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# NAD(P)$^+$-NAD(P)H MODELS. 66. STEREOSPECIFIC INTERCONVERSION BETWEEN DIFFERENT CHIRALITIES IN THE REDUCTION OF A QUINOLINIUM SALT

Atsuyoshi OHNO,* Masahiko OGAWA, and Shinzaburo OKA

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, JAPAN

**Abstract:** An axial chirality is converted into a central chirality with a high stereospecificity in the reduction of a chiral quinolinium ion into the corresponding 1,4-dihydroquinoline derivative. Mechanism of the reduction is discussed.

In previous papers of the series, we reported that 3-[N-methyl-N-(α-methylbenzyl)carbamoyl]-1,2,4-trimethylquinolinium ion ($Me_3MQP^+$) has axial chirality with respect to the (ring)$C_3$-$C_{carbonyl}$ bond[1,2] because this single bond cannot rotate freely and the carbonyl oxygen sticks out of the quinolinium plane in one isomer (9*S*-$Me_3MQP^+$), whereas it points down the plane in the other isomer (9*R*-$Me_3MQP^+$).[3,4]

When $Me_3MQP^+$ is reduced into 3-[N-methyl-N-(α-methylbenzyl)carbamoyl]-1,2,4-trimethyl-1,4-dihydroquinoline ($Me_3MQPH$), the axial chirality with respect to the (ring)$C_3$-$C_{carbonyl}$ bond disappears but a new central chirality appears at the (ring)$C_4$-position. The configuration of the predominant isomer in the product depends on the configuration of the reactant $Me_3MQP^+$ and the diastereomer excess (d.e.) depends on the reducing reagent employed: in the reduction of 9*S*-$Me_3MQP^+$, 4*S*- and 4*R*-$Me_3MQPH$ were formed in a ratio of 33 : 67 when sodium dithionite ($Na_2S_2O_4$) was employed as the reducing reagent, whereas the ratio was 7 : 93 when the salt was reduced by N-propyl-1,4-dihydronicotinamide (PNAH).[1,2] The 9*R*-$Me_3MQP^+$ afforded the 4*S*-$Me_3MQPH$ predominantly. Thus, despite the variation in the d.e. of reduction, it always follows that the hydrogen introduced into the major isomer of $Me_3MQPH$ comes from the face in which the carbonyl oxygen sticks out.

It is, therefore, quite interesting to know if the direction of the carbonyl dipole exerts a crucial role in determining the stereochemistry of the reduction, and we studied the reduction of $Me_3MQP^+$ by chiral 3-[N-(α-methylbenzyl)carbamoyl]-2,4-dimethyl-1-propyl-1,4-dihydropyridine (4*R*- and 4*S*-$Me_2PNPH$). The results will be discussed in comparison with the reduction/oxidation with other substrates.

In a typical run, 0.3 mmole of 9*R*-$Me_3MQP^+I^-$ was reacted with 1.5 equivalent amounts of 4*S*-$Me_2PNPH$ in 3 mL of methanol (or in acetonitrile) at room

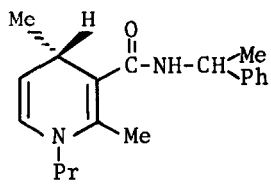
temperature under argon atmosphere for 14 hours in the dark. After usual work-up, the materials were subjected to $^1$H NMR spectroscopy, and found that all $Me_3$MQPH produced (98% chemical yield) had the 4*S*-configuration; no 4*R*-counterpart was detected. That is, the 4*S* : 4*R* isomer ratio must be larger than 97 : 3 (Scheme I). In addition to this expected product, another unidentified material was afforded in a small amount. The $^1$H NMR spectrum of this product suggests that one of N-methyl groups ( probably the one on the amide nitrogen) is eliminated from the substrate, and the material is unstable to column chromatography on silica gel to decompose into a compound which exhibits a $^1$H NMR spectrum similar to that of $Me_3MQP^+$.[5]

On the other hand, interestingly enough, the reaction of 9*R*-$Me_3MQP^+$ with 4*R*-$Me_2$PNPH did not proceed smoothly and 4*S*-$Me_3$MQPH (not the 4*R*-isomer) was afforded in only 6% chemical yield together with a large amount of the bi-product mentioned above. The reaction in the presence of magnesium perchlorate did not proceed with either isomers of $Me_2$PNPH. The reason is obvious; since the substrate is a cation, magnesium cation finds difficulty in forming a composite complex which undergoes the reaction.[6]

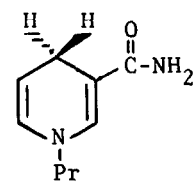
It is elucidated from the results that the molecular arrangement at the transition state of the reaction is required to be quite strict and the transferring hydrogen can attack $Me_3MQP^+$ only from the front face in which the carbonyl oxygen is involved and the hydrogen never comes from the rear face. The result seems to suggest that the initial electron-transfer[7] can take place even in unsatisfactorily arranged transition state, but the succeeding proton-transfer[7] does not proceed smoothly in the transition state arranged incorrectly.

There are two possibilities in intermolecular arrangement at the transition state to satisfy the results; one in which the carbamoyl moieties in $Me_3MQP^+$ and $Me_2$PNPH face against each other with the ring nitrogens of two reagents being set in opposite direction (Structure A). The other sets the carbamoyl moieties in the opposite direction to face the ring nitrogens against each other (Structure B). Careful studies on the stereochemistry of reduction of carbonyl compounds with $Me_2$PNPH has revealed that the polar group in a substrate always faces against the carbamoyl moiety of $Me_2$PNPH and the carbonyl oxygen of the substrate points toward the ring nitrogen of the reducing reagent.[8-10]

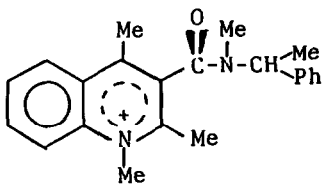
The reduction of an α-keto ester with $Me_3$MQPH also proceeds after this rule.[1,2,11] Thus, neither of the Structures A and B seems to satisfy, at



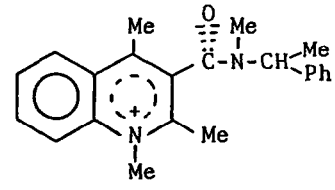

4*S*-$Me_2$PNPH



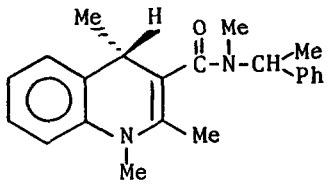

PNAH



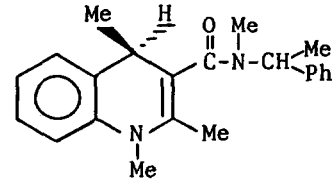
9*R*-$Me_3$MQP$^+$



9*S*-$Me_3$MQP$^+$

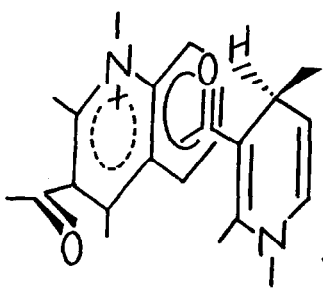


4*S*-$Me_3$MQPH

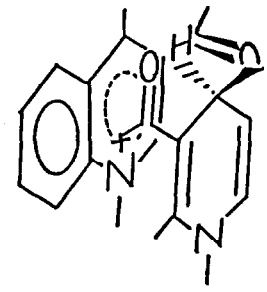


4*R*-$Me_3$MQPH

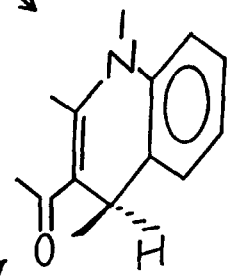
Scheme I



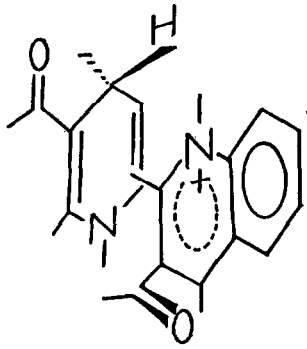
Structure A

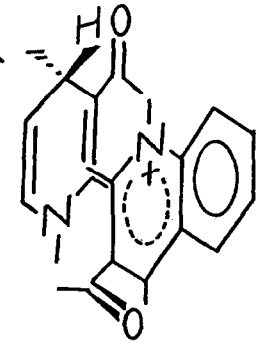


Structure B



4*S*$Me_3$MQPH





the first glance, the rule for the molecular arrangement elucidated previously. However, when one recognizes that the ring nitrogen is the positive center of the dipole in $Me_3MQP^+$, as is the carbon in a carbonyl group, it seems reasonable to assign the Structure A, in which the arrangement of carbamoyl moieties is also satisfied, as the plausible molecular arrangement at the transition state of the present reaction. The carbonyl compounds so far studied as the substrate of the reduction can be divided into three parts; polar substituent, non-polar substituent, and the reacting moiety. The vicinity of the ring nitrogen of $Me_3MQP^+$ seems, therefore, to constitute a polar substituent of the substrate instead of the reacting part.

Further studies are awaited before the proposal on the molecular arrangement at the transition state of the reaction is confirmed unequivocally and our effort is focused on the goal.

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2. A. Ohno, M. Ohara, and S. Oka, *J. Am. Chem. Soc.*, 108, 6438 (1986).
3. The *R* and *S* notations for this chirality were misused in the preceeding paper (ref. 2). The 9*R*-isomer described therein should be read as the 9*S*-isomer and *vice versa*.
4. Since the methylbenzyl group on the carbamoyl nitrogen of this compound has chirality of either *R* or *S*, the 9*R*- and 9*S*-isomers are diastereomeric instead of enantiomeric isomers each other. In order to simplify the expression, we will ignore the chirality on the methylbenzyl group in the following discussion. It has been proved that this chirality exerts no effect on the chemistry we are going to discuss.
5. we now tentatively assign the compound to be the 1,2-dihydro-isomer of de-methylated $Me_3MQPH$.
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11. Reduction of α,α,α-trifluoroacetophenone also proceeds with the same stereochemistry; A. Ohno and M. Ohara, unpublished result (1986).

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