Communications

Which Hydrogen Atom Is First Transferred in the NAD(P)H Model Hantzsch Ester Mediated Reactions via One-Step and Multistep Hydride Transfer?

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The reduced form of the nicotinamide-adenine dinucleotide coenzyme (NAD(P)H) plays an important role in many bioreductions by transferring a hydride ion or an electron to the surrounding substrates. The mechanism of the formal hydride transfer from NAD(P)H has been extensively studied by using a variety of NAD(P)H model mediated reactions.[1−3] The most widely used model compounds for NAD(P)H are 1-benzyl-1,4-dihydronicotinamide (BNAH) and 10-methyl-9,10-dihydroacridine ($ArcH_2$).[4,5] Hantzsch esters, which are also very close analogues of NAD(P)H, possess a high biological activity as a class of useful drugs, particularly as highly effective calcium antagonists with suitable pharmacological profiles,[6] but they have not been studied as NAD(P)H models as extensively as BNAH and $AcrH_2$ on the mechanism of oxidation, the main reason probably being that Hantzsch esters (HEH) have two hydrogen atoms (at the 1 and 4 positions) to lose in general oxidation reactions, which makes it hard to determine the reaction mechanism. The question of which hydrogen atom is first transferred from HEH by direct hydride transfer mechanism or by an $e-H^+-e$ or $e-H\cdot$ sequence is still interesting and debatable in NAD(P)H model mediated reductions. Since the hydrogen atom at the 1 position is connected with the nitrogen atom, and the hydrogen atom at the 4 position is associated with a carbon atom, one could believe that the hydrogen at the 1 position should be transferred more easily than that at the 4 position during the aromatization of Hantzsch esters, especially initiated by one-electron transfer.[7] In this paper, we choose (*Z*)-ethyl α-cyano-β-bromomethylcinnamate and its analogue (**1**) as a probe to investigate the mechanism of the aromatization of HEH under thermal and photoexcited conditions by using isotope tracer experiments. The results show that the hydrogen atom at the 4 position was transferred earlier than that at the 1 position in both cases.

Thermal Reaction of HEH. A mixture of **1** (0.40 mmol) and HEH (0.50 mmol) in dry deoxygenated acetonitrile (20 mL) was thermostated at room temperature for 7 h in the dark; over 90% conversion was achieved. The reaction mixture was then treated with water and chloroform. The aqueous layer was separated and gave a yellow precipitate with aqueous $AgNO_3$ solution, which showed the presence of Br^-. The organic layer was subjected to chromatography on a silica column with ether−ethyl acetate as eluant to give quantitatively the corresponding cyclopropane derivatives (**3**)[8] and Hantzsch pyridine (**2**). When **1a** was used as the substrate, only the *E* isomer of **3** was obtained.

On the basis of the structure **2**, it is clear that two hydrogen atoms at the 1 and 4 positions in HEH were lost during the reaction. To provide information necessary to postulate a mechanism for the reaction, HEH-*4,4-d*$_2$ and *N*-^{2}H-HEH were used to react with **1** under the same conditions, respectively. The results showed that deuterium was found in the 2-carbon in the three-menbered ring product **3** for the former, but no deutrium atom was found in **3** for the latter. Kinetic studies with HEH-4,4-d$_2$ and *N*-^{2}H−HEH by measuring the absorption of HEH at $\lambda_{max} = 365$ nm under pseudo first-order reaction conditions with **1** in more than 40-fold excess gave $k_H/k_D = 4.23$ and 1.15 for **1a**, and 4.10 and 1.09 for **1b** at 25 °C, respectively, which indicated that the cleavage of C_4-H bond should occur in the rate-determining step, whereas, the cleavage of N−H bond in nonrate-determining step. Determination of activation free energy for the reactions of HEH with **1a** and **1b** gave 87.47 kJ mol^{-1} and 78.11 kJ mol^{-1}, respectively. Electrochemical determinations of **1** and HEH provided that the oxidation potential of HEH is 0.507 (V vs Fc^+/Fc) and the reduction potential of **1** is −1.134 for **1a** and −1.129 for **1b** (V vs Fc^+/Fc).[9] The free energy change for the electron transfer from HEH to **1** was estimated to be a quite large positive value (+158.17 kJ mol^{-1} for **1a** and +155.61 kJ mol^{-1} for **1b**), about two times as large as the activation free energy of the reaction of HEH with **1a** and **1b**, respectively, implying that the reduction of **1** by HEH could not be initiated by single electron transfer.

On the basis of above experimental facts, it is reasonable

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(8) **3a**: EI-MS *m/z* 215 (M^+, 17); ^1H NMR ($CDCl_3$; 400.13 MHz) δ 1.39 (t, $J = 7$ Hz, 3H), 2.15 (dd, $J = 8$, 1.86 Hz, 2H), 3.20 (br t, $J = 8$ Hz, 1H), 4.33 (q, $J = 7$ Hz, 2H), 7.36 (br s, 5H). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.69; H, 6.11; N, 6.59. **3b**: EI-MS *m/z* 168 (M^+); ^1H NMR ($CDCl_3$, 400.13 MHz) δ 3.29 (t, $J = 9$ Hz, 1H), 2.23 (d, $J = 9$ Hz, 2H), 7.38 (s, 5H). Anal. Calcd for $C_{11}H_8N_2$: C, 78.6; H, 4.7; N, 16.6. Found: C, 79.2; H, 4.9; N, 16.3.

(9) Redox potentials were obtained by CV at 25 °C on a BAS-100B electrochemical analyzer. All sample solutions were prepared in MeCN and were 1.5 mM in concentration. The ferrocenium/ferrocene redox couple (Fc^+/Fc) was taken as an internal standard. Reproducibility is usually ⩽5 mV

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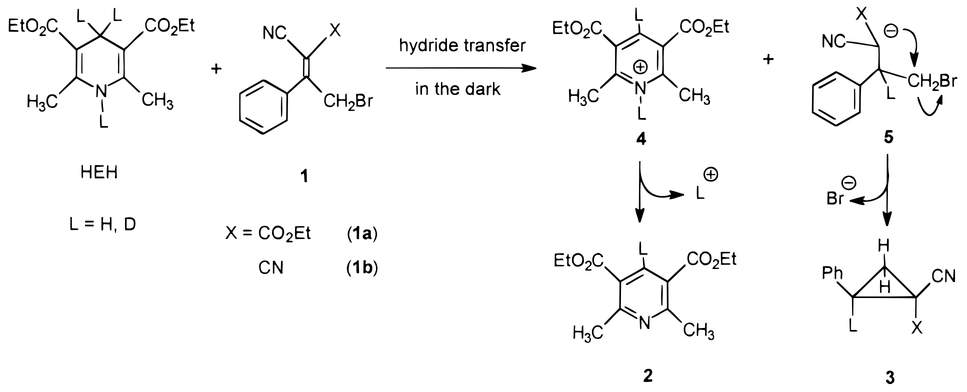
Scheme 1



to propose that an intramolecular nucleophilic substitution took place following an initial hydride transfer from the 4 position of HEH[10] to β-position of **1** (Scheme 1). It is interesting to note that the thermodynamic stability of the *E* isomer of **3** is much greater than that of the other isomer;[11] the formation of the *E* isomer of **3** as the sole product is to be expected with **1a** as the substrate.

Photoexcited Reaction of HEH. The progress of the irradiation of an argon-purged dry acetonitrile solution of **1** (0.4 mmol) and Hantzsch ester (0.6 mmol) at $h\nu > 420$ nm (500 W high-pressure Hg lamp) where only Hantzsch ester was excited[7b] was followed by thin-layer chromatography (TLC). On completion of the reaction the solution was removed. The residue was dissolved in chloroform and washed several times with water. The aqueous layer was found to contain anion Br^- by adding aqueous $AgNO_3$ solution. The chloroform layer was separated and evaporated to dryness in a rotary evaporator. The products were separated by column chromatography on silica gel to yield **2** and the corresponding debrominated products **9**.[12] When **1a** was used as the substrate, *E* and *Z* isomers were obtained, but the *E* isomer is the major product (70%). When HEH-*4,4-d*$_2$ was used in place of HEH to react with **1** under the same conditions, the deuterium atom from the 4 position of HEH-*4,4-d*$_2$ is incorporated at β-methyl group of products **9**. In contrast, if *N*-^{2}H-HEH was used in place of HEH to react with **1**, no deuterium atom was found in **9**.

To detect the photoinduced isomerization between (*E*)-**9** and (*Z*)-**9** under experimental conditions, either product in CD_3CN was submitted to irradiation ($\lambda > 420$ nm) at room temperature for 1.5 h and was monitored by ^{1}H NMR at 2.68 (s, $-CH_3$) for the *E* isomer and at 2.54 (s, $-CH_3$) for the *Z* isomer. The results showed that the *E* isomer gave no detectable *Z* isomer, while the *Z* isomer gave trace amounts of *E* isomer, indicating that the *Z* isomer was formed only from the reaction, whereas most of the *E* isomer is from the reaction, but a trace amounts from the *Z* isomer by isomerization.

On the basis of the above experimental results, we propose a tentative mechanism as depicted in Scheme 2 (Supporting Information). The reduction of **1** is presumed to be initiated by a single-electron transfer from HEH in its excited state to produce radical cation **6** and radical anion **5**. This is followed by a bromide anion loss from radical anion **7** to generate radical (*E*)-**8**, some of which isomerizated to give radical (*Z*)-**8**. The terminal γ-carbon centered radical of **8** abstracts a hydrogen atom from the 4-position rather than the 1-position of HEH radical cation **6** to give **9**.

To further support that the hydrogen atom at the 4 position is energetically more favorable than that at the 1 position for loss from **6** as a neutral hydrogen atom, the mass spectra of compounds HEH, HEH-*4,4-d*$_2$, and *N*-^{2}H-HEH under electron-impact conditions (70 eV) were studied. The results gave *m/z* (rel intensity) 253 (31), 252 (34) for HEH; 255 (32), 253 (35) for HEH-*4,4-d*$_2$ and 254 (31), 253 (35) for *N*-^{2}H-HEH, which are due to $M^{\cdot +}$, $(M - 1)^+$ for HEH; $M^{\cdot +}$, $(M - 2)^+$ for HEH-*4,4-d*$_2$ and $M^{\cdot +}$, $(M - 1)^+$ for *N*-^{2}H-HEH, respectively. A reasonable fragmentation pattern (HEH-*4,4-d*$_2$ as an example) is given in Scheme 3 (Supporting Information).[11]

In summary, the thermal reductions of (*Z*)-ethyl α-cyano-β-bromomethylcinnamate and its analogue by HEH proceed via a direct hydride-transfer mechanism to give the corresponding cyclopropane derivatives **3** and Hantzsch pyridine **2**. The hydrogen atom at the 4-position of HEH was transferred as a hydride anion in the initial step, which was followed by loss of the hydrogen atom at the 1-position. This reaction also provides a facile and high-yield method for the preparation of the stereospecific cyclopropane derivatives. The reduction of **1** by HEH under photoexcited conditions took place to yield the corresponding debrominated products via a sequential electron-hydrogen atom transfer mechanism. The hydrogen at the 4-position of HEH was lost as a neutral hydrogen atom from HEH cation radical **6** formed from initial single electron-transfer step and the hydrogen atom at the 1-position followed it to loss as a proton.

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Supporting Information Available: Photoinduced reaction mechanism of HEH and **1** (Scheme 2) and a reasonable fragmentation pattern of HEH-*4,4-d*$_2$ (Scheme 3). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) In fact, it is certain that the stability of quaternary cation **4** is much larger than that of the corresponding secondary ammonium cation **10**.

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(12) (*E*)-**9a**: EI-MS *m/z* 215 (M^+, 24); ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 1.38 (t, $J = 7.1$ Hz, 3H), 2.68 (s, 3H), 4.31 (q, $J = 7.1$ Hz, 2H), 7.46 (s, 5H). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.53; H, 6.09; N, 6.50. Found: C, 72.64; H, 6.05; N, 6.41. (*Z*)-**9a**: EI-MS *m/z* 215 (M^+, 24); ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 1.19 (t, $J = 7.1$ Hz, 3H), 2.54 (s, 3H), 4.14 (q, $J = 7.1$ Hz, 2H), 7.41 (s, 5H). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.53; H, 6.09; N, 6.50. Found: C, 72.14; H, 6.10; N, 6.37. **9b**: EI-MS *m/z* 168 (M^+); ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ: 7.5 (s, 5H), 2.6 (s, 3H). Anal. Calcd for $C_{11}H_8N_2$: C, 78.6; H, 4.7; N, 16.6. Found: C, 78.9; H, 4.8; N, 16.4.