Mechanisms of the Oxidations of NAD(P)H Model Hantzsch 1,4-Dihydropyridines by Nitric Oxide and Its Donor *N*-Methyl-*N*-nitrosotoluene-*p*-sulfonamide

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Received March 29, 2000

4-Substituted derivatives of Hantzsch 1,4-dihydropyridine were treated by nitric oxide (NO) or its donor *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide (MNTS) to give the corresponding pyridine derivatives. When the 4-substituted group was methyl, ethyl, *n*-propyl, and aryl groups, it was preserved, but when the group was isopropyl or benzyl one, it was lost. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used in place of NO and MNTS to react with the 4-substituted Hantzsch 1,4-dihydropyridines, no the corresponding 4-dealkyl Hantzsch pyridines were obtained from all the reactions. 1-Benzyl-1,4-dihydronicotinamide (BNAH), a close analogue of Hantzsch 1,4-dihydropyridine (HEH), was used instead of HEH to react with either of NO and MNTS, no reactions were observed for 3 days. Replacement of HEH by *N*-d-HEH and HEH-*4,4*-d_2 to react with NO, MNTS and DDQ gave the observed kinetic isotope effects of 3.1 and 1.4 for NO, 1.1 and 1.3 for MNTS, and 1.1 and 2.1 for DDQ, respectively. When *p*-dinitrobenzene, an electron-transfer inhibitor, was added into the title reaction systems, no remarkable inhibitory effect was observed. These results indicated that the oxidation of HEH by NO was initiated by hydrogen transfer from the N_1-position to give the corresponding aminyl radical, which then underwent homolytic cleavage to become the final aromatized product (**A**). But the reaction of HEH with MNTS was initiated by nitrosation to give the corresponding *N*-nitroso compound, which was subsequently subjected to two steps of homolytic cleavage to afford the aromatized Hantzsch pyridine **A**.

Introduction

Great interest has been accumulated in recent years in the chemistry of nitric oxide (NO) upon many striking discoveries of its active roles in a wide range of human physiological processes,[1] and the papers concerning the chemistry of NO have been gradually increasing. The published reports seem to be classified into three types: (i) the reactivities of NO with some biologically important molecules;[2] (ii) nitric oxide group transfer (including release) in some biological systems or the models;[3] (iii) development of the detection method of NO using organic reactions.[4] However, to the best of our knowledge, very little research has hitherto been reported in the literature on the reaction mechanisms of NO or its donor with some biologically important molecules.

The reduced form of nicotinamide adenine dinucleotide [NAD(P)H] is a typical coenzyme, which plays a vital role in many biological redox reactions. Much research[5] suggested that the fungal denitrification process contains an oxidation of NAD(P)H coenzyme by NO (eq 1), whereas some other people[6] promote an alternate opinion that NO from diverse sources in aqueous solution at physiological pH does not appreciable alter either the molecular properties or redox function of NAD(P)H. Thus, the following questions need to be further clarified: (i) Can NO oxidize NAD(P)H in vivo? (ii) If the oxidation could take place, how does it take place?

$$\mathrm{NAD(P)H + 2NO + H^+ \rightarrow NAD(P)^+ + N_2O + H_2O} \quad (1)$$

To further probe the possibility of the reaction (eq 1) and elucidate the details of the reaction mechanism (provided that the reaction could take place), the chemical mimic method will be used in this work as a powerful tool. As is well known, Hantzsch 1,4-dihydropyridine derivatives which contain the 1,4-dihydropyridine structure of natural reduced nicotinamide adenine dinucleotide [NAD(P)H] coenzyme and possess a high biological activity as a class of useful drugs, particularly as antioxidants, can be chosen as models of NAD(P)H to react with NO or its donor *N*-methyl-*N*-nitrosotoluene-*p*-sulfonamide (MNTS) to mimic the oxidation of NAD(P)H by NO in vivo. Ohsawa and co-workers, in their previous

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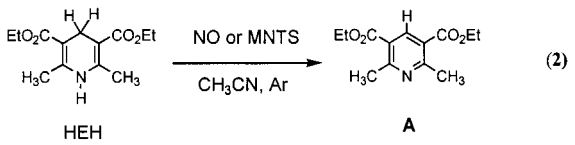
10.1021/jo000484h CCC: $19.00
Published on Web 11/03/2000

paper,[2a,7] reported that Hantzsch 1,4-dihydropyridines were oxidized by NO to give the corresponding Hantzsch pyridine derivatives in quantitative yields, but the reaction mechanism remains poorly understood, so it seemed desirable that more and better mechanistic probing compounds should be employed to reveal the full mechanistic details of this important reaction. As a part of our research in this field,[8] we in this paper have examined the reactions of a series of 4-substituted Hantzsch 1,4-dihydropyridine derivatives and their close analogue 1-benzyl-1,4-dihydronicotinamide (BNAH) with NO, MNTS (a good nitroso-transfer agent) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, a good hydride acceptor), respectively. On the basis of the experimental evidence collected, the oxidation mechanisms of Hantzsch 1,4-dihydropyridines by NO and MNTS can be clearly elucidated.

Results and Discussion

The treatment of Hantzsch 1,4-dihydropyridine (HEH) with excess pure NO gas or MNTS in dry acetonitrile in a closed system gave a sole aromatized Hantzsch pyridine (**A**) in quantitative yield as shown in eq 2.

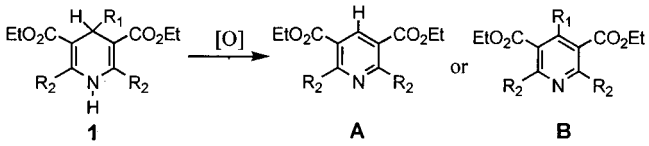


(2)

From eq 2, it is clear to be found that two hydrogen atoms at the 1 and 4 positions in HEH were lost during the reaction process. To provide information necessary to postulate the reaction mechanism, a series of 4-substituted Hantzsch 1,4-dihydropyridines and 2,6-diphenyl-4-(*p*-nitrophenyl)-HEH were prepared and oxidized by excess pure NO gas, MNTS, and DDQ, respectively, and two different types of the final aromatized products (**A** and **B**) were obtained. The full reaction results are tabulated in Table 1.

Kinetic isotope effects on the reaction (eq 2) were determined using N-deuterated Hantzsch 1,4-dihydropyridine (*N*-d-HEH) and 4,4-dideuterated Hantzsch 1,4-dihydropyridine (HEH-*4,4-d*$_2$) instead of HEH to react with NO (see Figure 1), MNTS and DDQ by the UV−vis method, respectively. The experimental results gave the observed kinetic isotope effects of 3.1 (k_{N-H}/k_{N-D}) and 1.4 (k_{C4-H}/k_{C4-D}) for NO, 1.2 and 1.1 for MNTS, and 2.1 and 1.1 for DDQ, respectively, which means that the three reactions could be carried out by different reaction mechanisms. When *p*-dinitrobenzene, a well-known electron-transfer inhibitor,[9] was added into the three reaction mixtures, no remarkable inhibitory effects were observed, indicating no electron transfer occurrence in the three reactions.

Table 1. Oxidations of Hantzsch 1,4-Dihydropyridine and Its Various Derivatives by NO, MNTS, and DDQ[a]



			[O]		
entry	R_1	R_2	NO[b]	MNTS[c]	DDQ[d]
1	H	Me	**A** (96)	**A** (41)	**A** (80)
2	C_2H_5	Me	**B** (86)	**B** (45)	**B** (75)
3	*n*-C_3H_7	Me	**B** (84)	**B** (47)	**B** (78)
4	*i*-Pr	Me	**A** (88)	**A** (51)	**B** (84)
5	benzyl	Me	**A** (84)	**A** (59)	**B** (75)
6	C_6H_5	Me	**B** (76)	**B** (67)	**B** (90)
7	*p*-CH_3-C_6H_5	Me	**B** (74)	**B** (68)	**B** (85)
8	*p*-Cl-C_6H_5	Me	**B** (76)	**B** (70)	**B** (85)
9	*p*-CN-C_6H_5	Me	**B** (79)	**B** (73)	**B** (83)
11	*p*-CH_3O-C_6H_5	Me	**B** (75)	**B** (79)	**B** (79)
10	*p*-NO_2-C_6H_5	Me	**B** (77)	**B** (71)	**B** (73)
12	*p*-NO_2-C_6H_5	Ph	**B** (70)	**B** (91)[e]	**B** (72)

[a] The yield of **A** or **B** are given in parentheses. Mixtures of products **A** and **B** from the same reaction were never observed. [b] The reactions were conducted in acetonitrile at room temperature for 4 h. [c] The reactions were conducted in acetonitrile at room temperature for 3 days except entry 12. [d] The reactions were conducted in THF at room temperature for 60 min. [e] The reaction was conducted in acetonitrile at room temperature for 2 days.

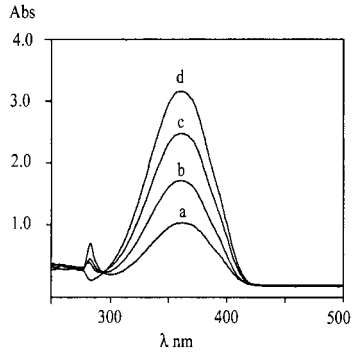


Figure 1. Absorption spectra changes of HEH (a), HEH-4,4-d_2 (b) and *N*-d-HEH (c) from the reaction beginning (d) ($[HEH]_0 = [HEH\text{-}4,4\text{-}d_2]_0 = [N\text{-d-}HEH]_0 = 2.5 \times 10^{-4}$ M) at the constant NO pressure (1 atm.) for 10 min.

1-Benzyl-1,4-dihydronicotinamide (BNAH), another NAD(P)H model, is a close analogue of HEH and was used in place of HEH to react with NO, MNTS, and DDQ, respectively, to compare the reactivities of HEH and BNAH with NO and MNTS. The experimental results are surprising in that no reactions of BNAH with NO and MNTS except for DDQ were observed (see Table 2).

According to the structure of the Hantzsch 1,4-dihydropyridines (**1**), the aromatizations of **1** by NO are presumably involved in three alternative reaction pathways as shown in Scheme 1: (i) a direct hydride transfer to NO to yield cations **3** and/or **4**, which subsequently take place by heterolysis to afford the final aromatized products **A** and/or **B**, respectively (path a); (ii) an initial one-electron transfer from HEH to NO to give radical

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Scheme 1

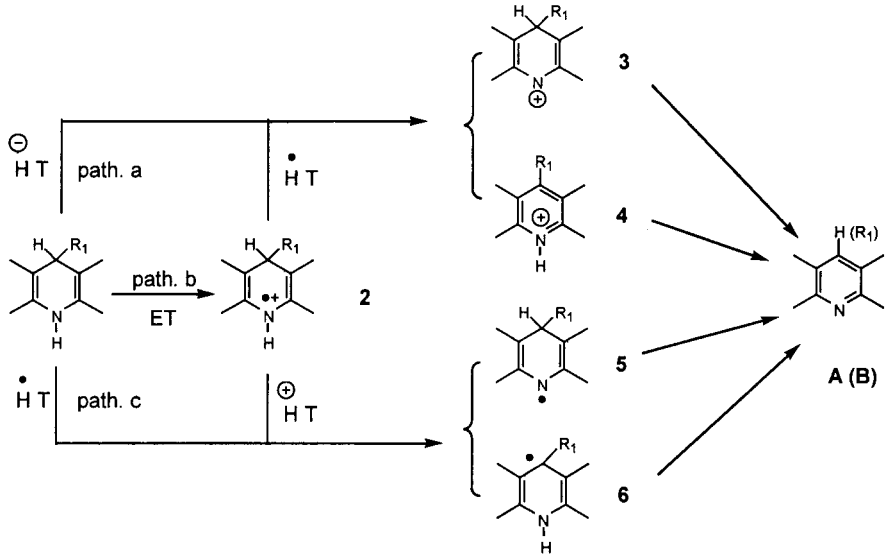
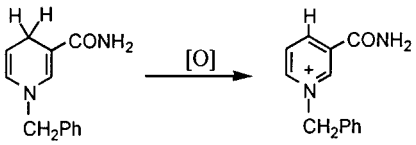


Table 2. Results from the Oxidations of BNAH by NO, MNTS and DDQ



[O]	*T* (°C)	time	yield (%)
NO[a]	rt	3 days	0
MNTS[b]	rt	2 weeks	0
DDQ[c]	rt	30 min	97

[a,b] The reactions were conducted in acetonitrile and were monitored by TLC. The experimental conditions are identical to those of the reactions of HEH with NO and MNTS, respectively. [c] The reaction was conducted in THF, the yield was determined by CG according to the consume of the corresponding reactant.

cations **2**, which then undergo decomposition by alternative pathways to provide the final products **A** and/or **B** (path b); and (iii) an initial H-atom abstraction with NO to form radicals **5** and/or **6**, which subsequently lose a hydrogen atom or a radical R_1 to give the final aromatized products (path c).

Inspection of Table 1 reveals that in the case of NO as the oxidant, when R_1 is a secondary alkyl or benzyl group, it was lost in the final aromatized products; in the case of DDQ as the oxidant, however, it was well preserved in the final aromatized products (entries 4 and 5). These results indicated that the possibility of path a (an initial direct hydride transfer pathway) in Scheme 1 may be excluded, because it has been proved that the aromatizations of 1,4-dihydropyridine derivatives by quinones were carried out via a direct hydride transfer mechanism.[10] If the aromatizations of 4-substituted (isopropyl, benzyl) Hantzsch 1,4-dihydropyridines by NO had conducted by one-step direct hydride transfer like the mechanism of the reactions with DDQ, the 4-substituents (i.e., isopropyl and benzyl groups) would have been well preserved in the final aromatized products. In addition, from Scheme 1 it is certain to conclude that the stability of cation **4** is much larger than that of **3**. If the reactions had taken place by one-step direct hydride transfer mechanism, the hydrogen atom at the C_4 rather than N_1 position on the 1,4-dihydropyridine ring would be removed initially, **B** rather than **A** would be a sole final aromatized product. Obviously, this hypothesis is in sharp contrast to the experimental results of Entries 4 and 5 (Table 1) and also is not accordant with the small observed kinetic isotope effect of 1.4 on the reaction of HEH-*4,4-d*$_2$ with NO.

In Table 2, no reaction of BNAH with NO was detected at room temperature for 3 days, which indicates that the oxidation of HEH by NO could not be initiated by one-electron transfer (path b). The reason is that BNAH has a higher reactivity toward NO reduction than that of HEH via one-electron-transfer on the basis of their redox potentials (E_{ox} = 0.29V vs Fc^+/Fc for BNAH and E_{ox} = 0.507V vs Fc^+/Fc for HEH). If the oxidation of HEH by NO had proceeded by an initial one-electron transfer, the oxidation of BNAH by NO would have more easily proceeded via the same way. The fact shows no reaction occurrence of BNAH with NO. Furthermore, the ineffectiveness of *p*-dinitrobenzene, an electron-transfer inhibitor, on the reaction can also support it.

It is seems most likely from the experimental results described above that the oxidations of HEH and its derivatives by NO commence with the abstraction of the H-atom (path c in Scheme 1). On the basis of the facts that sole dealkylated product was obtained from the reactions of 4-isopropyl and benzyl Hantzsch 1,4-dihydropyridines with NO and that when HEH was methylated at the N_1-position, no reaction was observed,[7] it may be inferred that the H-atom at the N_1- rather than C_4-position on the 1,4-dihydropyridine ring was first transferred. Thus, we may propose a tentative mechanism for the oxidations of HEH and its derivatives by NO as depicted in Scheme 2.

In Scheme 2, the oxidation of **1** by NO was initiated via hydrogen transfer from the N_1-position on the 1,4-dihydropyridine ring to NO to afford aminyl radical **5**,[11] which subsequently underwent homolysis of the C_4-H or C_4-R_1 bond to lose a hydrogen atom or a radical R_1

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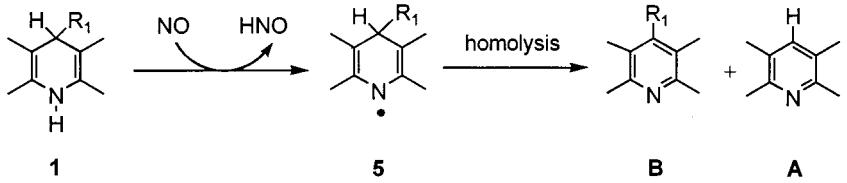
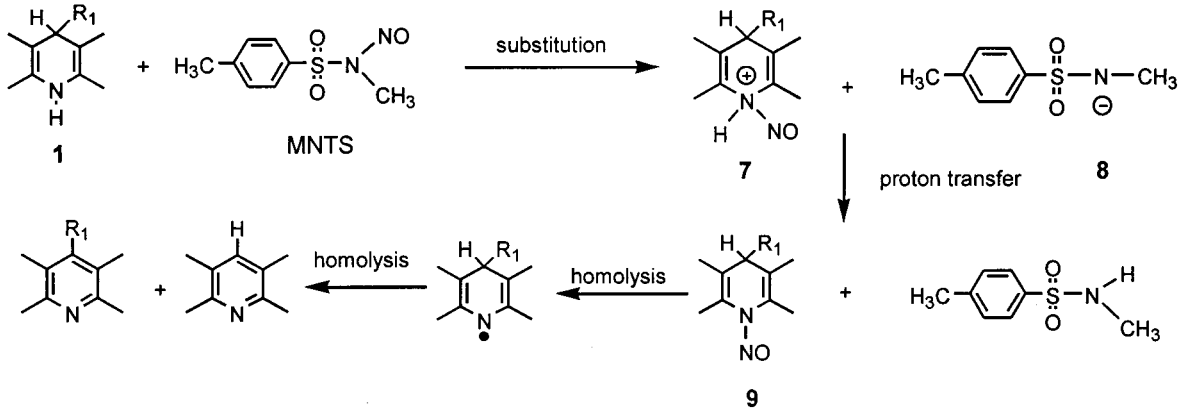
Scheme 2



Scheme 3



from the C_4-position on the dihydropyridine ring to give final aromatized product **B** or **A**, respectively. If R_1 is isopropyl or benzyl group, it was lost and **A** was obtained; if R_1 is a linear alkyl or aryl group, the hydrogen atom was lost and **B** was the final product. The main reason resulting in this result could be that the stability of the isopropyl and benzyl radicals is much larger than that of linear alkyl or aryl one, which, of course, are more easily removed from the parent radical **5** than the linear alkyl or aryl group. Whether dealkylation (**A**) or hydrogen atom loss (**B**) will occur, in other words, is governed by the stability of the potential leaving radical groups. According to the large kinetic isotope effect of 3.1 on the *N*-d-HEH reaction with NO and the small kinetic isotope effect of 1.4 on the HEH-*4,4*-d_2 reaction with NO, the initial hydrogen transfer in Scheme 2 would be in the rate-determining step, but the hydrogen atom transfer from the C_4-position would be in a non-rate-determining step.

N-Methyl-*N*-nitrosotoluene-*p*-sulfonamide (MNTS) is a good NO donor that can also oxidize **1** to give the corresponding aromatized pyridine derivatives **A** or **B** (see Table 1). From the fourth column in Table 1, it is clear that the 4-substituent is an isopropyl or benzyl group; it was lost, but the others were preserved. These reaction results are the same as the results of the reactions with NO as the oxidant, whereas kinetic isotope effects on the two reactions are different from each other. In the reaction with NMTS, the kinetic effect of the deuterium at the N_1-position of HEH is 1.1 (k_{N-H}/k_{N-D}), but in the reaction with NO, the corresponding kinetic isotope effect is 3.1. This result indicated that the NH bond dissociation in the former reaction is not in the rate-determining step, but in the latter reaction, it is in the rate-determining step. In a word, the above results could exclude the possibility of initial hydrogen transfer from the N_1-position of HEH to MNTS. To assess the possibility of initial one-electron transfer from HEH to MNTS, we determined the redox potentials of MNTS and HEH by CV electrochemical technique. The result shows that the reduction potential of MNTS is quite negative (−1.32 V vs Fc^+/Fc) and the oxidation potential of HEH is rather positive (0.507 V vs Fc^+/Fc). According to the redox potentials of the two reactants, the free energy change for the electron transfer from HEH to MNTS was estimated to be a quite large positive value (+175.9 kJ mol^{-1}), which indicates that the oxidation of HEH by MNTS initiated by one-electron transfer is extremely unfavorable in thermodynamics. In addition, the ineffectiveness of *p*-dinitrobenzene on the reaction can also support it. But on the basis of the previous papers,[12] it is well-known that MNTS is a good nitrosotransfer agent and has been extensively used to nitrosate many compounds containing NH group to form the corresponding *N*-nitroso compounds via a direct nucleophilic substitution. Since all the 4-substituted Hantzsch 1,4-dihydropyridines contain NH group on the 1,4-dihydropyridine ring, it is conceivable that the aromatizations of **1** by MNTS could be initiated by nitrosation to give N-nitrosated Hantzsch 1,4-dihydropyridine (**9**) which then were subjected to two-step decomposition to offer the final aromatized products **A** or **B**. The mechanism of the aromatizations is shown in Scheme 3. Unfortunately, no *N*-nitroso Hantzsch 1,4-dihydropyridines were obtained by using various nitrosation methods for all our best efforts, which indicates that compound **9** is likely unstable in the reaction systems and readily decompose to give radical **5**, since vinyl nitroso-compound like vinyl bromide is readily subjected to homolysis to release nitric oxide. In Scheme 3, the aromatization of **1** by MNTS was initiated via nitronium ion transfer from MNTS to HEH by nucleophilic substitution to give cation **7** and anion **8**, which subsequently took place by proton transfer to complete the nitrosation process of HEH by MNTS.

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Obviously, the nucleophilic substitution during the nitrosation of HEH is in rate-determining step, since the proton transfer is generally fast, which also can be supported by the small kinetic effect of the deuterium at the N_1-position on the reaction ($k_{N-H}/k_{N-D} = 1.1$).[13]

Comparing the product yields on the columns 4 and 5 in Table 1, it is worth noting that the reactivity of **1** is decreased with the increase of the 4-substituent bulk for the reactions with NO but increased with the substituent bulk increase for the reaction with MNTS. Obviously, the change is slight for the former reactions and remarkable for the latter reactions. For example, in the case of the reactions with NO, when the reductant was HEH (entry 1), the reaction took 3 h to provide the corresponding aromatized product in 96% yield; when the reductant was 2,6-diphenyl-4-(*p*-nitrophenyl)-HEH (entry 12), the reaction offered the corresponding aromatized product in 70% yield for the same time; whereas, in the case of the reactions with MNTS, when the reductant was HEH, the reaction gave the corresponding aromatized product in 41% yield for 3 days, but when the reductant is 2,6-diphenyl-4-(*p*-nitrophenyl)-HEH, the reaction time was shortened 1 day from 3 days to yield the corresponding aromatized product in 91% yield. These differences must be related to the bulk and the conformation of the reductants as well as the type of the reaction mechanisms. For the reactions with NO, since NO is a small molecule, which is considered to be volumeless, no large changes of the product yields were observed from entry 1 to entry 12 in Table 1. But for the reactions with MNTS, since the reactions were controlled by the rate of the nucleophilic substitution in the first reaction step (see Scheme 3), the bulk and the conformation of the reductants, of course, strongly affected the reaction rate. As is well known, HEH adopts a plane-conformation,[14] and the lone electron pair on N_1 is nearly vertically positioned above the plane of dihydropyridine ring which makes the lone pair orbital to delocalize to the dihydropyridine ring resulting in a great disadvantage to accept NO^+ from MNTS. But for 2,6-diphenyl-4-(*p*-nitrophenyl)-HEH, it was determined by X-ray structural analysis to show a boatlike puckered conformation (see Figure 2): the atoms N_1 and C_4 were located on the same side slightly away from the plane consisted of the two double bonds on the 1,4-dihydropyridine ring, and the phenyl ring connected to the C_4-position adopts a twist-conformation with respect to the central dihydropyridine ring. Partial related bond lengths and dihedral angles of the crystal structure are tabulated in Table 3. Obviously, in the boatlike puckered conformation of 2,6-diphenyl-4-(*p*-nitrophenyl)-HEH, the configuration of N_1 has an axially positioned lone electron pair that cannot delocalize to the dihydropyridine ring to result in a great advantage to accept NO^+ from MNTS in a nucleophilic substitution fashion. Since the puckered degrees of the dihydropyridine ring conformation are strongly dependent on the bulk of the substituents on it, larger substituents result in larger puckered degrees of the dihydropyridine ring and make the lone electron pair on N_1 more facile to accept NO^+ from MNTS. These analyses may not only be used to explain the change of the product yields with the substituents for the two reactions in Table 1 but also lend to support the mechanisms of the title reactions above-mentioned.

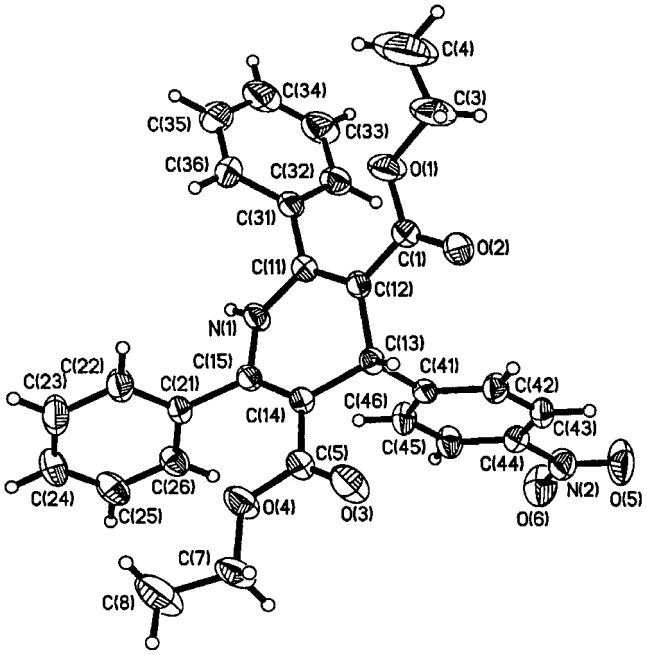

Figure 2. X-ray crystal structure for 2,6-diphenyl-4-(*p*-nitrophenyl)-HEH.

Table 3. Select Bond Lengths and Dihedral Angle of the Crystal Structure for 2,6-Diphenyl-4-(*p*-nitrophenyl)-HEH

bond	length, Å	plane[a]	dihedral angle, deg
N(1)−C(15)	1.380(3)	1−2	25.36
N(1)−C(11)	1.378(3)	3−2	13.86
C(11)−C(12)	1.358(3)	4−2	54.68
C(14)−C(15)	1.342(3)	5−2	73.63
C(12)−C(13)	1.521(3)	4−5	71.36
C(13)−C(14)	1.526(3)	6−2	85.56

[a] 1: C_{12}, C_{13}, C_{14}; 2: C_{11}, C_{12}, C_{14}, C_{15}; 3: N_1, C_{11}, C_{12}; 4: C_{21}−C_{36}; 5: C_{21}−C_{26}; 6: C_{41}, C_{46}, C_{42}.

Summary and Conclusions

The present work indicates that the aromatizations of NAD(P)H models Hantzsch 1,4-dihydropyridines by nitric oxide (NO) or its donor MNTS are initiated by hydrogen transfer from the N-position on the 1,4-dihydropyridine ring to give the corresponding aminyl radicals or by nitrosation of the NH group on the 1,4-dihydropyridine ring to give the corresponding *N*-nitroso compounds, which readily undergo the homolytic cleavage to provide the final aromatized products. Other mechanistic possibilities for the reactions were ruled out. 1-Benzyl-1,4-dihydronicotinamide (BNAH) is another NAD(P)H model, but no reactions with NO and its donor MNTS were observed. The reason could be that there is no NH group on the 1,4-dihydropyridine ring in BNAH. This conclusion suggests that NAD(P)H coenzyme could not be directly oxidized by NO itself in vivo, since NAD(P)H coenzyme like BNAH has not NH group on the 1,4-dihydropyridine ring. The effects of NO on an NAD(P)H-dependent redox reaction under physiological conditions presumably contribute to the effects of metabolites of NO, such as $ONOO^-$, heme(Fe^{III}-NO), etc., because NAD(P)H is readily oxidized by $ONOO^-$ and heme(Fe^{III}-NO) which are easily

(13) The reaction mechanism of MNTS with **1** initiated by decomposition of MNTS to give NO can be ruled out, since experiment shows that MNTS in acetonitrile at room temperature is quite stable.

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derived from the reactions of NO with $O_2^{\bullet-}$ [15] and ferric heme proteins[16] under physiological conditions, respectively. This and others aspects of these interesting reactions are under current study.

Experimental Section

Materials. All of the 4-substituted (including 4,4-dideuterated) Hantzsch 1,4-dihydropyridines were prepared in the same manner, using the appropriate aldehyde, ammonia, and ethyl acetoacetate, and identified on the basis of their spectral data and, eventually, their melting points. BNAH,[17] *N*-methylated and *N*-deuterated Hantzsch 1,4-dihydropyridines[18] and 2,6-diphenyl-4-(*p*-nitrophenyl)-HEH[19] were prepared according to the literatures. *N*-Methyl-*N*-nitrosotoluene-p-sulfonamide (MNTS) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were Aldrich products, and used without further purification. Pure dry NO gas was produced by the reaction of $NaNO_2$ with sulfuric acid in the absence of oxygen and passing the stream of NO gas through 10% NaOH to remove higher oxides of nitrogen and finally through the solid NaOH dry tube to remove water. Reagent grade acetonitrile was distilled from P_2O_5 being passed through a column of active neutral alumina to remove water and protic impurities. The other solvents were purified by standard methods before use.

General Procedure for the Aromatization of the Hantzsch 1,4-Dihydropyridines by NO. Hantzsch 1,4-dihydropyridine (0.2 mmol) in dry acetonitrile (20 mL) was placed in a two-necked flask equipped with a septum rubber and three-way stopcock, one way of which was attached to an Ar balloon, and another joined to a pump. The flask was cooled to −78 °C to freeze the solvent and degassed under vacuo and filled with Ar gas. Then the frozen solvent was allowed to warm to ambient temperature and refrozen to reiterate the evacuation-Ar purge procedure. The series of operations was repeated three times. 20 mL of pure NO gas was added into the reaction vessel, and closed. The reaction mixture was allowed to react with stirring for 4 h at room temperature. Then Ar gas was bubbled to expel excess NO. The reaction mixture was concentrated under reduced pressure, the residue was purified by column chromatography to give the pure aromatized products, all of which are identified to be in complete accord with those reported in the literature.[7] *Caution: nitric oxide is toxic, and reactions should be performed in a well-vented fume hood.*

General Procedure for the Oxidation of Hantzsch 1,4-Dihydropyridines by MNTS. A suspension of the Hantzsch 1,4-dihydropyridine (0.5 mmol) and MNTS (2 mmol) in 20 mL of deaerated dry acetonitrile was stirred at room temperature for 3 days, the reaction mixture was worked up as depicted above to yield pure products.

Typical Procedure for the Oxidation of Hantzsch 1,4-Dihydropyridines and BNAH by DDQ. To the solution of the reductant (0.5 mmol) in THF was added DDQ (0.5 mmol). The mixture was stirred for 30 min, and then some 0.1 N HCl was added to give the corresponding oxidized products.

Redox Potentials of HEH, BNAH, and MNTS. All electrochemical measurements were carried out in dry CH_3CN solution under argon atmosphere. *N*-Bu_4NPF_6 (0.1M) was employed as the supporting electrolyte. A standard three-electrode assembly was consisted of a Pt disk as the working electrode, $AgNO_3$/Ag as reference, and a platinum wire as counter electrode. All sample solutions were 1.5 mM. The ferrocenium/ferrocene redox couple (Fc^+/Fc) was taken as an internal standard. Reproducibility was generally less than 10 mV.

Acknowledgment. This work was possible by grants from the Natural Science Foundation of China (NSFC No. 29972028) and in part from the National Laboratory of Applied Organic Chemistry, Lanzhou University. X.-Q.Z. also thanks the reviewers for setting a high standard and for good suggestions on this work.

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