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 paper¹ Kametani et al report the stereoselective reduction of α -aminoproprophenone 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 state² In the course of work on the stereoselective synthesis of oxazolidines³ from aminoalcohols obtained by reduction of benzilmonoimines⁴ 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 model⁵ 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 (<u>erythro</u> in Kametani's paper) was obtained. Assignment of configurations was based on ¹H-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 <u>vs</u> 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, NR₂ = NHZ (Z = Ph,PhCH₂, Ph₂CH,PhCHMe,PhCHEt), for aminopropiophenones R' = Me, NR₂ = NAlkyl₂ TS^{\neq} I may

<u>Table</u> . Reduction of a-Aminodeoxybenzoin										
Deriva	atıves (1,2)	with Sodiu	n Borohy	dride						
Ph-CO	-CHPh-NHR	₽h-CO-CHPh-NH2R,C1 ⁻								
	(1)	(2)								
	Ph-CHOH	I-CHPh-NHR								
Compd	R	Solvent	Hrs	Yıeld(%) ^a						
1	Ph	EtOH	7	70						
2	Ph	Me0H	7.5	67						
2	Ph	EtOH	75	76						
2	Ph	Pr ¹ OH	75	66						
2	Ph	Bu ^t OH	8	81						
1	PhCH ₂	EtOH	2	94						
2	PhCH ₂	Me0H	8	78						
2	PhCH	EtOH	8	76						
2	PhCH	Pr ¹ OH	8	65						
2	PhCH	Bu ^t OH	8	76						
1	Ph ₂ CH ^D	EtOH	8	85						
1	PhCHMe ^{c,d}	Et ₂ 0	4	88						
2	PhCHMe ^C	EtÕH	3	84						
1	PhCHEt^C	EtOH	2.5	100						
2	PhCHEt^C	EtOH	8	85						

a) In crude reaction product showing only ¹H-NMR signals of (RS-SR)-Aminoalcohols.
b) Hydrochloride could not be isolated⁷.
c) With LiAlH₄. See Ref. 4 d) A mixture of RRR-SSS and RRS-SSR diastereoisomers was obtained



REACTANT-LIKE TS [≠]												
		0	0	<	ų	Y	<	15	0			
60	0		+	Ψ	•	\$	Θ	<	75°	+	Ψ	
	4	5	0	<	¥)	<	60	0			
<u>P</u>	R	0	DU		<u>r</u> -	Ŀ	<u>I K</u>	E	TS₹			
	1	5	0	<	y	ŗ	<	60	•			
30	0		t	Ψ	•		Θ	<	60°	+	Ψ	
	6	0	0	<	φ	I	<	90	o			

Fig. 1



be disregarded since the hydride attack occurs in a hindered face of the carbonyl group¹⁰, moreover the phenyl group attached to it is flanked by the two bulkiest α -substituents. The relative energies of TS[#] II and TS[#] III depend basically on the relative values of the interactions $[(-0 - R')_{1.2e} + (Ph-NR_2)_{1.2g}] \frac{vs}{(-0 - NR_2)_{1.2e}} + (Ph - R')_{1.2g}$. 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 bond¹¹ between carbonyl and amino groups present in the initial state would be partially preserved in TS[#] III. This will be true both for reactant-like and product-like transition states although in the latter TS[#] II may also benefit from a certain degree of hydrogen bond stabilization.¹² On the other hand, a destabilizing interaction $(-0 - Ph)_{1.2e}$ and $(Ph - R')_{1.2g}$ interactions persist unmodified in TS[#] 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 (=0 - NHR)_{1.2e} interaction in TS^{\neq} III as compared with the destabilizing effect of the (=0 - Ph)_{1.2e} interaction in TS^{\neq} II. These conclusions can be extended to reduction of aminodeoxybenzoin hydrochlorides and also to α -aminopropropriphenone 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 (=0 - Me)_{1.2e} interaction as compared to the (=0 - Ph)_{1.2e} ¹⁴ Finally this and the absence of hydrogen bond¹⁵ may account for the lack of stereoselectivity observed by Kametani in the reduction of free α -aminopropropriphenones

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- 10. We assume that here the interaction between H^- (H^{δ_-} ... BH_3 according to Wigfield⁸) and Ph is the lowest. The interaction of NHR with incoming H^- is probably larger due to polar repulsion
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