Stereoselective reduction of benzoin by the NADH model 3-(dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridine

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Stereoselective reduction of benzoin by the NADH model 3-(dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridine†

Nicoline A. Beijer*, Jozef A. J. M. Vekemans and Henk M. Buck

Department of Organic Chemistry, Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, The Netherlands
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Abstract. The $Mg(ClO_4)_2$-induced reduction of racemic benzoin by the racemic NADH model compound 3-(dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridine (**1**), in accordance to Cram's rule, leads exclusively to *meso*-1,2-diphenyl-1,2-ethanediol. However, while *R*-**1** equally reduces *S*-benzoin to afford *meso*-1,2-diphenyl-1,2-ethanediol, *S*-**1** is reluctant to react with *S*-benzoin. The intermediacy of a strictly organized transition state, composed of chelated substrate, dihydropyridine and magnesium ion is involved.

Introduction

Recently, it has been shown that the NADH model compound 3-(dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridine (**1**) combines high reactivity with excellent asymmetric induction[1].

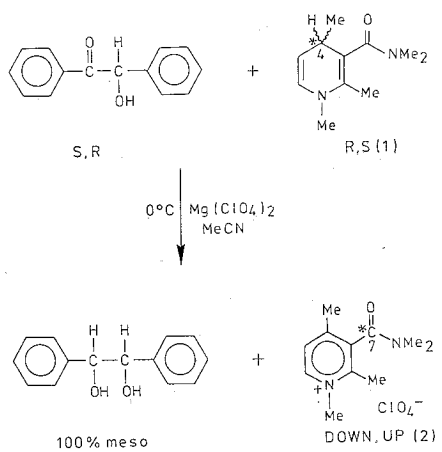
The induction of chirality in the reduction of carbonyl compounds has been studied extensively[1-4]. We have proposed a mechanism in which a strictly organized transition state intervenes, *i.e.*, the amide carbonyl dipole of the dihydropyridine system is rotated out of the pyridine plane with the amide oxygen atom facing the substrate (the migrating hydride and the amide carbonyl dipole are *syn* orientated). A magnesium ion plays a crucial role in inducing both high stereoselectivity and high reactivity. It acts as a Lewis acid which coordinates the substrate and hydride donor with concomitant *syn* 'out-of-plane' rotation of the amide carbonyl dipole. The conformation of the resulting axial chiral pyridinium cation **2** (CO up or CO down) has been correlated with the *S* and *R* configurations of **1**. This unambiguously demonstrated that, in the complex, the migrating hydride and the amide CO dipole are *syn* orientated[5-12].

The successful stereoselective reduction of several prochiral carbonyl substrates, *e.g.*, methyl benzoylformate*, by **1**[1], prompted us to extend our investigations to the stereoselective reduction of monosaccharide derivatives. The reaction of **1** with benzoin**, an α-hydroxy ketone, chosen as a carbohydrate model compound, has been investigated. We will show that, independent of the enantiomeric composition of either benzoin or **1**, *meso*-1,2-diphenyl-1,2-ethanediol (**3**, *meso*-hydrobenzoin) is exclusively formed. The formation of **3** itself is, also considering Cram's rule, not surprising, but the exclusive formation of the *meso* diol is remarkable and can only be explained by assuming a chelated ternary complex.

Results and discussion

It was observed that the dihydropyridine **1** was able to reduce benzoin in acetonitrile in the presence of magnesium perchlorate (Scheme 1). The reaction products were separated by partitioning between CH_2Cl_2 (**3**, 1,2-diphenyl-1,2-ethanediol) and water (pyridinium perchlorate).

^{1}H- and ^{13}C-NMR spectra of **3** in CD_3CN before and after chromatographic purification indicated the exclusive presence of the *meso* isomer[4]. The pyridinium perchlorate **2**,



Scheme 1. Reduction of benzoin with the NADH model compound **1**.

† Chem. Abstr. name: 1,4-dihydro-*N*,*N*,1,2,4-pentamethyl-3-pyridinecarboxamide.

* Chem. Abst. name: α-oxobenzeneacetic acid methyl ester.

** Chem. Abstr. name: 2-hydroxy-1,2-diphenylethanone.

*Table I Stereoselective reduction of benzoin[a] with the 1,4-dihydropyridine R-(**1**) and S-(**1**) in the presence of $Mg(ClO_4)_2$ at 0 °C.*

Entry	Dihydropyridine **1**		Benzoin	*meso*-Diol	Pyridinium **2**	
	Confign.	ee[b] (%)	Confign.	Yield[c]	Conform.	ee (%)
1	rac.	–	rac.	100	rac	–
2	*R*	96	*S*	95	DOWN	97
3	*S*	96	*S*	2	UP	65[d]
4	*R*	65	*S*	82	DOWN	80
5	*S*	64	*S*	20	UP	40[d]
6	*R*	65	rac.	70[e]	DOWN	62

[a] All reactions are carried out with commercially available racemic or *S*-benzoin. [b] Enantiomeric excess. [c] Using dihydropyridine and benzoin in a 1:1 ratio. [d] *S*-**1** is converted through autoxidoreduction to **2** (CO up) (at maximum 50%). [e] The yield of *meso*-diol is dependent on the ratio dihydropyridine/benzoin. With a ratio of 1/2 a 100% yield can be obtained.

derived from optically active **1**, was obtained in high enantiomeric excess.

Table I reveals that *S*-benzoin and *R*-**1** react exclusively to give *meso*-1,2-diphenyl-1,2-ethanediol, whereas *S*-benzoin with *S*-**1** does not react (entries 2 and 3). Presumably, the reactions of *R*-**1** with *S*-benzoin and *S*-**1** with *R*-benzoin will occur quickly, whereas those of *S*-**1** and *R*-**1** with the *S* and *R* substrate, respectively, will be rather slow. Support for this conclusion comes from the results of entry 4 (Table I) in which the enantiomeric excess increases upon conversion of the dihydropyridine **1** into the pyridinium cation **2**. No enantiomeric pure **2** (CO up)[1] is formed, since a part of *S*-**1** (at maximum 50%) is converted through autoxidoreduction. The results of entry 5 also show the difference in reactivity; the small quantity of diphenylethanediol originates from the minor presence of *R*-**1**.

The high optical yield of the axial chiral pyridinium perchlorate **2** obtained from *R*-**1** (entry 2), supports the intermediacy of a controlled transition state. By adopting a transition state in line with the proposed Mg^{2+} complex of methyl benzoylformate with **1**[1], in which the methoxycarbonyl group was located *syn* with respect to the amide function, the enantioselective reduction of benzoin can be explained. *R*-**1** should induce the *R* configuration in the prochiral carbonyl group of the substrate and *S*-**1** the corresponding *S* configuration. Reduction of *R*-benzoin by *S*-**1** leads, therefore, to *meso*-1,2-diphenyl-1,2-ethanediol (Figure 1). Similarly, *S*-benzoin and R-**1**, also give rise to the *meso* diol.

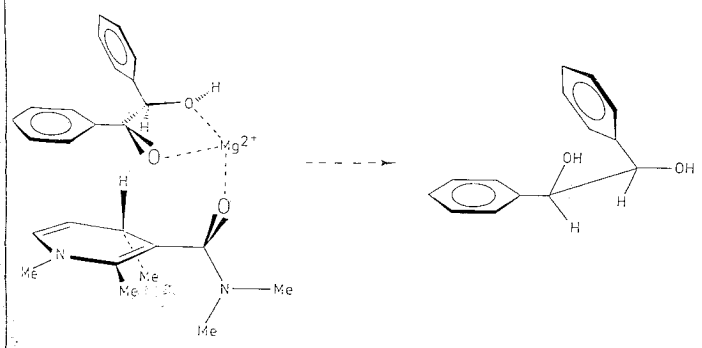


*Fig. 1. Schematic representation of the proposed ternary complex involved in the $Mg(ClO_4)_2$-mediated hydride transfer from S-**1** to R-benzoin, leading to* meso*-1,2-diphenyl-1,2-ethanediol.*

The formation of a chelate with the α-hydroxy group of benzoin on the one hand and the presence of a relatively bulky phenyl group on the other may explain the high diastereoselectivity of the reduction. Upon formation of the Mg^{2+} complex, discrimination takes place between the two optical isomers of benzoin, *i.e.*, *R*-**1** reacts with *S*-benzoin and not with *R*-benzoin; the opposite holds for *S*-**1**. These results further prove that a ternary complex including chelation with the substrate is operative in $Mg(ClO_4)_2$-induced NADH-model reactions[1].

Conclusions

The reduction of benzoin (either optically active or racemic) by the NADH model compound **1** (either optically active or racemic) yields exclusively *meso* 1,2-diphenyl-1,2-ethanediol. Together with the reluctancy of *S*-**1** to react with *S*-benzoin, this supports the intermediacy of a strictly organized transition state composed of chelated substrate, dihydropyridine and magnesium ion. The remarkable selectivity of the dihydropyridines *R*-**1** and *S*-**1**, towards *S*- and *R*-benzoin should, therefore, allow an efficient kinetic resolution of benzoin.

Experimental

NMR spectra were run on a Bruker AC200 spectrometer (^{1}H NMR at 200 MHz and ^{13}C NMR at 50.3 MHz) using TMS as internal standard.

3-(Dimethylcarbamoyl)-1,2,4-trimethyl-1,4-dihydropyridine (**1**) was synthesized in a few steps as outlined elsewhere[1]. Enantiomeric separation of **1** was accomplished by chromatography on a 100-mg scale on cellulose triacetate (Merck, 25 × 40 μm) upon elution with 2-propanol. A ^{1}H NMR study using (+)-Eu(hfc)$_3$ as shift reagent was applied to determine the enantiomeric excess of the enantiomer predominantly present.

Racemic benzoin (39.6 mg) was reduced, during 1 h, by 35 mg racemic dihydropyridine **1** in CD_3CN (0.4 ml) in the presence of an equivalent amount of magnesium perchlorate at 0 °C. The organic solvent was removed *in vacuo* at room temperature and the residue was partitioned between aqueous NH_4Cl (4 ml 0.1M) and CH_2Cl_2 (8 ml).

The organic phase was washed with water (2 × 1 ml), dried ($MgSO_4$) and concentrated. The solid residue was purified by chromatography (silica gel, Merck, 0.063–0.200 mm, 2 g) via elution with ethyl acetate/dichloromethane (1/7) to give **3** (R_f 0.3). ^{1}H NMR (CD_3CN) for benzoin: δ 4.5 (s, 1H, OH); δ 6.1 (s, 1H, H); δ 7.2–8.1 (m, 10H, Ph), **3**: δ 3.3–3.4 (s, 2H, OH); δ 4.6–4.7 (s, 2H, H); δ 7.2 (s, 10H, Ph) and (*S*,*S*)(–)-hydrobenzoin: δ 3.7–3.8 (s, 2H, OH), δ 4.5–4.6 (s, 2H, H); δ 7.2 (s, 10H, Ph); ^{13}C NMR (CD_3CN) for **3**: δ 78.3; 118.3; 128.1; 128.5; 142.7 and (*S*,*S*)(–)-**3**: δ 79.3; 118.3; 128.2; 128.6; 142.7. M.p. **3** 133–135 °C (as specified for the commercial Aldrich products, *meso* 137–139 °C; (*S*,*S*)(–) 148–150 °C).

The combined aqueous layers were evaporated below 30 °C at low pressure. The residue was suspended in CH_3CN and the filtrate

was concentrated to give the pyridinium perchlorate **2** (contaminated with some inorganic salt)[1].
The remaining reactions were carried out in a manner similar to the above.
The enantiomeric excess starting with optically **1** was established using (+)-Eu(hfc)$_3$ in CD_3CN to separate the *syn* and *anti* N–Me proton signals. The routine integration and the Glinfit method (Glinfit program, Copyright Bruker Spectrospin AG, Switzerland) (rms < 4%) established the enantiomeric excess (Table I).

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