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ASYMMETRIC HYDRIDE TRANSFER REACTIONS - THE NATURE OF TRANSITION STATE AND INTERPRETATION OF OBSERVED DISCREPANCIES IN ASYMMETRIC INDUCTION

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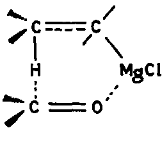
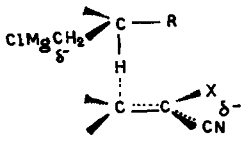
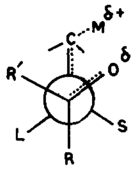
Asymmetric hydride-transfer reactions using Grignard reagents[1], alkoxymagnesium halides[2], and alkoxyaluminum dichlorides[3] have been widely used during the last few years for reduction of ketones and other electrophilic double bonds[4] with varied degree of asymmetric induction. Whitemore's cyclic mechanism, analogous to that accepted in Meerwein-Ponndorf-Verley reduction, has been often good enough to explain the results[5]. Recently, it has been suggested that the most favoured hydrogen transfer is linear, be it through a cyclic transition state (I)[6] or an acyclic one (II)[4]. Inspite of these refinements, however, one aspect of these reactions still remains unsolved: in the reduction of phenyl alkyl ketones, the asymmetric induction goes up as the effective bulk of the alkyl increases through the series, Me, Et, *n*-Pr, *i*-Bu, and *i*-Pr. It has been pointed out that electronic effect of phenyl group is somehow responsible for this behaviour[7]. Some time back, we put forward an explanation[8] based on Karabatsos model for 1,2-asymmetric induction[9] and an assumption that the stereospecificity of a reaction depends appreciably on rate[1]. The validity of this theory has since then been found doubtful from the reduction data of various p-substituted aryl alkyl ketones in our laboratory[10]. The isotope effect on asymmetric induction[11,12], previously attributed to rate factor, may as well be a consequence of isotopic disparity in the substrates (difference in bulk between H and D, for example), as pointed out by Morrison[13]. During the past one year, on several occassions[14], we suggested a transition state (III) to explain this discrepancy as well as some other curious observations. In view of a recent report[4] of an acyclic transition state (II) to which our



(I)



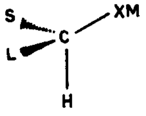
(II)



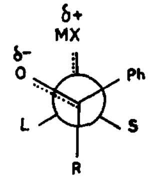
(III)

model has some formal analogy, we like to record our interpretation.

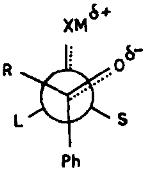
The transition state suggested by us is very similar to the one (I) proposed by Mathieu[6] differing from it in two important aspects: i) the model has been twisted along C··H··C axis to relieve steric and torsional strain, and ii) the two oppositely developing dipoles, $O^{\delta-}$ and $M^{\delta+}$ (M stands for halogenated Mg and Al) are loosely bound through space thus avoiding rigidity consequent to a cyclic model. The transition state is very much reactant-like and the steric interactions may be appraised from a Newman-type formula (III), viewed along C··H··C axis, the relatively short C-H bond[15] and the radial distribution of R, R', and O largely compensating for the extra H sandwiched between the two carbons.



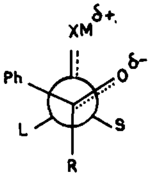
(IV)



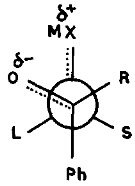
(Va)



(Vb)



(VIa)



(VIb)

For a reagent typified by the steric formula IV (X stands for -O- or $-CH_2-$, and L & S for large and small groups), six transition states could be envisaged for the reduction of PhCOR. Only four (Va, Vb, VIa, VIb) are of significance because they have the opposing dipoles, $O^{\delta-}$ and $XM^{\delta+}$ gauche to each other thus permitting to form a loose bond. Of the two conformations, Va and Vb leading to R-alcohol, Va is by far the stabler one both from steric (L and Ph anti) and electronic ($XM^{\delta+}$ placed between two negative dipoles, $O^{\delta-}$ and C-Ph) reasons. Similarly for S-alcohol, transition state VIa is more favourable (electronic reason), although the assessment of steric interaction is rather uncertain. The product ratio R/S will therefore be determined by the free energy difference between Va and VIa. Simple consideration of steric interactions shows that R-alcohol would be formed predominantly (compare Ph↔S + L↔O in Va against Ph↔L + S↔O in VIa) and that is actually the case [1-3].

Now if R is gradually increased in bulk, a buttressing effect will operate in the two conformations: rotation to separate L and R in VIa will push Ph and L together whereas a similar rotation in Va is quite easy. As a result, conformation VIa is further destabilised and more of R-alcohol formed. This explains the higher asymmetric induction in the phenyl alkyl series as the alkyl group changes from methyl to isopropyl or even to t-butyl*.

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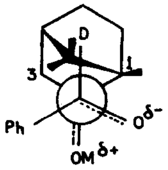
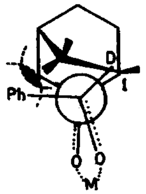
* Highest asymmetric induction (72%) has indeed been reported[16] in phenyl alkyl series when R= t-Bu using isobornylmagnesium bromide as reducing agent. In all these cases, phenyl behaves as effectively the bigger group of the two.

The present picture also clarifies one obscure point: it has been observed that the asymmetric induction in phenyl alkyl series is usually higher than in cyclohexyl alkyl or t-butyl series inspite of the comparable size of the three groups*. For instance, reduction of phenyl, t-butyl, and cyclohexyl isopropyl ketones with the same reagent, 2-methylbutylmagnesium chloride gave alcohols of optical purities 24, 5, and 2% respectively[13]. A simple explanation may be offered thus: in case of cyclohexyl or t-butyl ketones, the contributions of the other two transition states Vb and VIb (t-Bu or $-C_6H_{11}$ in place of Ph) could not be ignored, the electronic effect of Ph being absent. Between these two, VIb is clearly more stable (compare $L \leftrightarrow R + S \leftrightarrow O$ in Vb against $S \leftrightarrow R + L \leftrightarrow O$ in VIb). The product ratio R/S therefore drops down to moderate values.

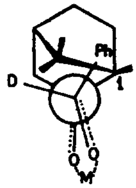
One further point may be mentioned before we close up the discussion. Benzaldehyde-1-d when reduced with bornyloxymagnesium bromide and bornyloxyaluminum dichloride, both from (-)-borneol, afforded respectively R-(-)-, and S-(+)-benzyl-α-d alcohol of high optical purity[12]. The preponderance of R-alcohol from bornyloxymagnesium bromide is in order with the preferred transition state VII which corresponds to Va in previous discussion. But the formation of S-alcohol from reagent of identical configuration is definitely unexpected. The only explanation we can offer is this: with the replacement of MgBr by $AlCl_2$ which is by far a stronger electrophilic species, the bond between $O^{\delta-}$ and $AlCl_2^{\delta+}$ becomes more tight and the transition state VII closes up to the cyclic model VIII. It is possible and also verified by models that the overhanging gem-dimethyl group now introduces an additional steric interaction with Ph in VIII thus upsetting the usual stability order based on having the two bigger groups, C_1-Me and Ph on different sides of the ring. As a result, conformation IX is favoured over VIII and S-alcohol formed overwhelmingly. It has indeed been found in several instances that the configuration of reduction products with bornyloxyaluminum dichloride does follow the above picture[17].



(VII)



(VIII)



(IX)

It appears therefore that while the magnesium derivatives of alcohols (as also the Grignard

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* The statement is over-simplified and true only when the alkyl groups are bulky. This lends additional support to our subsequent hypothesis (vide infra) that steric interactions are important in pushing the reaction towards acyclic mechanism.

reagents) in general react with ketones through acyclic transition state (as III), the corresponding chloroaluminum derivatives probably react through the cyclic one (as I), particularly when the two chiral carbon atoms in the transition state do not bear heavy substituents, i.e., eclipsing effect is small. On the other hand, when the substrate and the reagent are both sterically encumbered, the reactions go through acyclic transition state III. Unfortunately, bornyloxyaluminum dichloride does not reduce hindered ketones and we do not have any independent way to show that such change of mechanism does take place. Isobornyloxyaluminum dichloride is a good reducing agent[18] but it would afford products of identical configuration by either mechanism.

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