Stereochemistry of the Oxymercuration of Substituted Methylenecyclohexanes and Methylenecyclopentanes

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The oxymercuration–reduction of methylenecyclohexanes and methylenecyclopentanes in 50% aqueous tetrahydrofuran was studied. With unhindered methylenecyclohexanes attack of hydroxide ion occurs from the axial side of the molecule; the steric effect of the substituent is dominant in the reaction of hindered compounds. In the case of 2-substituted methylenecyclopentanes, the hydroxide ion attacks from the same side as the substituent. The stereochemistry of this reaction is discussed.

In the reduction of ketones by complex metal hydrides, the addition of nucleophiles to unhindered cyclohexanones yields predominantly the more stable equatorial alcohols, whereas the axial isomers are obtained in the reaction of hindered cyclohexanones. These additions have been discussed on the basis of ' product development control ' and ' steric approach control.' [1]

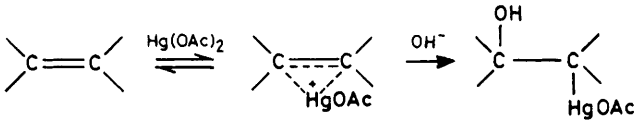
Explanations of the stereochemistry of these reactions

[1] W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, 1956, **78**, 2579.

based on pure steric approach considerations [2] or on eclipsing effects [3] have also been advanced. Kinetic work has shown that hydride reductions yielding the more stable equatorial alcohol predominantly, the outcome of which was previously assumed to be determined by the stability of the products, are in fact kinetically controlled.[4]

To determine the nature of steric effects in addition reactions, we studied the stereochemical course of the oxymercuration–reduction of a series of substituted methylenecyclohexanes and methylenecyclopentanes which have structures similar to the corresponding cycloalkanones.

We accept the premise that the oxymercuration of olefins involves rapid pre-equilibrium formation of a mercurium ion as an unstable intermediate, followed by rate- and product-determining attack of solvent.[5]



Within this context, the stereochemistry of oxymercuration–reduction is determined by the direction of the attack of the hydroxide ion to the unstable mercurium ion.

RESULTS AND DISCUSSION

The kinetically controlled oxymercuration–reduction of 4-methyl-1-methylenecyclohexane (6) and 1-methylene-4-t-butylcyclohexane (7) in 50% aqueous tetrahydrofuran at 0 °C produced predominantly the axial alcohols. The amounts of axial cyclohexanols were less in the reaction of 3-substituted methylenecyclohexanes. On introduction of a methyl group at the C-2 axial position of (7), the extent of attack of hydroxide ion from the opposite side to the methyl group was 79%, but with a C-2 equatorial methyl group the extent of attack from the axial side was only 44%. 2,2-Dimethyl-1-methylene-4-t-butylcyclohexane (9) shows almost the same product distribution as (7). The extent of attack of hydroxide ion on the mercurium ion of 2-methyl-1-methylenecyclohexane (1) is estimated on the basis of the results with *cis*- and *trans*-2-methyl-1-methylene-4-t-butylcyclohexane [*cis*- and *trans*- (8)] to be 56—79%. The oxymercuration product of (1) was 67% *cis*-isomer, obtained by the attack of hydroxide ion from the same side as the methyl group. This shows that steric hindrance by the methyl group determines the product distribution. The fact that the isomer distribution of the product from mobile (1) is between those of *cis*- and *trans*-(8) indicates that the axial methyl conformer, appreciable amounts of which are expected in (1) as a result of $A^{(1,3)}$ methyl–hydrogen interaction,[6] as well as the equatorial one, may contribute to the stereochemical results. With increase of the steric bulk of the 2-substituent, the amount of axial attack decreased and exclusive equatorial attack occurred in the reaction of 1-methylene-2-t-butylcyclohexane (3).

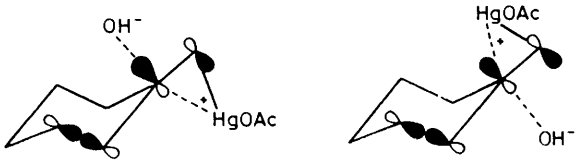
Oxymercuration–reduction of substituted methylenecyclohexanes and methylenecyclopentanes

Substrate	Reaction conditions: 0 °C, 15 min	20 °C, 15 min
Methylenecyclohexanes	Product % (axial attack)	
2-Methyl- (1)	33	37
2-Isopropyl- (2)	30	34
2-t-Butyl- (3)	3	4
3-Methyl- (4)	54	54
3-t-Butyl- (5)	58	58
4-Methyl- (6)	68	69
4-t-Butyl- (7)	71	69
cis-2-Methyl-4-t-butyl- [*cis*-(8)]	44	
trans-2-Methyl-4-t-butyl- [*trans*-(8)]	79	
2,2-Dimethyl-4-t-butyl- (9)	73	71
3,3,5-Trimethyl- (10)	71	70
trans-2-Isopropyl-5-methyl- (11)	24	25
Methylenecyclopentanes	Product % (*cis* attack)	
2-Methyl- (12)	90	79
2-Cyclopentyl- (13)	72	71
2-t-Butyl- (14)	No reaction	

The stereochemical results with unhindered methylenecyclohexanes are explained by the molecular-orbital distortion suggested by Klein.[7] Many structures have been suggested for mercurium ions. Which ever is used, it is agreed that the primary interaction involves overlap of the mercury 6*s* orbital with the π-electrons of an olefin.[8] Bach and Henneike suggested that the mercurium ion more closely resembles a π complex than a three-membered ring structure.[9] This implies that the hybridization of the carbons in the mercurium ion moiety is sp^2- rather than sp^3-like. Since the stereoisomer distribution in oxymercuration of substituted methylenecyclohexanes seems to be primarily controlled by steric hindrance, it is supposed that the transition state at the product-determining step is reactant-like, as in the cases of reduction of cyclohexanones [3,10] by complex metal hydrides and hydroboration of methylenecyclohexanes.[11] The distortion of the vacant π* bond orbital arising from the bonding C(2)–C(3) π*–σ interaction could occur in two stereochemically different transition states at the product-determining step [(A) and (B)]: therefore, the π* bond orbital of the lowest-unoccupied molecular orbital (l.u.m.o.) is distorted to the axial side. The attack of a nucleophile by interaction with the l.u.m.o. will be easier from the axial direction in (A) than the equatorial side in (B). When a 2-methyl group is introduced, its steric effect

[2] J. C. Richer, *J. Org. Chem.*, 1965, **30**, 324.
[3] M. Chérest and H. Felkin *Tetrahedron Letters*, 1968, 2205.
[4] J. Klein, E. Dunkelblum, E. L. Eliel, and Y. Senda, *Tetrahedron Letters*, 1968, 6127.
[5] W. Kitching, *Organometallic Chem. Rev.*, 1968, **1**, 61; W. L. Waters and E. F. Kiefer, *J. Amer. Chem. Soc.*, 1967, **89**, 6261; W. L. Waters, W. S. Linn, and M. C. Caserio, *ibid.*, 1968, **90**, 6741.
[6] S. K. Malhotra and F. Johnson, *Chem. Comm.*, 1968, 1149.
[7] J. Klein, *Tetrahedron Letters*, 1973, 4307; *Tetrahedron*, 1974, **30**, 3349.
[8] G. A. Olah and P. R. Clifford, *J. Amer. Chem. Soc.*, 1973, **95**, 6067.
[9] R. D. Bach and H. F. Henneike, *J. Amer. Chem. Soc.*, 1970, **92**, 5589.
[10] D. C. Ayres, D. N. Kirk, and R. Sawdaye, *J. Chem. Soc.* (*B*), 1970, 505.
[11] J. Klein and D. Lichtenberg, *J. Org. Chem.*, 1970, **35**, 2654.

becomes a major factor determining the stereochemical results. The hydroxide ion is expected to attack 3,3,5-trimethyl-1-methylenecyclohexane (10) predominantly from the equatorial side, since an axial methyl group at the 3-position has usually shown large



(A) (B)

steric hindrance to nucleophilic addition to cyclohexanones and electrophilic addition to methylenecyclohexanes. Unexpectedly, 71% axial attack was observed in the oxymercuration of (10). This result cannot be explained by the steric hindrance of the axial 3-methyl group.

In contrast to six-membered ring compounds, a hydroxide ion attacks methylenecyclopentanes from the same side as the 2-substituent. The oxymercuration of 2-methyl-1-methylenecyclopentane (12) gave 90% *cis* attack. It seems impossible to explain the prior formation of the *cis*-alcohol by steric hindrance. This result indicates that, in contrast to six-membered ring compounds, the oxymercuration of (12) reflects the relative stability of the two isomeric products; in other words, the transition state is considered to be product-like in the product-determining step, as in the cases of the reduction of cyclopentanones,[12] by complex metal hydrides and the catalytic hydrogenation of cyclopentanones and methylenecyclopentanes.[13]

With increase of the steric requirement of the 2-substituent, steric control is also operative. Less stereoselectivity was observed in the reaction of 2-cyclopentyl-1-methylenecyclopentane (13). When the t-butyl group is introduced, no product was obtained. This may mean that the *I*-strain in the product-like transition state is too large to allow the reaction to proceed.

[12] Y. Senda, S. Mitsui, R. Ono, and S. Hosokawa, *Bull. Chem. Soc. Japan*, 1971, **44**, 2737.
[13] S. Mitsui, H. Saito, S. Sekiguchi, Y. Kumagai, and Y. Senda, *Tetrahedron*, 1972, **28**, 4751.

EXPERIMENTAL

Materials.—Methylenecyclohexanes and methylenecyclopentanes were prepared from corresponding cycloalkanones by the procedure of Corey and his co-workers:[14] (1), b.p. 118—120 °C (yield 70%); (2), b.p. 111—112 °C (83 mmHg) (66%); (3), b.p. 111—114 °C (120 mmHg) (82%); (4), b.p. 112 °C (75%); (5), b.p. 102—103 °C (200 mmHg) (87%); (6), b.p. 123—125 °C (60%); (7), b.p. 72—73 °C (30 mmHg) (70%); (8), b.p. 86—87 °C (30 mmHg) (73%), as a mixture of *cis*- and *trans*-isomers, separated by preparative g.l.c.; (9), b.p. 105—106 °C (50 mmHg) (65%); (10), b.p. 89—90 °C (164 mmHg) (50%); (11), b.p. 134—135 °C (207 mmHg) (71%); (12), b.p. 78—80 °C (70%); (13), b.p. 103—104 °C (38 mmHg) (72%); and (14), b.p. 132 °C (76%). The structure of each substituted methylenecyclohexane and methylenecyclopentane was confirmed by ^{1}H n.m.r. spectra and analytical g.l.c. Authentic samples of substituted 1-methylcyclohexanols and 1-methylcyclopentanols were prepared by the Grignard reactions of cycloalkanones. Stereoisomeric 1,2-dimethyl-4-t-butylcyclohexanols and 1-methyl-2-t-butylcyclopentanols were estimated by g.l.c.

Oxymercuration–Reduction Procedure.[15]—To a solution of $Hg(OAc)_2$ (0.324 g, 1 mmol) in 50% aqueous THF (4.0 ml) was added 1-methyl-2-methylenecyclohexane (0.110 g, 1 mmol), and the mixture was stirred. It was then reduced by addition of 3N-NaOH (1.0 ml) and 0.5M-$NaBH_4$ in 3N-NaOH (1.0 ml). The solution was extracted three times with ether and the extracts were washed with saturated aqueous $NaHCO_3$ and then brine, dried (Na_2SO_4), and concentrated. The residual solution was subjected to g.l.c.

[7/1196 *Received*, 7*th July*, 1977]

[14] R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, 1963, **28**, 1128.
[15] H. C. Brown and P. Geoghegan, jun., *J. Amer. Chem. Soc.*, 1967, **89**, 1522.