NAD(P)$^+$-NAD(P)H Model. 54. Free Radical Mechanism for the Reductive Debromination of *vic*-Dibromides to Alkenes

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(Received January 30, 1985)

Synopsis. *vic*-Dibromides undergo reductive debromination with a model of NAD(P)H, *N*-benzyl-1,4-dihydronicotinamide, to afford the corresponding alkenes quantitatively. Stereochemistry of the reduction suggests that the reaction involves a free radical intermediacy.

Whether the reduction with NAD(P)H or its model compounds proceeds through a multi-step (electron-transfer) mechanism or through a one-step (hydride-transfer) mechanism has been a subject of current discussion.[1] There are several reports on reactions in which a model of NAD(P)H acts as a one-electron donor; it acts even as a radical-chain initiator in the reaction of bromotrichloromethane to chloroform,[2a] radical polymerization of acrylamide,[2b] and dediazoniation of arene diazonium salts.[2c] These reactions have been invoked to support the multi-step mechanism which involves initial one-electron transfer process. Nevertheless, since these reactions are not initiated by any provocations other than one-electron transfer onto the substrates, the models may be compelled to act as a one-electron donor in these reactions. Therefore, in order to obtain the definitive proof for the intrinsic ability of dihydropyridine derivatives as a one-electron donor, an alternative reaction system that is known to be susceptible both for one-electron and two-electron reductions should be taken.

A variety of reductants[3-5] as well as electrochemical reduction[6] convert *vic*-dibromide into the corresponding alkene by reductive debromination. Studies on the stereochemistry of these reductions have demonstrated that two-electron reductants such as iodide and hydride ions mainly give rise to concerted *anti*-elimination resulting in stereoselective formations of *trans*- and *cis*-alkenes from *meso*- (or *erythro*)- and *dl*- (or *threo*)-isomers, respectively. On the other hand, one-electron reductants such as copper(I) and iron(II) generate free radical species, which then give thermodynamically more stable alkenes predominantly[7,8] Thus, the reductive debromination of *vic*-dibromide is supposed to be an useful tool to diagnose whether a model of NAD(P)H acts as a one-electron donor or a hydride donor.

Results and Discussion

The results from the reactions of *vic*-dibromides **1a—c** with a model of NAD(P)H, *N*-benzyl-1,4-dihydronicotinamide (BNAH), are summarized in the Table. The table shows that *meso*- (or *erythro*)-bromide gave the *trans*-alkene (*trans*-**2**) quantitatively under anaerobic conditions with excess BNAH. On the other hand, the alkene from the *dl*-bromide is contaminated by a small amount of the *cis*-isomer (*cis*-**2**) under the same conditions. The results can be interpreted in terms of a free radical intermediacy in the course of the reaction. That is, **1** accepts one electron from BNAH and eliminates a bromide ion, and thus generated free radical species **3** can rotate around the central C–C bond to afford thermodynamically more stable isomer of the alkene predominantly.[8] A plausible reaction path is illustrated in the Scheme.

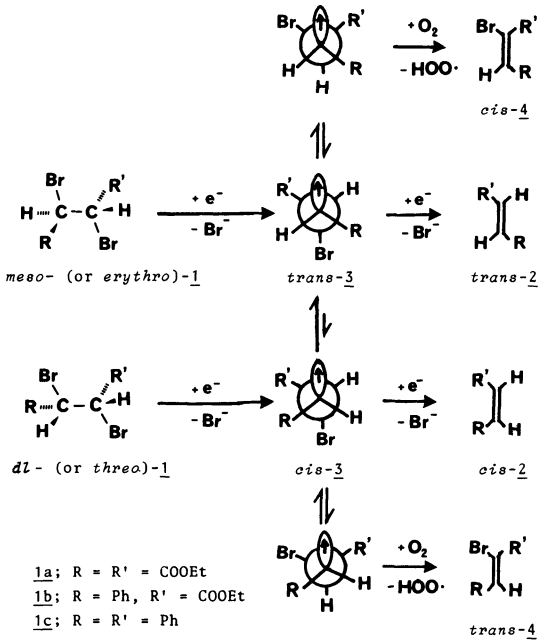
It has been reported that triphenylphosphine generates a carbanion from 1,2-dibromo-1-nitro-2-phenylethane (**5**) on its 1-position through the abstraction of a bromonium ion, which may afford the isomerized product.[9] However, the situation is not applicable to the present system, because BNAH is not a so strong nucleophile as triphenylphosphine and the substrates employed presently are not so electron deficient as **5**. Interestingly, an amine such as triethylamine gave rise to β-elimination of hydrogen bromide instead of reductive debromination.

Reductions under aerobic conditions also supports

Table 1. Reductive debromination of *vic*-dibromides with BNAH[a]

Dibromide	Atmosphere	React. time/h	Conv. /%	Yield/%[b] *trans*-**2**	*cis*-**2**	*trans*-**4**	*cis*-**4**
meso-**1a**	N_2	2	92	100	0	0	0
meso-**1a**[c]	N_2	28	75	98	0	Trace	Trace
meso-**1a**[d]	N_2	24	46	80	0	Trace	Trace
meso-**1a**	O_2	2.5	98	28	0	8	56
dl-**1a**	N_2	7	100	100	Trace	0	0
erythro-**1b**	N_2	3	96	96	0	0	4
erythro-**1b**	Air	3	47	66	0	0	28
meso-**1c**[e]	N_2	4	100	90	0	0	0
dl-**1c**[f]	N_2	2	58	52	26	0	0
dl-**1c**[f]	O_2	2	84	27	20	52	Trace

a) The reactions were carried out with 5.0×10^{-2} mmol of **1** and 1.5×10^{-1} mmol of BNAH in 1 cm^3 of MeCN at 323 K in the dark unless otherwise indicated. b) Based on **1** consumed. c) 1.0×10^{-1} mmol of BNAH was used. d) 5.0×10^{-2} mmol of BNAH was used. e) In DMSO. f) At 343 K.



Scheme 1.

the participation of a free radical intermediacy: an oxygen molecule, which is an effective free radical scavenger, suppresses the debromination and β-elimination of hydrogen bromide predominates. Thus, as illustrated in the scheme, a free radical **3** generated is immediately trapped by an oxygen molecule to form a peroxide, which subsequently undergoes β-elimination of hydrogen peroxide in *anti*-direction to give the corresponding bromoalkene (**4**) without isomerization.[10]

BNAH promoted neither interconversion between *trans*-**2** and *cis*-**2** nor between *meso*- (or *erythro*)-**1** and *dl*-**1** under the reaction conditions. It was also confirmed that BNAH does not convert **4** to **2**.

Stoichiometry of the present reduction is noteworthy. The completion of the reduction requires more than two equivalents of BNAH against **1**, which excludes the possibility that BNAH releases a hydride ion in one step. Unfortunately, the fate of the cation radical produced from BNAH is not clear at present.

In conclusion, BNAH acts as a one-electron reductant in the reductive debromination of *vic*-dibromides even though it has a potential to behave as a hydride-ion donor. The present finding supports our previous proposal that the reduction with NAD(P)H-models involves initial one-electron transfer process.

In addition, the reductive debromination of *vic*-dibromides is an useful procedure for the purification of alkenes or the protection of alkenyl groups. The present reaction system is available for these procedures, since the conversion of the reaction and the yields of the products are satisfactory under anaerobic conditions with a little excess of BNAH. The process is much simpler than those so far reported.[4,5]

Experimental

Materials. Diethyl *dl*-dibromosuccinate (*dl*-**1a**)[11] and *dl*-1,2-dibromo-1,2-diphenylethane (*dl*-**1c**)[12] were prepared by bromination of diethyl maleate and *cis*-stilbene, respectively. Diethyl *meso*-dibromosuccinate was prepared by esterification of the corresponding acid. Ethyl *erythro*-α,β-dibromohydrocinnamate (*erythro*-**1b**) and *meso*-**1c** were commercially available (Tokyo chemical industry Co., Ltd.). NMR, IR, and GC-MS spectra of these compounds were satisfactory.

General Procedure. To a solution of 5.0×10^{-2} mmol of **1** in 0.5 cm³ of acetonitrile was added, using a syringe, a solution of 1.5×10^{-1} mmol of BNAH in 0.5 cm³ of acetonitrile through a silicone-rubber stopper. The mixture was left at 323 K in the dark for an appropriate time: then a 0.20-cm³ aliquot of the mixture was quenched with 1 cm³ of water. The aliquot was extracted with 1 cm³ of benzene containing *p*-diethoxybenzene as an internal standard for VPC analysis. The organic layer was analyzed on a Yanaco G-180 gas chromatograph (OV-17 column). Identification of products was done by comparison of IR, NMR, and GC-MS spectra of isolated products with those of the corresponding authentic smaples.

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8) It may be claimed that the cis/trans ratio of the product, alkene, is determined also by relative stabilities of rotamers of the intermediate, property of the leaving atom (group), or bulkiness and charge of counter cation(s). Although such a point is not investigated in detail in the present study, this does not interfere our present discussion. It is important for the present study to point out that the intermediate has a chance to change its conformation.

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