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ASYMMETRIC INDUCTION. RATIONALISATION OF SOME EARLIER DATA ON ASYMMETRIC REDUCTION

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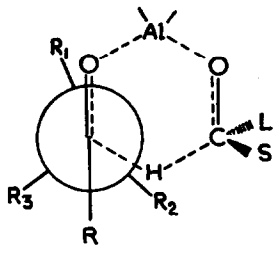
Recently, we carried out asymmetric reduction of a variety of ketones with (-)isobornyloxyaluminium dichloride (1), a reagent of ready availability and high stereoselectivity (2). During these reductions, it was observed that the extent of asymmetric induction went on increasing in the alkylphenyl series, as the size of the alkyl groups increased in passing through methyl, ethyl, propyl, isobutyl, and isopropyl. The value however dropped down at t-butyl rather abruptly. In each case, the configuration of the major enantiomer was such that phenyl must have behaved as the bulkiest group, and so the increase of bulk of the alkyl groups was expected to lead to lower asymmetric induction. Similar observations were made by other workers using different reagents, in this series and to a lesser extent in alkylcyclohexyl and alkyl-t-butyl series. Some of the data are shown in the table below:

TABLE*

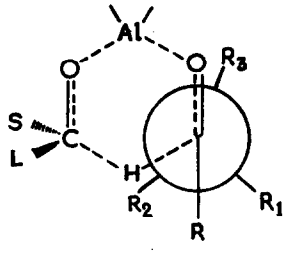
Series: R =	Me	Et	n-Pr	i-Bu	i-Pr	Cyclohexyl	t-Bu	Ph	Ref.
PhCOR	3.9	5.7	5.9	9.9	24.0	25.0	16.0	-	(5)
	47.2	52.2	-	53.2	82.1	-	15.8	-	(4)
	27.0	58.0	44.0	66.0	84.0	40.0	23.0	-	(1)
$C_6H_{11}COR$	3.6	8.8	8.1	16.1	2.1	-	-2.5	-25.0	(5)
$t\text{-}C_4H_9COR$	13.0	11.8	11.0	6.0	5.0	2.5	-	-16.0	(6)
CH_3COR	-	2.8	-	5.0	15.0	-	18.0	27.0	(7)

*The extent of asymmetric induction is expressed as $[\alpha]_D^{expl}/[\alpha]_D^{max.} \times 100$; the negative figures indicate that the major isomer has got configuration opposite to those of others in the series.

With the exception of the alkylmethyl series and two or three other entries in the table, the results could hardly be rationalised in terms of the usual steric interactions of groups in the six-membered cyclic transition state assumed for these reactions. Mosher et al (5) who first pointed out these anomalies ascribed them to factors other than steric such as rate and electronic. A slower rate of reduction would lead to greater stereoselectivity and hence to higher asymmetric induction. The increasing order of asymmetric induction in the alkylphenyl series is thus a consequence of the decreasing rates of reduction of the ketones as the alkyl groups become bulkier (8). The view was strengthened by a further observation that the asymmetric induction in neopentyl alcohol-1-d was three fold as high when formed by deuterium transfer from a Grignard reagent as by hydrogen transfer (9). The former reaction is known to be much slower (10). The effect of rate on stereoselectivity of the reaction thus seems to be well established. However, this factor alone is hardly expected to overshadow the steric effect to the extent seen in the alkylphenyl series. It must be assumed therefore that the steric interactions of groups are somehow modified in the transition state so as to lose their usual significance in the ground state. In this communication, we suggest a simple explanation how this can happen, based on an empirical model recently proposed by Karabatsos (11). According to this, the following two diastereoisomeric transition states (I & II) for the reduction of ketones with optically active alkoxyaluminium dichloride (or similar reagents) may be considered :



I



II

The hydride transfer reactions using either Grignard reagents or alkoxyaluminium dichlorides, are generally fast and exothermic and so the assumption that the arrangement of groups in the transition state with respect to carbonyl is similar to that of the ketone in the ground state may be well justified. This would require that one of the substituents,

either the medium or the large (R_1 and R_3 in the diagrams) be in eclipse with the carbonyl double bond (12), while the small group, R_2 be nearest to the incoming hydrogen. If we now consider the steric interactions between the group, $-CR_1R_2R_3$ and the substituents, L and S on the asymmetric carbon in the two transition states, these would be reduced to two simpler terms, $R_2 \leftrightarrow L$ (in I) and $R_2 \leftrightarrow S$ (in II), the other two α-substituents, R_1 and R_3 being too far away to have any appreciable effect* on L and S. A comparison of these two terms with those represented by $R \leftrightarrow S$ and $R \leftrightarrow L$ respectively, will then determine the preference of one transition state over the other and consequently the extent of asymmetric induction, provided the other non-common interactions, e.g., $R_1 \leftrightarrow O$ and $R \leftrightarrow R_3$ in (I) and $R_3 \leftrightarrow O$ and $R \leftrightarrow R_1$ in (II), are equal. In ketones which do not contain any asymmetric carbon as in the present instances, atleast two of the three groups, R_1, R_2 and R_3, are identical and the reactive conformations (I & II) may be so written that these interactions are exactly the same with the smallest group, R_2 still nearest to the approaching reagent. It will be now apparent that in a particular series, say alkylphenyl (R = Ph in I & II), all alkyl groups containing atleast one α-hydrogen, e.g., CH_3, C_2H_5, n-C_3H_7, i-C_4H_9, and i-C_5H_7, will have very similar steric effects with respect to L and S in the transition states because R_2 is hydrogen in each case. Other interactions being equal, the energy difference between the pairs of transition states (I & II) will therefore remain reasonably constant throughout the series and no appreciable fall in asymmetric induction is expected on steric ground. However, the slower rate of reduction as one passes from methyl to isopropyl (due mainly to electronic factor) will result in increasing stereoselectivity and the overall effect is an orderly rise in asymmetric induction. The situation is different when the alkyl is t-butyl; R_2 becomes necessarily methyl and the steric effect is now more pronounced and almost parallels that of phenyl with a consequent drop in asymmetric induction†. The enhanced rate of reduction of t-butyl ketone (8), this being less of an aromatic ketone, may also be a contributing factor. That phenyl still behaves as a bulkier group than t-butyl is probably due to nonplanarity of the benzene ring with the carbonyl as suggested by Mosher et al.

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*The substituents, R_1 and R_3 may however raise the activation energy of both the transition states as a result of skew interactions, or if sufficiently large, bring about significant distortion of the model.

†Vavon and Angelo, Compt. rend., 224, 1435 (1947), however reported highest asymmetric induction with t-butyl phenyl compound in this series, which is contrary to the results of ours as well of Moshers et al.

The observed data in the alkylcyclohexyl and alkyl-t-butyl series can similarly be rationalised. The drop in asymmetric induction in these cases, however, has appeared earlier than expected. The situation here is more complex because of the possibility of rotamers around other bonds, which will make the nature of the transition state rather uncertain. The low asymmetric induction in methylethyl- and methylisobutyl-carbinols (last series in the table) is consistent with the idea that very little difference exists in the steric effects of methyl, ethyl, and isobutyl. The comparatively high asymmetric induction in the aromatic series is almost certainly linked up with the decreased reactivity of the alkyl phenyl ketones in general. The above model together with a consideration of the rate factor thus provides a rationale for the results so far obtained in these asymmetric reductions.

Investigations on further examples and on the effect of lowering the reactivity both in the substrates and the reagents, as well as the effect of temperature on the extent of asymmetric induction are in progress.

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