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Reduction of mononitroarenes by hydroxide ion in water catalyzed by β-cyclodextrin: enhanced reactivity of hydroxide ion

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Abstract—Ordinarily the reducing ability of HO^- in water is extremely low as a result of its stabilization by hydration. Reductions by hydroxide ion have only been observed previously in aprotic organic solvents. We find that several mononitroarenes are reduced to azoxyarenes by NaOH in water in the presence of β-cyclodextrin. HO^- acts as a one-electron reductant with enhanced reactivity.
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Common reactions of HO^- include proton transfer, nucleophilic substitution (or addition) and redox reactions in which HO^- acts as Brönsted base, nucleophile or reductant, respectively. Among these, the reductions of organic substrates by HO^- are least studied simply because alkali metal hydroxides are only soluble in water and the reducing ability of HO^- in water is extremely low.[1] The latter is a result of its stabilization by hydration (∼100 kcal/mol).[1] Nevertheless, a few reductions of one-electron organic oxidants by quaternary ammonium hydroxides in aprotic polar solvents (DMSO, acetonitrile, and THF) have been reported.[1–7] These oxidants include the free radicals: perchlorotriphenylmethyl,[2] perchlorinated diphenylmethyl,[3] triphenylmethyl,[1,3a,4] 9-phenylfluorenyl[5] and neutral perchlorochsone ($O=C_6Cl_4=C(C_6Cl_5)_2$),[6] and anthraquinone.[7] The increase in reducing power of HO^- is believed to result from decreased solvent stabilization in aprotic solvents. For example, the redox potential of HO^- is about 1 V more negative in acetonitrile than in water.[1,8] Since water is an environmentally benign medium for organic synthesis and is the only solvent for metal hydroxides, finding favorable reaction conditions for reductions by HO^- is highly desirable.

In order to decrease the hydration stabilization of HO^- and thus increase its reducing power in water, aprotic and less polar microenvironment is needed. Since cyclodextrins (CDs) are water soluble and possess hydrophobic cavities that can provide such microenvironment,[9] studies of the performance of HO^- as a one-electron reducing agent in the aqueous solution of CDs are warranted. Since mononitroarenes are good electron acceptors and possess structural prerequisites (appropriate size and polarity in terms of benzene structure) for inclusion in the CD cavity, in our first work that tests the possible enhancement of the reducing power of HO^- in water, they were selected as the oxidant substrates. We now report that several such nitroarenes (**1a–f**) are reduced to the corresponding azoxyarenes (**2a–f**) by sodium hydroxide in water catalyzed by β-CD (Scheme 1). HO^- functions as a one-electron reductant in these reactions. To our knowledge, this is the first observation of reductions of organic substrates by HO^- in water.

Mononitroarenes **1a–f** (1.1 mmol) were added to a clear solution of β-CD (1.5 mmol) in 20 ml 20% aqueous solution of NaOH in a flask equipped with a condenser. The mixtures were magnetically stirred at 80–85 °C for a certain period of time until the nitroarenes were consumed. The consumption of the nitroarenes was monitored by TLC. Upon cooling, some of the reaction mixtures (**1a–c**) gave rise to the yellow precipitates. They were isolated by filtration, washed with dilute HCl and water, and purified by recrystallization. Other reaction mixtures were extracted three times with diethyl ether. The combined ethereal solutions were washed with dilute HCl and water and dried with anhydrous $MgSO_4$. The extracts were purified by column chromatography (column packed with silica gel). These isolated major

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Scheme 1.

G = *m*-Cl(**a**), *p*-Cl(**b**), *p*-Br(**c**), *p*-I(**d**), *m*-CH₃(**e**), *m*-OCH₃(**f**)
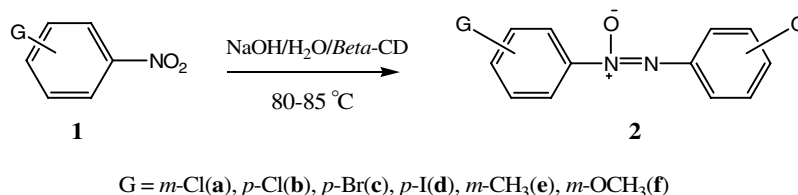
Table 1. Reductions of mononitroarenes (**1a–f**) into the corresponding azoxyarenes (**2a–f**) by NaOH in water catalyzed by β-CD[a]

| Entry	Mononitroarene	Reaction time (h)	Yield (%)[b]
1	**1a**	1	75
2	**1b**	1	41
3	**1c**[c]	1	62
4	**1d**[c,d]	2	46
5	**1e**	10	42
6	**1f**	10	44

[a] Under 80–85 °C unless otherwise specified.
[b] Yields refers to purified products **2**.
[c] [NaOH] = 28%.
[d] 95–100 °C.

products were the corresponding azoxyarenes (**2a–f**). They were characterized by comparing their ¹H NMR and melting points with those of the authentic compounds (see Supplementary data). The β-CD was recovered in the form of a solid by acidifying the aqueous phase of the reaction mixtures. The reaction times and yields are listed in Table 1. Reaction conditions that deviate from that described above are specified in the table. It should be stressed that these reactions could hardly take place without the presence of the CD.

The reductions of mononitroarenes to the corresponding azoxyarenes by alkoxide ions (RO⁻) in their parent alcohols (ROH) or DMSO have long been known[10] and the relevant complex reaction mechanisms have been extensively discussed.[11] The detailed one-electron reduction mechanisms proposed are depicted in Schemes 2 and 3 in which the electrons are provided by RO⁻ and protons are from ROH.[11] We infer that the reductions by HO⁻ in water catalyzed by β-CD may follow a similar reaction mechanism except that HO⁻ here acts as a one-electron reductant and water as the source of protons. That is, the first step of the reduction most likely involves the single electron transfer from HO⁻ to the nitroarenes (step (i) in Scheme 2). The resulting nitro-

arene radical anion then sequentially abstracts a proton from water, then accepts a second electron from HO⁻ followed by the second proton abstraction and dehydration to form the corresponding nitrosoarene (steps (ii)–(v) in Scheme 2). Dimerization of the nitrosoarenes into the corresponding azoxyarenes then occurs through their radical anions formed on the one-electron reductions by HO⁻ (Scheme 3).[11] Since the reactive radicals could not have a lifetime long enough to escape the CD cavity for dimerization, two CDs most likely cooperate in a way such that the two anion radicals in them would dimerize without diffusing outside the cavity (step (ii) in Scheme 3).

The reduction by HO⁻ in water can be qualitatively ascribed to the desolvation activation of both HO⁻ and the nitroarene substrates in the special microenvironment provided by the CD. The activated hydroxide ions may be limited to those interfaced with the cavity which would be less highly solvated and thus have enhanced reactivity and reduction potential. The activation process of the HO⁻ may be visualized as described in Scheme 4. In water, the CD is surrounded by water and its hydrophobic cavity accommodates only a few polar water molecules (**A**). When HO⁻ is added, because of its ionic nature, it might not enter the cavity but would be sparsely distributed in the cavity–water interface (**B**). The possibility that OH⁻ may enter the cavity after partial loss of hydration cannot be excluded.[12] In the presence of a nitroarene substrate, water molecules are extruded from the cavity and the polar nature of the substrate would change the composition of the interface through an electrostatic effect, that is, more HO⁻ would aggregate in the interface (**C**). The partially 'naked' HO⁻ thus could be able to transfer its single electron to the nitrobenzene due to its enhanced reducing ability. It is conceivable that high [HO⁻], high temperature and high pressure would be conducive to the otherwise thermodynamically unfavorable aggregation of HO⁻ at the interface.
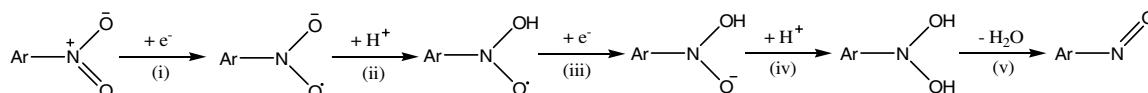
Scheme 2.
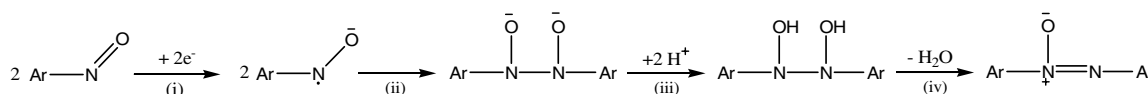
Scheme 3.
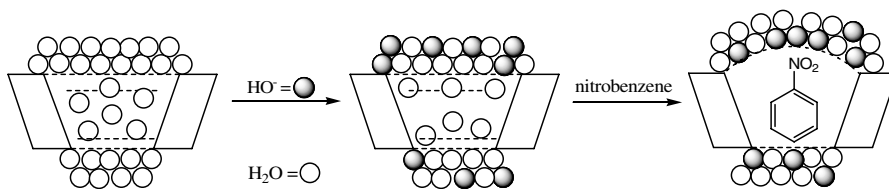
Scheme 4. The proposed activation process of HO⁻ in water.

The 'one-electron' reduction would benefit from the activation of both reactants as a result of desolvation. However, a calculation derived from the gas-phase electron affinity values for HO·/HO⁻ (1.83 eV)[1] and PhNO₂/PhNO₂⁻· (1.00 eV)[13] indicates that the first electron transfer step from HO⁻ to nitrobenzene is endothermic at 298 K with a free energy change of +19 kcal/mol (0.83 eV), suggesting that the separate initial single electron transfers from HO⁻ to the nitroarene substrates are unlikely. However, loss of hydration is expected to substantially increase the reducing power of OH⁻ and to activate the nitroarenes toward reduction. Also, the thermodynamics of the redox reaction may be more favorable at 358 K than at 298 K.

The fate of the hydroxyl radical (HO·) derived from the oxidation of HO⁻ is not very clear. One possibility is that it dimerizes into H_2O_2 which then decomposes into H_2O and O_2 under the reaction conditions.

Table 1 shows that reactions of **1a–d** with halogen substituents take distinctly less time than those of the remaining two nitroarenes (1–2 h vs 10 h). This may be explained in terms of the combination of the electronic effects of the substituents and the spatial orientation effects of the nitroarenes in the CD cavity. That is, nitroarenes with electron withdrawing groups and geometries in which their nitro groups are favorably oriented toward the HO⁻ would be readily reduced.

To summarize, HO⁻ acts as a one-electron reductant with enhanced reactivity in reactions with mononitroarenes in water containing β-CD. All the reactions gave as major reduced products the corresponding azoxyarenes. The enhancement of these reactions by the CD suggests that reductions by HO⁻ in water that have not been observed previously may be accomplished in the presence of CD. Further studies centering on the optimization of the reaction conditions, thorough analysis of the reduction products (possibly including anilines and derivatives) and extension of the reactions to other organic compounds are under way.

Acknowledgments

Supplementary data

Data of ¹H NMR spectra and melting points of the products (**2a–f**) and their purification methods are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.150.

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