Reduction by a Model of NAD(P)H. 32. Stereoselective Reduction of Camphoroquinone by a Chiral NAD(P)H Model

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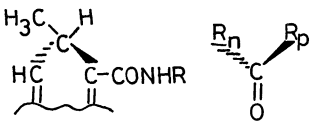
(+)-, (−)-, and racemic camphoroquinones (CQ) were reduced by each of four NAD(P)H-models such as *N*-(α-methylbenzyl)-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (Me_2PNPH) in the presence of magnesium ion in acetonitrile with a view to elucidating the intermolecular arrangement in the transition state for asymmetric reduction. Partial rate factors for each attacking mode were calculated. Electronegative substituents in the substrate prefer to facing the carbamoyl group in Me_2PNPH, which is the most important factor determining the stereochemical course of the reduction. 1-Methyl group in CQ has a tendency to interfere with the dihydropyridine moiety in Me_2PNPH approaching the C_2-carbonyl group in CQ. This interference is more important for the selectivity than the intrinsic *exo/endo* reactivity difference.

Quite a few organic chemists have tried to design their reactions after the model of biochemical transformations which exhibit too high reactivity and stereospecificity. Dihydropyridine nucleotides, NADH and NADPH, are coenzymes of NAD(P)H-dependent dehydrogenases that reduce carbonyl and other unsaturated compounds stereospecifically in almost all organisms. Hence, for bioorganic chemists, reduction by models of NAD(P)H has been an interesting subject to study. In the course of our study on the biomimetic chemistry of NAD(P)H, we have found that bivalent metal ions such as Mg^{2+} and Zn^{2+} affect reduction of carbonyl compounds by models of NAD(P)H.[1-9] A series of investigations has revealed that the reduction is composed of a three-step electron-proton-electron transfer process and that the bivalent metal ion catalyzes the process of initial electron-transfer.[3,6,9,10]

The bivalent metal ions also control stereospecificity of the reduction.[1,2,11-15] For example, reduction of certain carbonyl compounds with *N*-(α-methyl benzyl)-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (Me_2PNPH) in the presence of magnesium ion results in an excellent asymmetric induction.[15] The configuration of predominant enantiomer of product alcohol is determined from the configuration of the C_4-position of Me_2PNPH. On an assumption that the carbonyl-oxygen in a substrate points toward the ring-nitrogen of Me_2PNPH, it has been proposed that an electronegative polar group in a substrate faces the electronegative carbamoyl group in Me_2PNPH in the transition state for reduction (**1**) and that the relative



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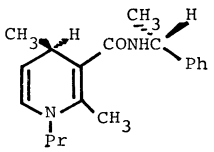
R_p: polar substituent
R_n: nonpolar substituent

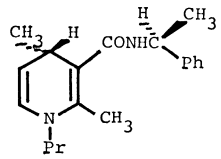
bulkiness of substituents R_n and R_p plays no important role in determining the configuration of product alcohol.[15] The proposal that two electronegative groups face each other contradicts to a common idea of electronic effect. However, when it gets proved to be correct, it may suggest that the magnesium ion positions itself between the substrate and Me_2PNPH by coordinating two electronegative groups to freeze the intermolecular configuration in the transition state, as an origin of the stereospecificity of the magnesium ion-catalyzed reduction. Thus, it is important, for understanding the role of magnesium ion in the reduction, to get information about the intermolecular arrangement in the transition state for the reduction; for this reason we studied the reduction of 1,7,7-trimethylbicyclo[2.2.1]heptane-2,3-dione (camphoroquinone, CQ) with Me_2PNPH. CQ has two carbonyl groups constrained in a rigid framework, and the oxygen atom in the reacting carbonyl group will be caused to point toward the ring-nitrogen of Me_2PNPH in the transition state because of the large steric effect.

Results

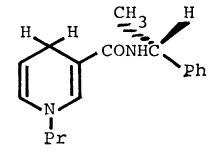
(−)-CQ, (+)-CQ, and (±)-CQ were reduced by (4*R*)-N-[(*R*)-α-methylbenzyl]-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (*RR*-Me_2PNPH), *SS*-Me_2PNPH, [(*R*)-α-methylbenzyl]-1-propyl-1,4-dihydronicotinamide (*R*-PNPH), 1-propyl-1,4-dihydronicotinamide (PNAH), or 1-benzyl-1,4-dihydronicotinamide (BNAH). All reactions were carried out in dry acetonitrile in the presence of magnesium ion in equivalent amount at room temperature under an argon atmosphere in the dark. The reduction did not proceed without magnesium ion. (−)-CQ afforded a mixture of diastereomeric isomers of four α-keto



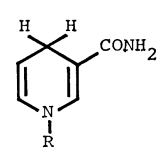
RR-Me_2PNPH



SS-Me_2PNPH



R-PNPH

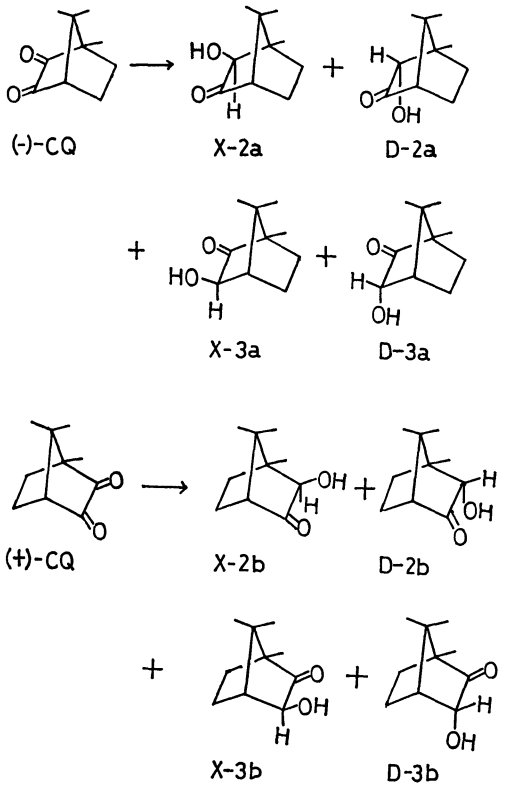


R = Pr : PNAH

R = $PhCH_2$: BNAH

alcohols: (2*S*)-2-*exo*-hydroxy-1,7,7-trimethylbicyclo-[2.2.1]heptan-3-one (2*S*-*exo*-hydroxyepicamphor, *X*-**2a**), (2*R*)-2-*endo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]-heptan-3-one (2*R*-*endo*-hydroxyepicamphor, *D*-**2a**), (3*R*)-3-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-on (3*R*-*exo*-hydroxycamphor, *X*-**3a**), and (3*S*)-*endo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one(3*S*-*endo*-hydroxycamphor, *D*-**3a**), whereas (+)-CQ afforded a mixture of their corresponding enantiomeric isomers *X*-**2b**, *D*-**2b**, *X*-**3b**, and *D*-**3b** (Scheme 1).

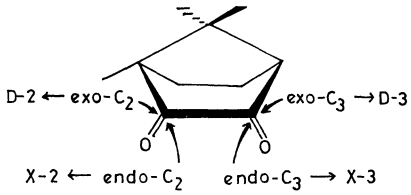
Structures and relative yields of products were determined on the basis of ^{1}H-NMR spectra.[16] Results for the reductions with BNAH, PNAH, and *R*-PNPH are summarized in Table 1 and those with Me_2PNPH in Table 2. It was confirmed that no isomerization took place between isomeric products.



Scheme 1.

Discussion

CQ has two prochiral carbonyl groups and it is potentially possible that four isomers are to be formed as reduction products. Since these carbonyl groups are frozen to the *Z*-configuration on a rigid hydrocarbon framework which has diastereotopic faces, the ratio of the yields of these isomers reflects the configurational requirement for the carbonyl group in the transition state for the reduction. The results in Table 1 indicate that the *exo*-C_3-attack (see Scheme 2) is the most preferential process in the reduction with such models as have two available hydrogens on the C_4-position, whereas the other modes of attack



Scheme 2.

Table 1. Reduction of camphoroquinone with NAD(P)H-models

Substrate	Model	*T*/h[a]	CQ_{rec}(%)[b]	*Y*/%[c]	Product ratio[d]			
					X-**2a**	*D*-**2a**	*X*-**3a**	*D*-**3a**
(−)-CQ	BNAH	235	42.3	7.3	14	13	16	57
(−)-CQ	PNAH	48	65.6	4.3	13	11	24	52
(−)-CQ	*R*-PNPH	91	50.2	8.6	15	9	14	62
					X-**2b**	*D*-**2b**	*X*-**3b**	*D*-**3b**
(+)-CQ	*R*-PNPH	91	61.6	6.8	8	10	20	62

a) *T* is reaction time. b) CQ_{rec} is the recovered, isolated CQ. c) *Y* is the yield of product isolated. d) Relative intensities of ^{1}H-HMR signals.

Table 2. Reduction of camphoroquinone with *N*-(α-methylbenzyl)-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (Me_2PNPH)

Substrate	Config. of Me_2PNPH	*T*/h[a]	CQ_{rec}(%)[a]	*Y*/%[a]	Product ratio[a]			
					X-**2a**	*D*-**2a**	*X*-**3a**	*D*-**3a**
(−)-CQ	*RR*	52	57.7	40.6	8	19	68	5
(−)-CQ	*SS*	52	36.2	67.6	20	16	6	58
					X-**2b**	*D*-**2b**	*X*-**3b**	*D*-**3b**
(+)-CQ	*RR*	52	53.1	47.3	21	14	7	58
(+)-CQ	*SS*	52	50.9	58.7	7	21	62	10
					X-**2**[b]	*D*-**2**[b]	*X*-**3**[b]	*D*-**3**[b]
(±)-CQ[c]	*SS*	52	46.0	54.1	14	16	27	43

a) See footnotes in Table 1. b) Mixture of **a** and **b**. c) Racemic camphoroquinone.

appear to have no practical predominance. The chirality of the side chain of *R*-PNPH plays no important role in determining the stereochemistry of the product. The observation reveals that the stereochemistry of the reduction depends on the structural preference of substrate and that no enantiotopic difference for the dihydropyridine ring has any effect. It should be noted that it is the C_1-methyl group that makes the C_3-attack preferential to the C_2-attack. Although not yet given any reasonable explanations, this methyl group plays an important role in determining the intermolecular arrangement in the transition state for the reduction, for which mention will be made later.

Contrary to the above, the stereochemistry of the reduction with Me_2PNPH mainly reflects the configuration of this model compound, the intrinsic reactivity of each position in CQ having only a minor influence. Validity of the product ratios listed in Table 2 is supported by the fact that identical results have been obtained from the following two pairs of reactants essentially the same with each other in composition: (−)-CQ and *RR*-Me_2PNPH *vs.* (+)-CQ and *SS*-Me_2PNPH; and (−)-CQ and *SS*-Me_2PNPH *vs.* (+)-CQ and *RR*-Me_2PNPH. Since the plane of dihydropyridine-ring in Me_2PNPH is not enantiotopic but diastereotopic, these results can be interpreted only on the basis of such an idea that CQ and Me_2PNPH have a preference for the orientation of substituents in the transition state for the reduction.

Before discussing the orientation, it is helpful to evaluate partial rate factors with all the reaction modes for (−)- and (+)-CQ; this evaluation may be effected by solving linear simultaneous equations for eight variables (eight reaction modes) by using the data listed in Table 2. The result is shown in Table 3. First of all, the calculated values predict that the susceptibility of (−)-CQ toward reduction with *SS*-Me_2PNPH will be 66/34 times greater than that of (+)-CQ. This prediction was in excellent agreement with an experimental result that, after the reaction with racemic CQ, the recovered CQ was subjected to a measurement for optical rotation $[\alpha]_D$ and a ratio 61/39 of consumed CQ's was obtained.

The most preferable mode of attack is *exo*-C_3 for (−)-CQ. In this mode the carbamoyl moiety in *SS*-Me_2PNPH will face the electron-rich carbonyl group of the substrate. It is interesting that for (+)-CQ the second preferable mode is not *exo*-C_2 but *endo*-C_3. Although, as already mentioned, CQ has a higher intrinsic reactivity for the *exo*-attack than for the *endo*-attack, the presence of the C_1-methyl group prevents so much the reaction of (+)-CQ from preceding in this mode that even the less realizable *endo*-attack is chosen. Thus, the effect of the methyl group overwhelms the *exo*/*endo* reactivity difference. Alcohol *D*-**2b** is one of the least abundant products. A similar result has been obtained in our laboratory for reductions of a series of 2-pyridyl alkyl ketones.[17]

Table 3. Partial rate factors in the reduction of (−)- and (+)-camphoroquinone with (4*S*)-*N*-[(*S*)-α-methylbenzyl]-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (*SS*-Me_2PNPH)

Reaction mode	Product	Camphoroquinone (−)	Camphoroquinone (+)
endo-C_2	*X*-**2**	0.13	0.02
exo-C_2	*D*-**2**	0.10	0.07
endo-C_3	*X*-**3**	0.04	0.22
exo-C_3	*D*-**3**	0.39	0.03
Total		0.66	0.34
Obsd[a]		0.61	0.39

a) See text.

Two explanations are feasible for this phenomenon: it is established that magnesium ion will interact with non-reacting electron-rich substituents of substrates.[8] Since the methyl group is an electron-releasing group, the carbonyl-oxygen on C_2 becomes more electron-rich than the one on C_3. Consequently, the carbonyl-oxygen on C_2 becomes the coordinating site, with the carbonyl group on C_3 remaining as the reacting moiety. The other possibility is that the steric effect of 1-methyl group prevents the approach of the dihydropyridine moiety of Me_2PNPH. Although no investigations with CPK-molecular models have predicted such an effect, the orientation of methyl group seems quite important, if this is the case, because none of such effects have been recognized for the *endo*-attack.

For concluding the discussion, we would like to emphasize that the intermolecular arrangement in the transition state for the reduction has proved to be such as shown in **1**, with polar groups facing each other, possibly because the magnesium ion assists their approach by getting into coordination with these groups.

Experimental

Melting points were not corrected. ^{1}H-NMR spectra were recorded on a JNM-FX100 spectrometer. Optical rotation was observed on a Perkin-Elmer 241 polarimeter.

Materials. Racemic camphoroquinone purchased from Aldrich Chemical Co. was recrystallized from hexane: mp 199 °C.

Anhydrous magnesium perchlorate was dried at 80 °C overnight and used immediately. Acetonitrile was distilled three times over phosphorus pentaoxide before use.

(−)- and (+)-Camphoroquinone (CQ). The Evans' procedure[18] with modifications was employed as follows. A mixture of (+)-camphor (10 g, 0.07 mol) and selenium dioxide (15 g, 0.14 mol) in 10 cm^3 of acetic anhydride was heated at 150 °C overnight. After the mixture had been cooled to room temperature, selenium metal was removed from the mixture by filtration and the metal was washed with acetic acid. The combined orange-yellow filtrate was neutralized carefully with a 30% aqueous potassium hydroxide. Yellow crystals appeared, which were filtered and washed with water to yield 10 g (93% yield) of (−)-CQ. The crude (−)-CQ thus obtained was recrystallized several times from hexane: mp 199 °C (lit,[18] mp 199 °C); $[\alpha]_D^{27}$ −108° (c=1.93, benzene) (lit,[16] $[\alpha]_D^{23}$ −122±3° (c=1.825, benzene)).

(+)-CQ was prepared by the same method: mp 199 °C; $[\alpha]_D^{20}$ +105° (c=1.96, benzene).

Models of NAD(P)H. The methods of preparation adopted for BNAH,[19] PNAH,[19] *R*-PNPH,[12] and Me_2PNPH[15] have already been described in literature.

General Procedure. To a mixture of a substrate, a model compound, and magnesium perchlorate, each of 1 mmol, in a flask filled with argon and sealed, 20 cm^3 of dry acetonitrile was added through a syringe. The mixture was allowed to react at room temperature for an appropriate period with stirring in the dark. The reaction was quenched by addition of 10 cm^3 of water and the solution was concentrated *in vacuo* below 30 °C. The organic materials were extracted with chloroform several times and the solvent was evaporated slowly from the extract *in vacuo* below 30 °C. Ample caution was exercised so as not to cause the materials to sublime. The residue was chromatographed on a column of silica gel (Wakogel 200 M) with benzene–ether (4:1 v/v) as eluent, affording unchanged CQ and a mixture of reduction products. The mixture and the recovered CQ were weighed to obtain their yields. An analysis of ^{1}H-NMR spectra of the products in $CDCl_3$ led to the assignment of a mixture of four isomeric α-keto alcohols *X*-**2**, *D*-**2**, *X*-**3**, and *D*-**3**:[16] δ=3.55 s, 1H for *X*-**2**), 3.75 (s, 1H for *X*-**3**), 3.87 (s, 1H for *D*-**2**), and 4.22 (s, 1H for *D*-**3**). Relative yields of these four isomeric products were obtained from the peak areas for each.

Optical rotation observed for the recovered (±)-CQ was $[\alpha]_D^{20}$ +22.4 (c=1.935, benzene), indicating that the mixture was composed of 61% (−)-CQ and 39% (+)-CQ.

Conversion of Physical Unit. The unit used for temperature is correlated with the SI-unit by

$$t/°C = T/K - 273.15.$$

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