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KINETIC CONTROL IN THE BENZYLIDENATION OF SOME 1-ALKYL-CYCLOHEXANE-*cis*-1,2-DIOLS*

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ABSTRACT

Acid-catalysed benzylidenation reactions of a series of alkyl substituted derivatives of cyclohexane-*cis*-1,2-diol have been studied. Preferential formation of the *exo*-phenyl benzylidene acetal was observed in the initial kinetic phase of the reaction of the 1-*tert*-butyl derivative, whereas the *endo*-phenyl acetal was preferentially formed from other diols. This behaviour has been rationalised by consideration of the probable stabilities of conformations of the oxocarbonium ion intermediate.

INTRODUCTION

Initial kinetic control to give preferential formation of a particular stereoisomer has been observed in several acetalation reactions[2], including the benzylidenation of cyclohexane-*cis*-1,2-diol[3]. Studies of this reaction have now been extended to a series of 1-alkylcyclohexane-*cis*-1,2-diols to determine whether the bulk of the alkyl group has an important influence on the kinetic control phase.

DISCUSSION

The diols required in this study were prepared by hydroxylation of the corresponding olefins. The preparation of 1-methyl- and 1-ethyl-cyclohexene was accomplished by addition of the appropriate Grignard reagent to cyclohexanone followed by dehydration of the resulting 1-alkylcyclohexanol[4]. This method was not satisfactory for the higher alkyl derivatives, but reduction of cumene and of *tert*-butylbenzene with lithium in a mixture of primary and secondary amines gave 1-isopropylcyclohexene and 1-*tert*-butylcyclohexene in yields of 65 and 77%, respectively. In the latter reduction, a longer reaction time (40 h) and use of diethylamine in place of dimethylamine gave better results than the published condi-

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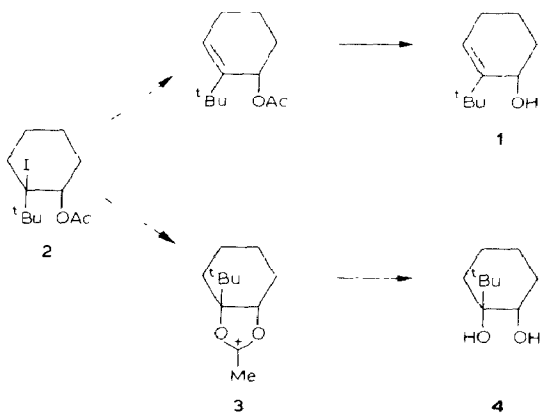
tions[5]. Cyclohexane-*cis*-1,2-diol and its 1-methyl, 1-ethyl, and 1-isopropyl derivatives, all of which are known[6], were prepared from the corresponding cyclohexenes by the Woodward procedure[7] with iodine and silver acetate in wet acetic acid. The yield of 1-isopropylcyclohexane-*cis*-1,2-diol (31%) was poor, and attempts to obtain 1-*tert*-butylcyclohexane-*cis*-1,2-diol by the general procedure were unsuccessful. Using conditions developed for hydroxylation of steroidal olefins[8], or conditions similar to the Woodward procedure except that the reaction was performed at room temperature and under nitrogen, 1-*tert*-butylcyclohexene gave a product that contained at least four components (t.l.c.) and was fractionated by column chromatography. The first component to be eluted was a liquid (19.6%) that was characterised as its crystalline *p*-phenylazobenzoate and identified as 2-*tert*-butyl-2-cyclohexen-1-ol (**1**) on the basis of spectral data. The component eluted second was the expected 1-*tert*-butylcyclohexane-*cis*-1,2-diol (**4**). The infrared spectrum of a 5mM solution of **4** in carbon tetrachloride had absorption at ν_{max} 3621 (ε_{max} 59) and 3587 cm^{-1} (ε_{max} 57) characteristic[6] of free and intramolecularly bonded hydroxyl groups, respectively. Strong intramolecular hydrogen-bonding occurs in 1-isopropylcyclohexane-*cis*-1,2-diol, whereas the corresponding *trans* isomer shows no infrared absorption associated with hydrogen-bonded hydroxyl groups[6]. The occurrence of intramolecular hydrogen-bonding in **4** is therefore indicative of the *cis*-1,2-diol structure. The third and fourth components eluted from the column were not purified and characterised.

The formation of 2-*tert*-butyl-2-cyclohexen-1-ol (**1**) in the hydroxylation reaction is analogous to the production of 3β,6β-diacetoxycholest-4-ene from cholesteryl acetate[8] and may be due to elimination of hydrogen iodide from the presumed intermediate, 2-acetoxy-1-*tert*-butyl-1-iodocyclohexane (**2**), followed by deacetylation. Participation by the acetyl group in the displacement of iodide from **2**, to give the acetoxonium ion **3** and eventually the diol **4**, may be expected to be sterically hindered by the *tert*-butyl group, thus explaining the low yield (9%) of **4** and the occurrence of the elimination side-reaction.

The reactions of cyclohexane-*cis*-1,2-diol and the 1-alkyl derivatives (1–3M



solutions in *tert*-butyl alcohol) with benzaldehyde and toluene-*p*-sulphonic acid (0.05–3%) were carried out at ~35° and were monitored by observing the appearance of the benzyl proton signals in the n.m.r. spectra of the reaction mixtures (see Table I and Fig. 1). Data for the thermodynamic products isolated from the alkyl substituted diols are listed in Table II together with data for the kinetic products isolated from similar experiments in which less acid was used. The assignments of configuration to 2-phenyl-1,3-dioxolane derivatives were made on the basis of the chemical shifts of the benzyl proton signals in the n.m.r. spectra of the acetals, the comparatively high-field signals being attributed to the *endo*-phenyl isomer in each case[9].

The assignments for the *tert*-butyl derivatives were confirmed by the observation of a nuclear Overhauser effect. Using an ~4% solution of the major thermodynamic product in deuteriochloroform, saturation of the *tert*-butyl signal gave rise to ~15% enhancement of the benzyl proton signal, whereas no significant effect was observed with the kinetic product. These experiments confirm that the major thermodynamic product has the *tert*-butyl group and the acetal hydrogen in *cis*-relationship and therefore the *endo*-phenyl structure.

Inspection of the results (Table I and Fig. 1) for these kinetically controlled benzylidenation reactions reveals several trends. The stereoselective formation of the *endo*-phenyl isomer of the benzylidene acetal became less marked as the substituent at position 1 of the diol was changed from hydrogen to methyl and then ethyl, and the overall equilibration reaction (as judged from the time to reach equilibrium) became slower. At equilibrium, the *endo*- and *exo*-phenyl stereoisomers were present in comparable amounts. A further decrease in the stereoselective formation of the *endo*-phenyl isomer was observed with the isopropyl-diol and, because of the extremely slow (60 days) equilibration in this reaction, the early appearance of the *exo*-phenyl isomer may be attributed to its direct formation; the *endo*-phenyl acetal was slightly more stable than the *exo*-isomer in this case. With the *tert*-butyl-diol, the stereoselectivity was reversed and the *exo*-

TABLE I

TOLUENE-*p*-SULPHONIC ACID-CATALYSED REACTION OF BENZALDEHYDE WITH 1-ALKYLCYCLOHEXANE-*cis*-1,2-DIOLS IN *tert*-BUTYL ALCOHOL

1-Alkylcyclohexane-cis-1,2-diol	*Time to reach maximum yield of kinetic product (min)*	*Time to reach equilibrium (days)*	*Ratio of* endo- *to* exo-*phenyl product*	
			Initial	*At equilibrium*
Parent[a]	3	3 h	58	1.0
1-Methyl[a]	15	10	53	0.8
1-Ethyl[a]	17	30	27	1.0
1-Isopropyl[b]	30	60	19	1.6
1-*tert*-Butyl[b]	60	40	0.05	4.7

[a]0.8% Acid used. [b]2.9% Acid used.

TABLE II

PROPERTIES OF BENZYLIDENE DERIVATIVES OF 1-ALKYLCYCLOHEXANE-*cis*-1,2-DIOLS

Cyclohexane-cis-*1,2-diol*	*Acetal*	*Yield (%)*	*B.p./mmHg or m.p (degrees)*	*Found (%)*		*Mol. formula*	*Calc. (%)*		*Chemical shift of acetal proton (δ)*
				C	*H*		*C*	*H*	
1-Methyl-	mixture	71	105–110/0.9	77.0	8.2	$C_{14}H_{18}O_2$	77.1	8.3	5.84, 5.98
	endo-phenyl	78	28–29[a]	77.0	8.1				5.84
1-Ethyl	mixture	63	125–130/0.9	77.2	8.6	$C_{15}H_{20}O_2$	77.6	8.6	5.86, 6.05
	endo-phenyl	74	45–47[a]	77.8	8.85				5.86
1-Isopropyl	mixture	50	175–180/12	77.8	8.8	$C_{16}H_{22}O_2$	78.0	8.9	5.75, 6.02
	endo-phenyl	72	72–73[a]	78.15	8.6				5.75
1-*tert*-Butyl	mixture	48	39–42[a]	78.4	9.2	$C_{17}H_{24}O_2$	78.5	9.2	5.69, 5.96
	exo-phenyl	64	37–38[a]	78.4	9.1				5.96

[a]From hexane

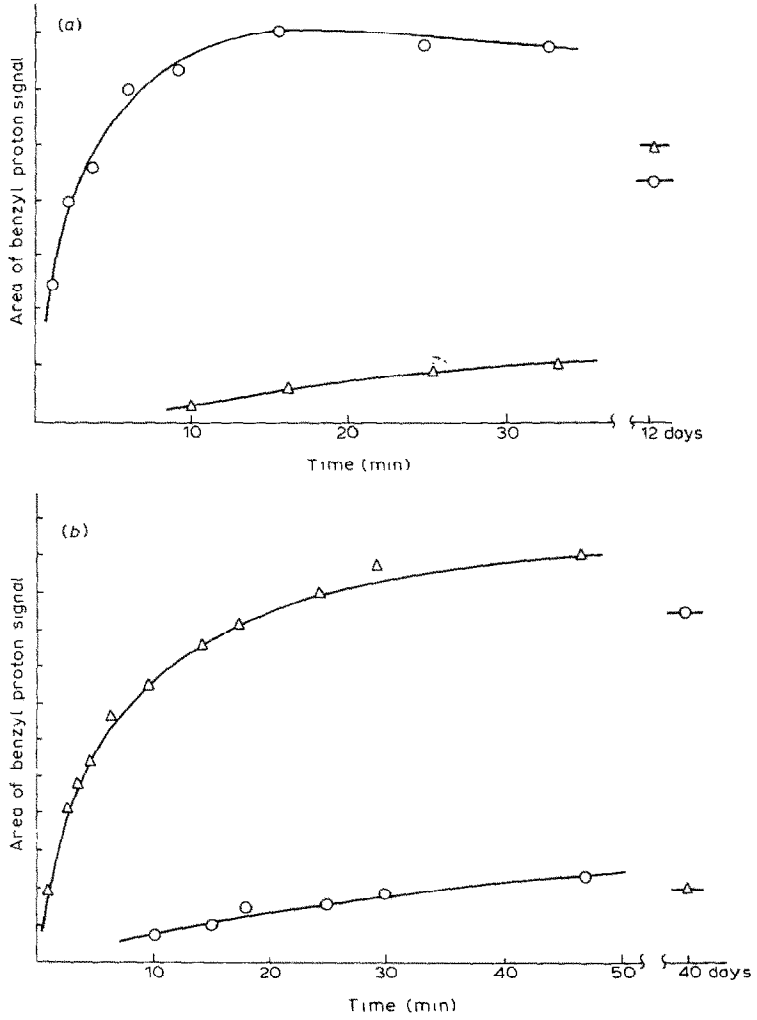
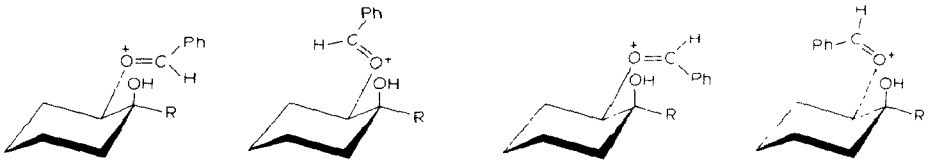


Fig. 1. Progress of reaction during benzylidenation of (*a*) 1-methylcyclohexane-*cis*-1,2-diol and (*b*) 1-*tert*-butylcyclohexane-*cis*-1,2-diol. Key: —○—, *endo*-phenyl isomer; —△—, *exo*-phenyl isomer.

phenyl isomer was preferentially formed in the early stage of benzylidenation, although the *endo*-phenyl acetal was preponderant by a factor of 4.7:1 at equilibrium.

Kinetic control in the benzylidenation of 1-alkylcyclohexane-*cis*-1,2-diols may be rationalised by assuming that the rate-limiting transition state for the reaction resembles the presumed oxocarbonium ion intermediate in one of its rotamer forms in which the hydroxyl group is suitably placed for attack leading to cyclisation[2,10]. The assumption that an *anti-transoid* conformation for the oxocarbonium ion should be most stable is supported by n.m.r. observations on oxocarbonium ions[11] and protonated aldehydes[12]. If the reaction proceeds *via* the equatorial, secondary

hemiacetal rather than the axial, tertiary hemiacetal, then four transition states may be depicted and designated* *anti-transoid* (**5**), *syn-transoid* (**6**), *anti-cisoid* (**7**), and *syn-cisoid* (**8**). Both **5** and **8** lead to *endo*-phenyl product, whereas **6** and **7** lead to *exo*-phenyl product. When R is small, the *anti-transoid* arrangement **5** should be the least sterically hindered of these structures, and preferential formation of the *endo*-phenyl product would therefore be predicted. This preference was observed in the cases where R was hydrogen, methyl, ethyl, or isopropyl. However, in a series of alkyl derivatives, it is probable that the normally preferred transition state **5**, leading to *endo*-phenyl product, will become less stable as the alkyl group becomes sufficiently large to interact with the substituents at the carbonium ion. This effect should be less serious for conformation **6** than for **5**, because of the greater distance of the alkyl group from the carbonium ion. With bulky alkyl groups, a situation could then be reached where **6** would be more stable than the *anti-transoid* conformation **5**, and this would result in kinetic formation of the *exo*-phenyl acetal. The observation that benzylidenation of 1-*tert*-butylcyclohexane-*cis*-1,2-diol gives the *endo*- and *exo*-phenyl acetals in the ratio of 1:20 in the kinetic phase is explicable on these grounds.



5 6 7 8

These results provide further evidence for the occurrence of oxocarbonium ion intermediates during the formation of 1,3-dioxolanes. The suggestion that cyclisation during 1,3-dioxolane formation is concerted with loss of water from the protonated hemiacetal[13] is not consistent with the results of these or earlier[2] stereochemical studies. In a concerted mechanism, ring formation is already well advanced in the transition state so that the relative stabilities of diastereoisomeric transition states should reflect the relative stabilities of the diastereoisomeric products. For most diastereoisomeric pairs of simple 2-phenyl-1,3-dioxolane derivatives, the two diastereoisomers have comparable stabilities and their formation at similar rates would be expected if cyclisation occurred by a concerted mechanism. However, a marked preference for the formation of one of these diastereoisomers is usually observed in the kinetic control phase of benzylidenation reactions[9], and this behaviour suggests that the cyclisation process is not concerted.

The greater equilibrium preference for the *endo*-phenyl acetal in the case of the 1-isopropyl (1.6:1) and the 1-*tert*-butyl derivatives (4.7:1) is interesting in view of the observation that isomeric 4-substituted 2-phenyl-1,3-dioxolanes are of com-

*These terms have been defined[10]; in this case, *syn* and *anti* refer to the relationship of the incipient acetal carbon to C-3

parable thermodynamic stability[9] even when the substituent is a *tert*-butyl or phenyl group. If the relative stabilities of the isomers in the fused-ring systems are influenced by the bulk of the 1-alkyl group, it seems reasonable to assume that the isomer which becomes less stable with increasing size of the alkyl group should be that having the phenyl group and the alkyl group on the same side of the 1,3-dioxolane ring, *i.e.*, the *exo*-phenyl isomer. These equilibration reactions thus confirm the assignments of configuration made to these compounds.

EXPERIMENTAL

Routine n.m.r. spectra were recorded for solutions in tetrachloromethane (internal Me_4Si) with a Varian A60 spectrometer under normal working conditions. Nuclear Overhauser effects were recorded for solutions in deuteriochloroform with a Varian XL100 spectrometer. Infrared spectra of 5mM solutions of diols in tetrachloromethane in 2-cm cells were recorded with a Perkin–Elmer 125 spectrometer equipped with a Golay pneumatic cell and diffraction gratings.

1-Alkylcyclohexenes. — 1-Methylcyclohexene (b.p. 108–111°) and 1-ethylcyclohexene (b.p. 134–136°) were prepared in yields of 62 and 63%, respectively, by the method of Bartlett and Rosenwald[4].

Cumene (7.5 g) was reduced using lithium wire (5 g) in a mixture of ethylamine (100 mL) and dimethylamine (100 mL), essentially as described by Benkeser *et al.*[5], to give 1-isopropylcyclohexene (5.1 g, 65%), b.p. 145–153°; lit.[5] b.p. 155°.

tert-Butylbenzene (13.4 g) was reduced during 40 h using lithium wire (7 g) in ethylamine (100 mL) and diethylamine (100 mL), to give 1-*tert*-butylcyclohexene (10.6 g, 77%), b.p. 165–170°; lit.[5] b.p. 170°.

1-Alkylcyclohexane-cis-*1,2-diols.* — (*a*) Hydroxylation of the corresponding 1-alkylcyclohexene by the method described by Brutcher and Evans[7] gave the following diols: 1-methylcyclohexane-*cis*-1,2-diol, m.p. 66–67° (lit.[14] m.p. 67°), in 47% yield; 1-ethylcyclohexane-*cis*-1,2-diol, m.p. 80–81° (lit.[15] m.p. 81°), in 50% yield; 1-isopropylcyclohexane-*cis*-1,2-diol, m.p. 105–106° (lit.[15] m.p. 106°), in 31% yield.

(*b*) Powdered iodine (15 g) was added in portions during 30 min to a stirred mixture of *tert*-butylcyclohexene (5 g) and silver acetate (20 g) in glacial acetic acid (500 mL) under nitrogen at room temperature. After a further 30 min, water (7.5 mL) was added and stirring was continued for a further 20 h. The mixture was then filtered, the residue was washed with glacial acetic acid, and the combined filtrates were evaporated under reduced pressure. The residue was taken up in methanol (40 mL), and the filtered solution was treated with a solution of sodium hydroxide (10 g) in water (20 mL). The mixture was boiled under reflux for 90 min, cooled, neutralised with conc. hydrochloric acid, and extracted with chloroform. The chloroform solution was dried ($MgSO_4$) and evaporated to a syrup (5.1 g) which showed several components in t.l.c. (benzene–ether, 1:1), and was fractionated on a column of silica gel (250 g).

Initial elution with 4:1 benzene–ether gave 2-*tert*-butyl-2-cyclohexen-1-ol (0.88 g, 15.8%), b.p. 90–95°/12 mmHg. ^{1}H-N.m.r. data: δ 1.10 (s, 9 H, CMe_3), 2.57 (s, 1 H, OH, removed with D_2O), 4.20 (bs, 1 H, H-1), and 5.60 (m, 1 H, H-3). Its *p*-phenylazobenzoate, prepared (54%) in the usual way[16], had m.p. 82–83° (Found: C, 76.0; H, 7.4; N, 7.6%. $C_{23}H_{26}N_2O_2$ calc.: C, 76.2; H, 7.2; N, 7.7%).

Subsequent elution of the column with 3:1 benzene–ether gave 1-*tert*-butylcyclohexane-*cis*-1,2-diol (0.56 g, 9%), m.p. 112° (from tetrachloromethane); ν_{max} (5mM in CCl_4) 3621 (ε_{max} 59, free secondary OH) and 3587 cm^{-1} (ε_{max} 57, bonded tertiary OH). ^{1}H-N.m.r. data: δ 1.03 (s, 9 H, CMe_3), 2.31 (s, 2 H, OH), and 3.72 (t, 1 H, H-2) (Found: C, 69.7; H, 11.6. $C_{10}H_{20}O_2$ calc.: C, 69.8; H, 11.6%).

The third and fourth components eluted from the column with mixtures of benzene and ether were not purified and characterised; both had strong hydroxyl absorptions (ν_{max} ~3510 cm^{-1}) in their infrared spectra (liquid film).

*Acid-catalysed reactions of cyclohexane-*cis*-1,2-diols with benzaldehyde.* — (*a*) To a solution of the cyclohexanediol (1 mmol) in *tert*-butyl alcohol (0.3 mL) was added a solution of toluene-*p*-sulphonic acid in benzaldehyde (0.3 mL), and the n.m.r. spectrum of the mixture was monitored. The results are summarised in Table I and Fig. 1.

(*b*) For the 1-alkyldiols, the reactions in (*a*) were repeated on a preparative scale. When no further change was observed in the n.m.r. spectrum, the acid was neutralised with anhydrous potassium carbonate, the solvents were evaporated, and the residue was extracted with ether to give, after evaporation, a liquid product which was fractionated on a column of 60 parts of alumina. Elution with light petroleum (b.p. 40–60°)–benzene (9:1) gave the mixture of *endo*- and *exo*-phenyl acetals in each case (see Table II for data on these products).

(*c*) The reactions were repeated as in (*b*), but using less acid. When a second benzyl-proton signal had just appeared in the n.m.r. spectrum of the reaction mixture, the reaction was stopped and the mixture processed as in (*b*), to give the acetal product of kinetic control. Each of these acetals was obtained crystalline (see Table II for relevant data).

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