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THE STEREOSELECTIVE REDUCTION OF α-AMINODEOXYBENZOIN DERIVATIVES WITH SODIUM BOROHYDRIDE

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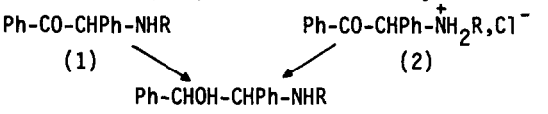
Abstract Total stereoselectivity is observed in the sodium borohydride reduction of α-aminodeoxybenzoins and their hydrochlorides in various hydroxylic solvents RS-SR isomer (erythro) was the only aminoalcohol obtained

In a recent paper[1] Kametani et al report the stereoselective reduction of α-aminopropiophenone derivatives with sodium borohydride The lower stereoselectivity observed in the reduction of free bases as compared to the reduction of hydrochlorides is accounted for on the basis of initial formation of an "aminoborine" followed by the formation of Cram's five-membered cyclic transition state[2] In the course of work on the stereoselective synthesis of oxazolidines[3] from aminoalcohols obtained by reduction of benzilmonoimines[4] we found the reduction of α-aminodeoxybenzoin derivatives with sodium borohydride to be totally stereoselective both for free bases and for their hydrochlorides

Both Kametani's and our results may be accounted for by the use of Pérez-Ossorio's model[5] for the stereoselective path of the reduction of polar carbonyl compounds Reductions were carried out under reflux in various hydroxylic solvents as shown in Table In all cases only the RS-SR isomer (erythro in Kametani's paper) was obtained. Assignment of configurations was based on ^{1}H-NMR and IR data for both diastereoisomers[4,6]

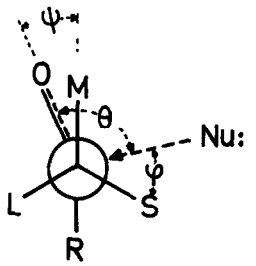
Fig. 1 shows the geometrical parameters of a generic transition state ($TS^{\neq}$) in the reduction of a carbonyl compound according to Pérez-Ossorio's treatment[8] As shown, particular values for these parameters are dependent on the transition state type.[9] The nucleophile attack occurs on the less hindered side (medium M and small S groups vs medium and large L groups) In agreement with this the three competitive transitions states for the reduction of aminoketones are those shown schematically in Fig 2. For deoxybenzoins R' = Ph, NR_2 = NHZ (Z = Ph,$PhCH_2$, Ph_2CH,PhCHMe,PhCHEt), for aminopropiophenones R' = Me, NR_2 = $NAlkyl_2$ $TS^{\neq}$ I may

Table. Reduction of α-Aminodeoxybenzoin Derivatives (1,2) with Sodium Borohydride



Compd	R	Solvent	Hrs	Yield(%)[a]
1	Ph	EtOH	7	70
2	Ph	MeOH	7.5	67
2	Ph	EtOH	7 5	76
2	Ph	Pr^iOH	7 5	66
2	Ph	Bu^tOH	8	81
1	$PhCH_2$	EtOH	2	94
2	$PhCH_2$	MeOH	8	78
2	$PhCH_2$	EtOH	8	76
2	$PhCH_2$	Pr^iOH	8	65
2	$PhCH_2$	Bu^tOH	8	76
1	Ph_2CH[b]	EtOH	8	85
1	$PhCHMe$[c,d]	Et_2O	4	88
2	$PhCHMe$[c]	EtOH	3	84
1	$PhCHEt$[c]	EtOH	2.5	100
2	$PhCHEt$[c]	EtOH	8	85

a) In crude reaction product showing only ^{1}H-NMR signals of (RS-SR)-Aminoalcohols.
b) Hydrochloride could not be isolated[7].
c) With $LiAlH_4$. See Ref. 4 d) A mixture of RRR-SSS and RRS-SSR diastereoisomers was obtained



REACTANT-LIKE TS$^{\neq}$

$0° < \Psi < 15°$

$60° + \Psi < \Theta < 75° + \Psi$

$45° < \varphi < 60°$

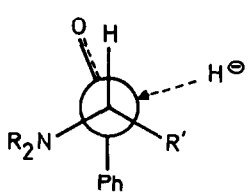
PRODUCT-LIKE TS$^{\neq}$

$15° < \Psi < 60°$

$30° + \Psi < \Theta < 60° + \Psi$

$60° < \varphi < 90°$

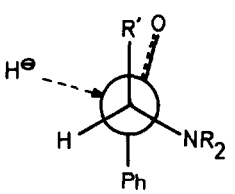
Fig. 1



I

↓

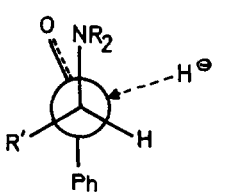
erythro
RS-SR



II

↓

threo
RR-SS



III

↓

erythro
RS-SR

Fig. 2

be disregarded since the hydride attack occurs in a hindered face of the carbonyl group[10], moreover the phenyl group attached to it is flanked by the two bulkiest α-substituents. The relative energies of $TS^{\neq}$ II and $TS^{\neq}$ III depend basically on the relative values of the interactions $[(=O - R')_{1.2e} + (Ph\text{-}NR_2)_{1.2g}$ vs $(=O - NR_2)_{1.2e} + (Ph - R')_{1.2g}$. The carbonyl group interactions are carried over from the initial to the transition state with modifications which depend upon the situation of the latter in the reaction coordinate. If the amino group is secondary the intramolecular stabilizing hydrogen bond[11] between carbonyl and amino groups present in the initial state would be partially preserved in $TS^{\neq}$ III. This will be true both for reactant-like and product-like transition states although in the latter $TS^{\neq}$ II may also benefit from a certain degree of hydrogen bond stabilization.[12] On the other hand, a destabilizing interaction $(-O - Ph)_{1\ 2e}$[13] should operate in $TS^{\neq}$ II. The $(Ph - NR_2)_{1.2g}$ and $(Ph - R')_{1.2g}$ interactions persist unmodified in $TS^{\neq}$ with respect to those in the carbonyl compound. With the help of appropriate molecular models it may be shown that the value of both interactions in the aminoketone are very similar.

Thus it may be concluded that the origin of stereoselectivity in the aminodeoxybenzoin reductions is a consequence of the favourable $(=O - NHR)_{1.2e}$ interaction in $TS^{\neq}$ III as compared with the destabilizing effect of the $(=O - Ph)_{1\ 2e}$ interaction in $TS^{\neq}$ II. These conclusions can be extended to reduction of aminodeoxybenzoin hydrochlorides and also to α-aminopropiophenone hydrochlorides for which hydrogen bond interactions between carbonyl and ammonium groups are possible. The lower stereoselectivity in the latter case may follow from the smaller value of the $(=O - Me)_{1.2e}$ interaction as compared to the $(=O - Ph)_{1\ 2e}$[14]. Finally this and the absence of hydrogen bond[15] may account for the lack of stereoselectivity observed by Kametani in the reduction of free α-aminopropiophenones.

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REFERENCES AND NOTES

1 T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, T. Kohagizawa and H. Inoue, Heterocycles, 14, 775 (1980).

2 D. J. Cram and K. R. Kopecky, J. Am. Chem. Soc., 81, 2748 (1959).

3 B. Alcaide, C. López-Mardomingo, R. Pérez-Ossorio and J. Plumet, J. Heterocyclic Chem., in press.

4. B. Alcaide, R. Fernández de la Pradilla, C. López-Mardomingo, R. Pérez-Ossorio and J. Plumet, J. Org. Chem., 46, 3234 (1981) and references therein.

5 O. Arjona, R. Pérez-Ossorio, A. Pérez-Rubalcaba and M. L. Quiroga, J. C. S. Perkin II, 597 (1981) and references therein.

6. For the synthesis of RR-SS isomers see:
a) R. Haro, A. Jimenez-Tebar, R Pérez-Ossorio and J Plumet, Tetrahedron Letters , 1355 (1979)
b) B. Alcaide, C López-Mardomingo, R Pérez-Ossorio and J. Plumet, An. Quim., in press.
7. B. Alcaide, G. Escobar, R. Pérez-Ossorio and J. Plumet, Org. Prep Proc Int., accepted for publication
8 C. Alvarez-Ibarra, F. Fernández González, A. García Martínez, R. Pérez-Ossorio and M L. Quiroga, Tetrahedron Letters, 2715 (1976)
9. For the sodium borohydride reduction of ketones D. C Wigfield [Tetrahedron, 35, 449 (1979)] has proposed a stepwise mechanism with a product-like $TS^{\neq}$ and solvent participation. Acceptance of either a reactant-like or a product-like $TS^{\neq}$ in our case is not possible with the data obtained so far, but, in any case, the above discussion would not be essentially modified Moreover, it should be noted the independence of the stereochemical result from the nature of hydroxylic solvent (see Table).
10. We assume that here the interaction between H^- ($H^{\delta-} \ldots BH_3$ according to Wigfield[8]) and Ph is the lowest. The interaction of NHR with incoming H^- is probably larger due to polar repulsion
11. See, for example, L J. Bellamy, "The Infrared Spectra of Complex Molecules", Vol II, 2nd ed , Chapman & Hall Ed., 1980, Ch 8
12 Intramolecular association in final aminoalcohols has been shown by variable dilution infrared measurements as in similar cases See ref 4 and references quoted therein. Also: R. Mathis, M. T Maurette, Ch Godechot and A Lattes, Bull. Soc Chim. France, 3047 (1970).
13 G. J Karabatsos and N. Hsi, J. Am. Chem. Soc., 87, 2864 (1965).
14. According to Ref 11 $(=O - Ph)_{1\ 2e}$ is 1 67 KJ/mol larger than $(=O - Me)_{1\ 2e}$ in carbonyl compounds
15 Differences in the stereochemical behaviour of some secondary and tertiary aminoketones in their $NaBH_4$ reduction are in agreement with this interpretation See S Yamada and K Koga, Tetrahedron Letters, 1711 (1967).

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