Tetrahedron Letters,Vol.30,No.15,pp 1923-1926,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

THE MECHANISM OF THE INTERACTION OF N-ARYL-O-PIVALOYLHYDROXYLAMINES WITH REDUCING METAL IONS

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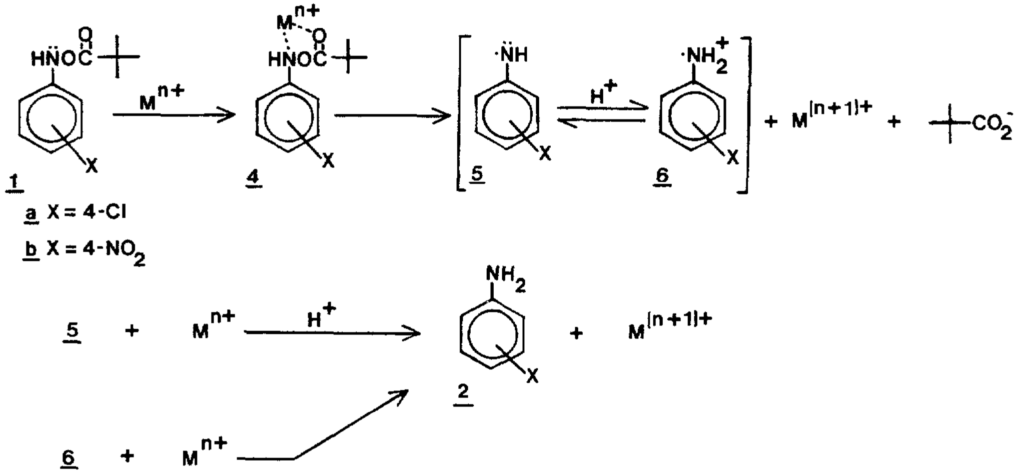
Abstract: *Evidence which supports a stepwise electron transfer process for the reduction of* 1 *by* Fe^{2+} *and* Cu^{+} *is presented.*

Previously we reported that the N-aryl-O-pivaloylhydroxylamines (1), model compounds for carcinogenic metabolites of polycyclic aromatic amines[1], are reduced in aqueous solution by Fe^{2+}.[2] This reaction is of potential importance in vivo because it does not occur via a nitrenium ion intermediate which is usually invoked to explain the effects of these compounds,[1] but it does involve other reactive species which may cause cellular damage. We favored an electron transfer mechanism proceeding in two one electron steps (Scheme I), but there was no direct evidence for the intermediate species 5 or 6. It was shown that a complex of Fe^{2+} and 1 (4) must be formed for reduction to occur, and pivalic acid is produced in high yield which rules out N-O bond homolysis.[2] Reduction of a nitrenium ion by Fe^{2+} can be ruled out by the large rate acceleration of the reduction process over the N-O bond heterolysis which occurs in the absence of Fe^{2+}.[2] Here we report results of trapping experiments with the hydroxylamines 3a and b, and studies with Cu^{+}, that provide support for the mechanism of Scheme I.



SCHEME I

Table 1.

Yields of Reduction Products 2a and 2b, and Nitroso compounds 7a and 7b under Various Conditions.[a]

Ester	Conditions	% Yields[b,c] 2	7
1a	1 mM Fe^{2+}, pH 4.7	40±2 (2a)	
1a	1 mM Cu^{+}, pH 1.0	78±2 "	
1a	1 mM Cu^{+}, pH 4.7	74±1 "	
1a	1 mM Cu^{+}, pH 6.7	79±2 "	
1a	1 mM Fe^{2+}, pH 4.7, 1 eq of 3a	56±1 "	38±1 (7a)
1a	1 mM Fe^{2+}, pH 4.7, 1 eq of 3b	51±1 "	26±3 (7b)
1b	1 mM Fe^{2+}, pH 4.7	95±1 (2b)	
1b	1 mM Cu^{+}, pH 4.7	93±1 "	
1b	1 mM Fe^{2+}, pH 4.7, 1 eq of 3a	94±2 "	53±2 (7a)
1b	1 mM Fe^{2+}, pH 4.7, 1 eq of 3b	95±2 "	39±3 (7b)

[a] 5 vol % CH_3CN-H_2O solvent, 40°C. pH maintained by HCl, KOAc/HOAc or K_2HPO_4/KH_2PO_4, 0.01 M total buffer. Ionic strength maintained at 0.5 M with KCl. All solutions were demetallized and degassed as described in ref. 2. Source of Fe^{2+} and Cu^{+} were $FeCl_2$ and CuCl. Initial concentration of 1 was ca. $7.5x10^{-5}$ M.

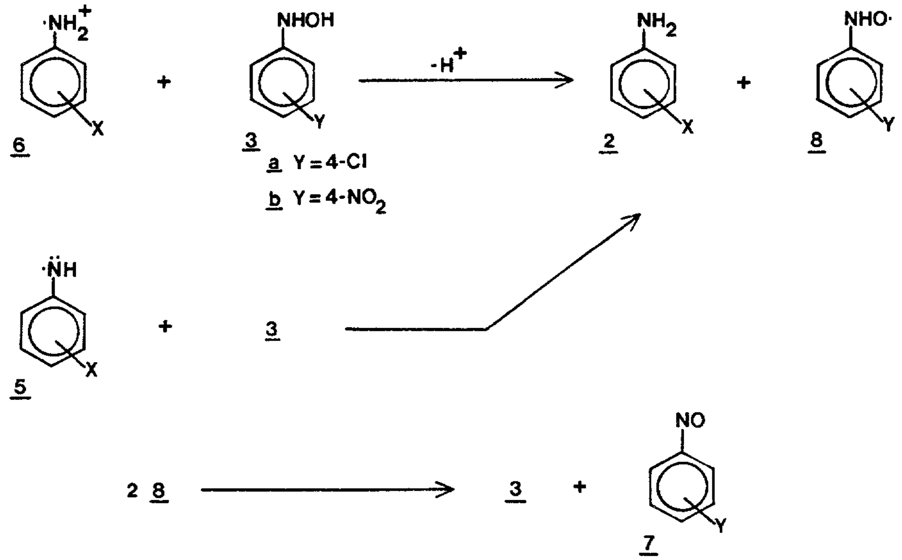
[b] Determined by HPLC analysis at completion of reaction. Identities of products were confirmed by comparison with authentic materials. Yields are based on initial concentrations of 1 or 3. Reaction times were less than 30 s in all cases.

[c] Control experiments show that no reaction occurs when 1 and 3 are combined in aqueous solution in the absence of Fe^{2+}.

Data in Table 1 show that a significant increase in the yield of 2a occurs when 1a (initial concentration 7.5 x 10^{-5} M) undergoes reduction by 1mM Fe^{2+} in the presence of 1 eq of 3a or 3b, and there is corresponding formation of 7a or 7b in the ratio 2a/7 of ca. 1.5-2.0. In all cases 2a is the only identifiable product derived from 1a. The normal products of N-O bond heterolysis (2,4-dichloroaniline, p-benzoquinone, and 4-chloro-2-hydroxypivalanilide)[2] are completely suppressed. Some amorphous tarry materials are always isolated by extraction of the reaction mixtures into CH_2Cl_2. The oxidation of 3 by Fe^{3+} produced during the reduction process could, in principle, account for the formation of 7.[3] Control experiments show that this reaction is too slow under our conditions to account for more than a small fraction (< 5%) of the observed yields of 7. The half-lives for the oxidation of 3a and 3b are > 1 h under Fe^{3+} concentrations similar to those present in the reduction process (ca. 10^{-4} M Fe^{3+}). The reduction itself is over in < 30 s and the yields of 2a and 7 were recorded within 5-10 min of initiation of the reactions.

Our interpretation of these results is shown in Scheme II. Donation of H· from 3 to 6a (or 5a) yields 2a and the nitroxyl radical, 8, which can comproportionate to 3 and 7. It is known that hydroxylamines are efficient H· donors to nitroxyl radicals,[3] and NH_2OH donates $H\cdot$ to $NH_2\cdot$ rapidly in the gas phase.[4] The 2/1 stoichiometry for 2/7 predicted by Scheme II will not hold if 8 can react efficiently with Fe^{3+} to generate 7. That may be the case for 8a. In the case of 1b, the yield of 2b is already close to quantitative in 1 mM Fe^{2+}, so the addition of 3 has little effect on the yield of that species, but 7a and 7b are produced in significant yield indicating that 3 must compete effectively with Fe^{2+} to reduce 6b(or 5b). Again, the yields of 7 produced in these cases cannot be accounted for within the time scale of the experiment by Fe^{3+} induced oxidation of 3. The relative yields of 2a and 2b and the effectiveness of 3a and 3b as $H\cdot$ donors are in accord with the mechanisms of Schemes I and II. In the two trapping experiments in which the substituents X and Y were different (1a with 3b, and 1b with 3a) the only products observed are those listed in Table 1. The lack of "crossover" products eliminates certain disproportionation processes which might otherwise explain some of this data.

Cu^{+1} is a better one-electron reducing agent than Fe^{2+} (reduction potentials for Fe^{3+} and Cu^{2+} are 0.77 and 0.16 V, respectively[5]) so the greater yields of 2a observed in 1 mM Cu^{+} are expected, if, as appears to be the case from the trapping data, the second electron transfer step of Scheme I is relatively sluggish with Fe^{2+}. Data in Table 1 show that the yield of 2a is invariant to pH in the pH range



SCHEME II

1.0-6.7 in 1 mM Cu^+. Previously we showed that the yield of 2 decreases with increasing pH in 1 mM Fe^{2+}.[2] This difference in behavior is explainable if, as we previously suggested,[2] Fe^{2+} cannot reduce 5 (which will predominate under neutral conditions), but the stronger reducing agent, Cu^+, can. It has been shown previously that SO_3^{2-} and HSO_3^-, which are similar to Fe^{2+} as reducing agents (the reduction potentials of SO_3^- to form SO_3^{2-} and HSO_3^-, respectively, are 0.63 and 0.84 V) can reduce unsubstituted (X=H) 6, but not 5.[6]

Non reducing metal ions such as Fe^{3+} and Ni^{2+} have little observable effect on the rate or product distribution of the decomposition of 1a or b in aqueous media. One exception to this generalization is Cu^{2+} which accelerates the decomposition of both 1a and 1b. Catalysis of ester hydrolysis by Cu^{2+} [7] can be eliminated as a possibility since neither the hydroxylamines 3a or b or their Cu^{2+}-oxidation products 7a or b are detected in these experiments. The products which have been observed (anilines, and azo- and azoxybenzenes) are those expected from a nitrene reaction.[2] The mechanism of the Cu^{2+} reaction is currently under investigation.

Acknowledgement: This work is supported by a grant from the American Cancer Society (BC-348).

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(Received in USA 22 December 1988)