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STEREOCHEMISTRY OF THE HYDROBORATION OF 2-SUBSTITUTED METHYLENECYCLOHEXANES AND METHYLENECYCLOPENTANES

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Abstract—Hydroboration of 2-substituted methylenecyclohexanes and methylenecyclopentanes occurred predominantly from the opposite side of the substituents at C-2. The ratios of the *cis* to the *trans* products tend to increase with increase of the steric bulkiness of the substituents. These results are discussed in terms of the reactant-like transition state and the distortion of the filled π-bond orbital.

The stereochemical results of several substituted cyclohexanones by complex metal hydrides were first explained by Dauben *et al.*, who suggested the concepts of "steric approach control" and "product development control".[1] The stereochemistry of this nucleophilic reaction has been discussed by a large number of chemists, but the factors, other than "steric approach control", that determine the stereochemistry remain an area of great interest and controversy.[2] In this paper, the electrophilic addition of B_2H_6 to 2-substituted methylenecyclohexanes and methylenecyclopentanes which have structures similar to the corresponding cycloalkanones is reported and the stereochemical results are discussed comparing with those of the nucleophilic addition to cycloalkanones.

Klein *et al.* have reported that the Hammett ρ value of hydroboration is approximately zero from the results of the reaction of *p*-substituted styrenes and suggested that hydroboration has a reactant-like transition state.[3] This indicates that the stereochemistry of this reaction is governed primarily by the steric hindrance or the torsional strain of the substituents with the attacking reagents.

The 68% equatorial attack was observed in the hydroboration of 4-t-butylmethylenecyclohexane (**1**). Introduction of a methyl group on the C-2 equatorial position increased the amount of the equatorial attack to 77%. On the other hand, when a methyl group is introduced on the C-2 axial position, the equatorial attack was no longer predominant. The hydroboration of *trans* - 2 - methyl - 4 - t - butylmethylenecyclohexane (*trans*-**5**) gave 71% axial attack. The hydroboration of 2,2 - dimethyl - 4 - t - butylmethylenecyclohexane (**6**) gave 55% axial and 45% equatorial attack. These results show that the steric hindrance or the torsional strain of the C-2 axial methyl group is larger than that of the C-2 equatorial methyl group or the C-2 axial hydrogen. The 83% equatorial attack was observed in the hydroboration of 2-methylmethylenecyclohexane (**2**). Since Malhotra and Johnson have reported that the $A^{1,3}$ methyl-hydrogen interaction is approximately 1.4 kcal/mol,[4] appreciable amounts of the axial methyl conformer are expected for **2**. The amount of the attack of B_2H_6 on this compound from the *trans* side of the C-2 Me group is estimated on the basis of the results of *cis* and *trans*-**5** to be in between 71% and 77%. The observed isomeric distribution of the hydroboration product was 83% *cis* isomer. Such a deviation between the observed value and the estimated one may be due to the ring flattening of this molecule by the introduction of the t-Bu group to the cyclohexane ring.

When a Me group is introduced at C-2, the attack of the opposite side of this group increased especially in the case of the axial conformer. This observation is primarily explained by the steric hindrance of this group with incoming B_2H_6. In addition to the above explanation, the distortion of the π-bond orbital of the HOMO may also participate in the stereochemical results.[5] When a Me group is introduced at the C-2 equatorial position, the interaction of the filled π-bond orbital (HOMO) with the antibonding C_2–C_3 orbital (LUMO) may be more favoured than that with the antibonding C_2–CH_3 orbital (LUMO) owing to their orientation. As a consequence, the equatorial attack of electrophiles is favoured similarly as the case of unhindered methylenecyclohexane.[5] On the other hand, when the axial Me group is introduced, the distortion of the filled π-bond orbital arising from the axial C_2–CH_3 $\pi - \sigma^*$ interaction would occur; therefore, the π-bond orbital of the HOMO is distorted to the axial side (opposite side of the axial Me group) compared to those of unhindered methylene cyclohexane, increasing the electrophilic attack from this side (Fig. 1).

When the isopropyl or the t-Bu group is introduced at C-2, the steric hindrance becomes larger and the equatorial attack which is the opposite side of the substituent

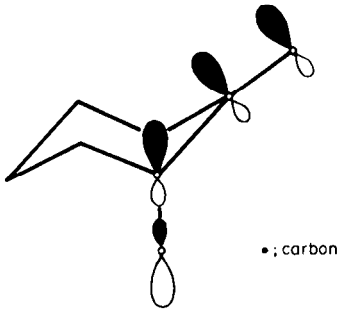

Fig. 1.

increased. The 96% equatorial attack of B_2H_6 occurred on 2-t-butylmethylenecyclohexane (**4**), while 3,3,5-trimethylmethylenecyclohexane (**7**) gave the 85% equatorial attack. Comparing the nucleophilic reaction to 2-t-butyl- and 3,3,5-trimethylcyclohexanone, such as Grignard reaction or reduction with B_2H_6, $NaBH_4$ or LAH, the greater stereoselectivity of 3,3,5-trimethylcyclohexanone compared to 2-t-butylcyclohexanone could be ascribed to the larger steric hindrance by the C-3 axial Me group than that by one of the t-butyl Me groups on the nucleophiles which attack the CO carbon.

It has been shown that hydroboration proceeds by a four centre transition state in which the B–C link is more developed than the forming C–H bond.[3,6] The B atom begins to attach itself to the exocyclic carbon in the transition state of the hydroboration of methylenecyclohexanes, and the ring carbon retains its original trigonal geometry.[7] Since the B atom first attacks the terminal methylene carbon, the steric hindrance of one of the t-butyl Me groups, which is close to this carbon, is larger than that of the C-3 axial Me group.

The hydroboration of 2-methylmethylenecyclopentane (**8**) gave 79% *trans* attack. This stereoselectivity may be primarily controlled by the steric hindrance of the Me group. The preferred conformation of methylenecyclopentane (half-chair model, similar to cyclopentanone) has a C_2 axis of symmetry which allows the same contribution of antibonding C_2–C_3 and C_4–C_5 orbitals to the filled π-bond orbital from the opposite side with each other. The pseudo-equatorial antibonding C_2–CH_3 orbital may little contribute to the distortion of the filled π-bond orbital. No molecular orbital distortion may, therefore, participate in the stereochemistry of the hydroboration of the conformer, the Me group of which is in pseudo-equatorial position. However, since appreciable amounts of the pseudo-axial Me conformer are

Table 1. The hydroboration of methylenecyclohexanes and methylenecyclopentanes

Methylenecyclohexane	Equatorial Attack(%)
4-t-Butyl- (1)	68[a]
2-Methyl- (2)	83
2-Isopropyl- (3)	91
2-t-Butyl- (4)	96
cis-2-Methyl-4-t-butyl- (cis-5)	77
trans-2-Methyl-4-t-butyl- (trans-5)	29
2,2,-Dimethyl-4-t-butyl- (6)	45[b]
3,3,5-Trimethyl- (7)	85[b]
Methylenecyclopentane	
2-Methyl- (8)	79
2-Cyclopentyl- (9)	92
2-t-Butyl- (10)	99

[a] Klein and Lichtenberg reported 68% cis(equatorial attack); Ref 7.

[b] Analysed as acetates

Table 2. Some nucleophilic reactions of 2-t-butyl- and 3,3,5-trimethylcyclohexanone

Cyclohexanone	MeMgI	$LiAlH_4$	$NaBH_4$	B_2H_6
		Equatorial attack (%)		
2-t-Butyl-	90	58[a]	50[b]	81[c]
3,3,5-Trimethyl-	100[d]	75[e]	55[f]	82[g]

[a] H. C. Brown and G. H. R. Deck, J. Am. Chem. Soc. , 87, 5620 (1965).

[b] A. V. Kamernitzky and A. A. Akhrem, Tetrahedron, 18, 705 (1962).

[c] H. C. Brown and V. Varma, J. Org. Chem., 39, 1631 (1974).

[d] S. R. Landor, P. W. O'Connor, A. R. Tatchell and I. Blair, J. Chem. Soc. Perkin 1, 473 (1973).

[e] Ref. 2.

[f] H. Haubenstock and E. L. Eliel, J. Am. Chem. Soc., 84, 2368 (1962).

[g] Klein and Dunkelblum reported 66% equatorial attack; J. Klein and E. Dunkelblum, Tetrahedron, 23, 205 (1967).

Table 3. Reduction of 2-substituted cyclopentanones with diborane

Cyclopentanone	trans attack
2-Methyl-	31[a]
2-Cyclopentyl-	48
2-t-Butyl-	81

[a]Brown and Bigley reported 25% *trans* attack; H. C. Brown and D. B. Bigley, *J. Am. Chem. Soc.* **83**, 3166 (1961).

expected for **8**, the distortion of filled π-bond orbital by the interaction with the pseudo-axial antibonding C_2–CH_3 orbital makes the favourable attack of an electrophile from the opposite side of the 2-Me group. This is one of the reasons for the stereoselectivity of the hydroboration of **8**.

The stereoselectivity becomes larger with increase of the steric requirement of the substituent at the 2-position and the *cis* alcohol was obtained exclusively in the hydroboration of 2-t-butylmethylenecyclopentane (**10**). The steric hindrance of the C-2 substituent appeared in the hydroboration of methylenecyclopentanes is larger than in the B_2H_6 reduction of corresponding cyclopentanones. This is because the incoming B_2H_6 experiences the different steric hindrance by the C-2 substituent at the transition state depending on the reaction pattern.

EXPERIMENTAL

Materials. Methylenecyclohexanes and methylenecyclopentanes were prepared from corresponding cycloalkanones with the procedure described by Corey *et al.*[8]: **1**. b.p. 72–73°C/30 mmHg (yield, 70%); **2**, b.p. 118–120°C (70%); **3**, b.p. 111–112°C/83 mmHg (66%); **4**, b.p. 111–114°C/120 mmHg (82%); **5**, b.p. 86–87°C/30 mmHg (73%); *cis*/*trans* = 10, these isomers were separated by preparative glc; **6**, b.p. 105–106°C/50 mmHg (65%); **7**, b.p. 89–90°C/164 mmHg (50%); **8**, b.p. 78–80°C (70%); **9**, b.p. 103–104°C/38 mmHg (72%); **10**, b.p. 132°C (76%). All compounds used in the present study were checked by glc and IR and ^{1}H NMR spectra. The authentic samples of substituted cyclohexyl- and cyclopentylmethanols were prepared by LAH reduction of corresponding carboxylates in the usual manner. Stereoisomeric 3,3,5-trimethylcyclohexanemethanols and 2-t-butylcyclopentanemethanols were estimated by the relative retention time of glc.

Hydroboration reactions.[9] To a well stirred suspension of 0.034 g (0.9 mmol) of pulverized $NaBH_4$ in 10 ml of THF containing 0.11 ml (1 mmol) of 2-methylmethylenecyclohexane was added 0.20 ml (1.6 mmol) of BF_3 etherate over a period of 1 hr, while the temp. was maintained at 0°. The flask was kept for 3 hr at room temp. before the excess hydride was decomposed with water. The organoborane was oxidized at 35° (water bath) for 3 hr by the addition of 0.320 ml of a 3 N NaOH, followed by the dropwise addition of 0.320 ml of 35% H_2O_2. The soln was extracted three times with ether which had been washed with sat. $NaHCO_3$, and then by brine, and dried over Na_2SO_4. The soln was concentrated, and the residual solution was subjected to gas chromatography.

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