J. Swoboda, H. C. Dunathan, and W. S. Johnson, *J. Amer. Chem. Soc.*, 1973, **95**, 2656 and refs. given there.

⁵ For possible examples see K. Sakai, J. Ide, O. Oda, and N. Nokamura, *Tetrahedron Letters*, 1972, 1287; S. F. Martin, T. Chou, and C. W. Payne, *J. Org. Chem.*, 1977, **42**, 2520; and S. F. Martin and T. Chou, *J. Org. Chem.*, 1978, **43**, 1027.

⁶ W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Amer. Chem. Soc.*, 1970, **92**, 741.

⁷ R. Ratcliff and R. Rodehorst, *J. Org. Chem.*, 1970, **35**, 4000.