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Stereospecific Electrochemical Oxidation of NAD(P)H Analogs Mediated by Radical Cation of Anilines[1)†]

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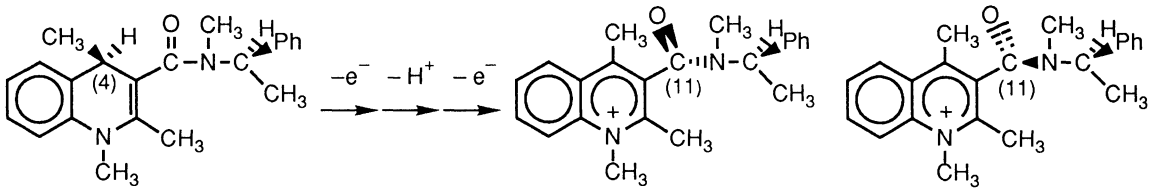
Net hydrogen-atom (H•) transfer was observed in electrochemical oxidation of NAD(P)H analogs in the presence of aniline or its derivatives. The reaction mechanism is discussed on the basis of stereospecificities.

We previously reported that stereospecificity was observed in the chirality conversion between the central chirality at the C_4-position of 3-(N-methyl-N-α-methylbenzylcarbamoyl)-1,2,4-trimethyl-1,4-dihydroquinoline (Me_3MQPH) and the axial chirality with respect to the C_3-$C_{carbonyl}$ bond in 3-(N-methyl-N-α-methylbenzyl-carbamoyl)-1,2,4-trimethylquinolinium ion (Me_3MQP^+) under base-catalyzed electrochemical oxidation.[2)] The conversion of the reduced form to the oxidized form proceeds along a stepwise electron-proton-electron transfer mechanism, the proton transfer being catalyzed by a base.[3-5)] Since the proton-transfer step is rate-determining and the earliness or lateness of the transition state is determined by the base-strength, which is proportional to pK_a of its conjugated acid, the stereospecificity and pK_a of the base is correlated each other.[2,3)] A comparable correlation was also observed in the same reaction with 3-(N-methyl-N-α-methylbenzylcarbamoyl)-1-propyl-2,4-dimethyl-1,4-dihydropyridine (Me_3PNPH).[2)]



(4*R*)-Me_3MQPH (11*R*)-Me_3MQPH (11*S*)-Me_3MQPH

In the previous report,[2)] the amines employed as the catalyst were mainly substituted pyridines, whereas substituted anilines were almost excluded because it was found that substituted anilines of pK_a 4 - 6 behaved differently from the other amines on the stereospecificity in the oxidation reaction by Fe(III) complex.[3)] In this paper, we would like to report that another mechanism on stereospecific electrochemical oxidation is observed in the presence of a series of substituted anilines. The mechanism is partly identical with that of stereospecific oxidation by benzoquinone derivatives reported previously.[6,7)]

The electrochemical oxidation was carried out with a platinum electrode at 298 K for 6 h at appropriate oxidation potential (*vs.* Ag/AgCl in saturated aq. KCl).[7,8)] The reaction solution containing 2 mM (1 M = 1 mol dm^{-3}) Me_3MQPH or Me_3PNPH, 2 mM amine and 0.1 M $NaClO_4$ as the supporting electrolyte in acetonitrile (10

† Dedicated to celebrate 80th birthday of Professor Emeritus Osamu Simamura of The University of Tokyo.

Table 1. Stereospecificity in the Electrochemical Oxidation in the Presence of Substituted Anilines

base	pK_a [a)]	E_{pa} [b)] (*vs.* Ag/AgCl)	log(*R*/*S* ratio) Me_3MQPH	Me_3PNPH
4-Nitroaniline	0.98	1.52	–0.32	–0.44
4-Chloroaniline	3.81	1.09	–0.45	–0.40
Aniline	4.62	1.09	–0.66	–0.40
4-Methylaniline	5.08	0.99	–0.63	–0.53
4-Methoxyaniline	5.29	0.73	–0.67	–0.73
p-phenylenediamine	6.08	0.43	–0.70	–0.86

a) Ref. 9. b) Oxidation peak potentials of substituted anilines (10 mM) in acetonitrile containing 0.1 M $NaClO_4$ at 298 K.

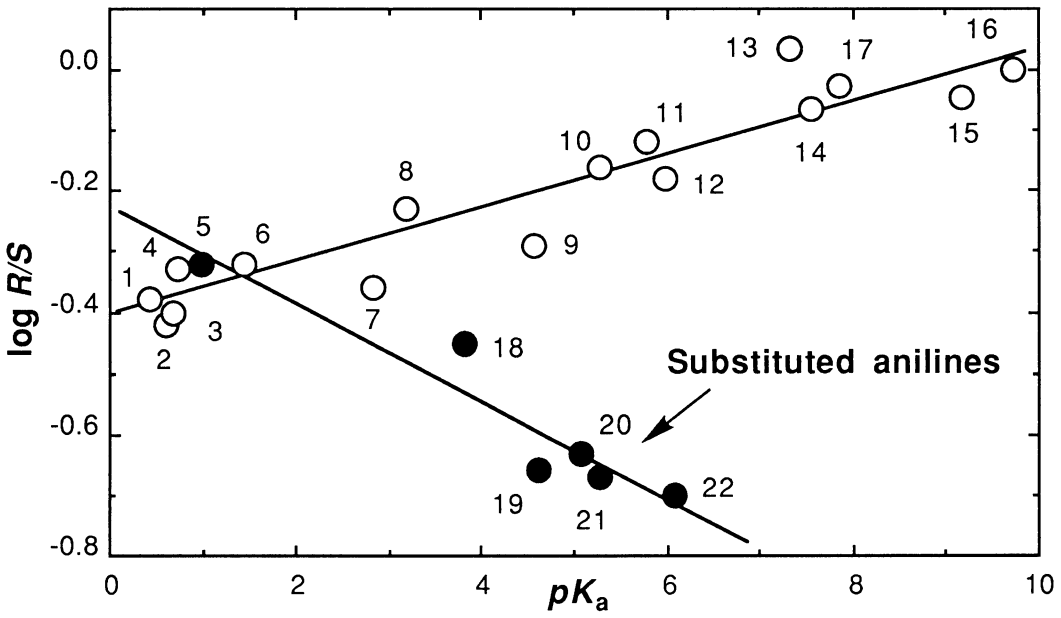


Fig. 1. Effect of substituted anilines and other amines on the stereospecificity (log *R*/*S*) in the electrochemical oxidation of (4*R*)-Me_3MQPH; **1**: 2-fluoropyridine. **2**: 4-nitro-N,N-dimethylaniline. **3**: 3,5-dichloropyridine. **4**: 2-chloropyridine. **5**: 4-nitroaniline. **6**: 3-cyanopyridine. **7**: 3-chloropyridine. **8**: 3-acetylpyridine. **9**: 3-phenylpyridine. **10**: pyridine. **11**: 3-methylpyridine. **12**: 4-methylpyridine. **13**: 1-methylimidazole. **14**: 2-methylimidazole. **15**: 4-aminopyridine. **16**: 4-(N,N-dimethylamino)pyridine. **17**: 1,2-methylimidazole. **18**: 4-chloroaniline. **19**: aniline. **20**: 4-methylaniline. **21**: 4-methoxy-aniline. **22**: *p*-phenylenediamine. The data shown by ○ were reported previously.[2)]

ml) was deoxygenated by argon gas before the oxidation. The results observed from the reaction with (4*R*)-Me_3MQPH or (4*R*)-Me_3PNPH are summarized in Table 1 and the stereospecificity of the reaction of (4*R*)-Me_3MQPH, expressed by logarithm of the *R*/*S* ratio with respect to the axial chirality in the product, is plotted in Fig. 1 against the pK_a of amine.

It is recognized that the stereospecificity with substituted anilines is different from the one with the other amines as shown in Fig. 1. Namely, the slope of the Brønsted-type correlation is apparently reversed to the other indicating that the reaction mechanism in the presence of substituted anilines differs from the mechanism of electrochemical oxidation catalyzed by a series of substituted pyridines, where the electron- and proton-transfer steps are perfectly separated from each other.[4,5)]

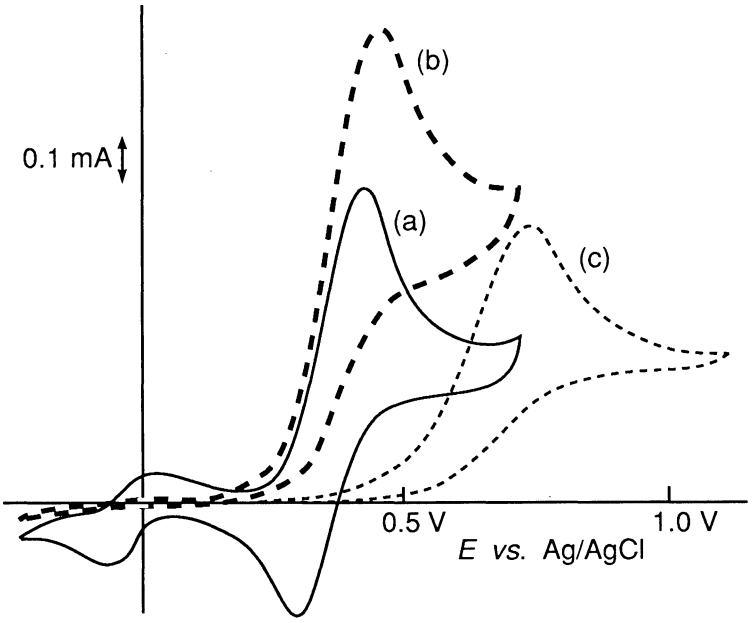


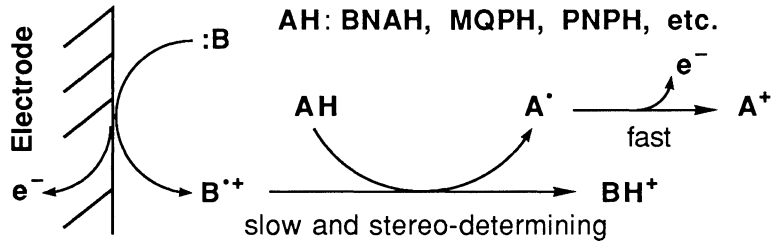
Fig. 2. Cyclic Voltammograms, where the potential is referred to *vs.* Ag/AgCl in saturated aq. KCl, at 298 K with 0.1 V/s scan rate. (a) *p*-phenylenediamine 10 mM; (b) *p*-phenylenediamine 10 mM and BNAH 10 mM; (c) BNAH 10 mM.

Figure 2 shows cyclic voltammograms of sample solutions containing 0.1 M tetraethylammonium perchlorate and a reagent or a combination of reagents in acetonitrile deoxygenated by argon bubbling. In the measurement, N-benzyl-1,4-dihydronicotinamide (BNAH) and *p*-phenylenediamine (*p*-$C_6H_4(NH_2)_2$) were used as the typical NAD(P)H analog and the substituted aniline, respectively. It was confirmed that amines other than substituted anilines are not oxidized at this potential and only act as a proton acceptor. On the other hand, *p*-$C_6H_4(NH_2)_2$ as well as the other anilines is oxidized at this potential to generate a cation radical *p*-$C_6H_4(NH_2)_2^{\bullet+}$; that is, both the oxidation peak of *p*-$C_6H_4(NH_2)_2$ at 0.43 V and a reduction peak of *p*-$C_6H_4(NH_2)_2^{\bullet+}$ at 0.29 V are observed in Fig. 2(a). The radical cation of anilines such as *p*-$C_6H_4(NH_2)_2^{\bullet+}$ is not only an one-electron acceptor but also an electron- and a proton- (net hydrogen atom) acceptors.

In the cyclic voltammogram of a sample solution containing BNAH and *p*-$C_6H_4(NH_2)_2$, the oxidation peak of *p*-$C_6H_4(NH_2)_2$ only is observed as depicted in Fig.2(b) and both the oxidation peak of BNAH which can be observable in Fig. 2(c) and the reduction peak of *p*-$C_6H_4(NH_2)_2^{\bullet+}$ which appeared in Fig. 2(a) can not be observed. Further, a current at the oxidation peak is much larger in Fig. 2(b) than that shown in Fig. 2(a) where BNAH is absent. It is, therefore, suggested that BNAH is oxidized by the cation radical of aniline and the oxidation apparently proceeds *via* an hydrogen-atom transfer, not a separated electron and proton transfers.

If the cation radical of aniline acted as the one-electron oxidant only in the same way as the electrode oxidation or the oxidation by an Fe(III) complex,[2,3,10] the apparent stereospecificity exerted by the present system might be similar to the other amine-catalyzed oxidations because it has been confirmed that the proton-transfer step is the stereo-determining step in these oxidations. However, the stereospecificity in the presence of substituted anilines is so clearly different from the others that the electron and proton have to be transferred concertedly or continuously (*i.e.*, net hydrogen-atom transfer) from NAD(P)H analog to a cation radical of aniline. The present mechanism may be comparable to the net hydride-transfer mechanism for the oxidation of NAD(P)H analog with benzoquinone derivatives, where the second electron-transfer step is not stereo-

determining.[7,11] The *R/S* ratio changes linearly from large to small values as the redox potential of benzoquinone becomes smaller.[6] In a similar manner, the *R/S* ratio in the presence of substituted anilines becomes smaller when the oxidation peak potential (E_{pa}), which is considered to be parallel to a redox potential of the cation radical of aniline, becomes smaller as summarized in Table 1.[12] Therefore, it is proposed that the initial electron-transfer step, which is accelerated by the C_4-H bond deformation, is the stereo-determining step.[6,7]



While the reaction of NAD(P)H analogs is interpreted in terms of a multi-step mechanism (*i.e.*, electron-proton-electron-transfer mechanism),[2-7,10,11] many oxidation reactions with NAD(P)H analogs have been observed as apparent net hydride-transfer reactions.[6,7,11] At the same time, obvious stepwise multi-step mechanism has been observed in the oxidation reactions with an electrode and/or with metal oxidants in the presence of a base. The present result demonstrates that the (net) hydrogen-atom transfer is observed in the oxidation by the cation radical of an aniline and the mechanism is comparable to a part of (net) hydride-transfer mechanism in the oxidation with benzoquinones. Thus, we believe that the mechanism of the (net) hydride transfer from an NAD(P)H analog is essentially multi-step, but its appearance differs depending on the chemical property of the oxidant and reaction conditions.

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8) The applied potentials were 1.0 V for Me_3MQPH and 0.8 V for Me_3PNPH. It was determined by the scanning-rate method[11] that the redox potentials of Me_2MQPH and Me_2PNPH are 0.87 and 0.66 V (*vs.* Ag/AgCl), respectively.
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12) Although 4-nitroaniline acts as a base only at oxidation potentials employed, the *R/S* ratio from this base lies on the line defined by other aniline derivatives of low oxidation potential in Fig. 1.

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