



# Kinetic and mechanistic investigation on the oxidation of Hantzsch 1,4-dihydropyridines with the tropylium cation: a model for NADH oxidation

Bingjun Zhao,<sup>a</sup> Xiaoqing Zhu,<sup>a</sup> Yun Lu,<sup>a</sup> Chi-Zhong Xia<sup>b</sup> and Jin-Pei Cheng<sup>a,\*</sup>

<sup>a</sup>Department of Chemistry, Nankai University, Tianjin 300071, China

<sup>b</sup>Department of Chemistry, Shanxi University, Taiyuan 030006, China

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## Abstract

The reaction kinetics of the reactions of Hantzsch esters (HEH) and Hantzsch 4-aryl-1,4-dihydropyridines (4-aryl-HEH) with the tropylium cation as a formal hydride acceptor were investigated. The observed kinetic isotope effect (KIE,  $k_H/k_D$ ), using HEH and 4,4- $d_2$ -HEH as substrates, was 4.16, suggesting that the C–H bond cleavage was involved in the rate-limiting step. Correlation analysis on the reactions of *para*-substituted Hantzsch 4-aryl-1,4-dihydropyridines generated a linear Hammett plot ( $r=0.9946$ ), with  $\rho$  equal to  $-1.16$ , which is also consistent with the one-step hydride removal (from 4-C) mechanism. Comparisons of the kinetics and of the reaction thermodynamics between the reactions of HEH and 4-phenyl-HEH both disfavor the one-electron-transfer-initiated multistep mechanism. © 1999 Elsevier Science Ltd. All rights reserved.

**Keywords:** Hantzsch 1,4-dihydropyridines; hydride transfer; tropylium cation; kinetics.

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Oxidation of Hantzsch 1,4-dihydropyridines is generally the key step in their numerous reactions of biological importance.<sup>1–3</sup> In addition to being used in modeling the NADH coenzyme in its biological redox processes, this type of compound was also found to be a highly effective calcium antagonist with a suitable pharmacological profile.<sup>4</sup> Because it is demonstrated that the metabolism of Hantzsch esters, utilized in the treatment of hypertension, also proceeds through oxidation (i.e., aromatization) of 1,4-dihydropyridines,<sup>5,6</sup> significant research has been carried out to study the features of these oxidations and new approaches to their aromatization.<sup>7–11</sup> Despite these intensive efforts, the dehydrogenation mechanisms of HEH, like the long-debated formal hydride transfer mechanisms of other NADH models, still remain puzzling. The debate has mainly focused on: (i) whether the reaction occurs by a one-step hydride transfer or by an electron-transfer-initiated multistep hydride transfer mechanism (i.e.,  $e^- - H^+ - e^-$  or  $e^- - H^{\cdot}$ ); and (ii) whether the reaction center is on the carbon at the 4-position or on the nitrogen at the 1-position of the 1,4-dihydropyridine ring. Experimental evidence in support of the

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\* Corresponding author. Tel: 0086 22 23501316; fax: 0086 22 23504853; e-mail: jpcheng@sun.nankai.edu.cn

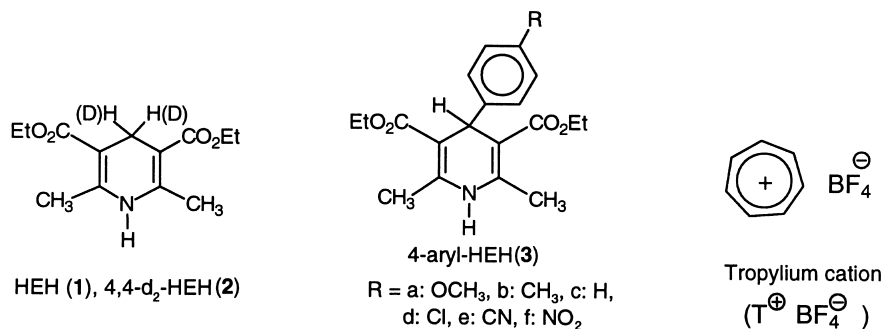


Figure 1.

direct hydride transfer mechanism<sup>12–14</sup> and of the electron-transfer-initiated multistep hydride transfer mechanism<sup>15</sup> or the hydrogen-atom-transfer mechanism<sup>16</sup> for the HEH oxidations has been diversely reported. On the other hand, while the initial dehydrogenation is often found to take place at the 4-carbon position of HEH,<sup>12–14,16</sup> arguments in favor of the 1-nitrogen as the initial reaction site in some Hantzsch dihydropyridine oxidations also seem to be quite convincing.<sup>15,17,18</sup> However, little work on the kinetics and thermodynamics of the HEH-type reactions has been reported. We have recently conducted research focusing on elucidations of the mechanisms for some NADH model-mediated reactions by a combinative analysis of reaction kinetics and thermodynamics.<sup>19–22</sup> Now this work is extended to the currently important HEH-related reactions. In the present paper, we wish to report the kinetic study on the oxidation of 1,4-dihydropyridines (**1–3**) by the tropylium cation (Fig. 1) in order to clarify the mechanism of this process.

The 4-aryl-HEH derivatives (**3a–3f**) were prepared from condensation of ethyl acetoacetate, ammonia, and the corresponding aldehydes according to a literature procedure,<sup>23</sup> and were verified by checking their m.p.'s and spectral properties against those of the authentic samples. Tropylium tetrafluoroborate (T<sup>+</sup>) was chosen as the mechanistic probe because it is capable of serving either as an electron acceptor or as a hydride acceptor in its reaction with the Hantzsch type compounds.<sup>24</sup> The reactions of T<sup>+</sup> with 4-aryl-HEH were carried out in 30% aqueous acetonitrile at 298 K. All the reactions were followed spectrophotometrically using UV–vis under pseudo-first-order conditions with T<sup>+</sup> in 20–70 fold excess ([HEH]=0.05mM) at constant pH. The pseudo-first-order rate constants (*k*<sub>obs</sub>) were calculated by the Guggenheim method and the apparent second-order rate constants (*k*<sub>2</sub><sup>app</sup>) were derived from the slopes of the plots of *k*<sub>obs</sub> versus ([T<sup>+</sup>]+[TOH]). The pH-dependent pseudo-second-order rate constants (*k*<sub>2</sub><sup>app</sup>) were then evaluated using Eq. 1.

$$k_2^{\text{app}} = k_2 / (1 + K_{R+} / [H^+]) \quad (1)$$

Eq. 1 may be further simplified to give Eq. 2, if  $K_{R+} \gg [H^+]$  is assumed.

$$\log k_2^{\text{app}} = \log k_2 + pK_{R+} - pH \quad (2)$$

The second-order kinetics (*k*<sub>2</sub>) thus derived for the two reaction systems using HEH and 4-phenyl-HEH as the model are summarized in Table 1.

The oxidation rates of 1,4-dihydropyridines by T<sup>+</sup> obey second-order kinetics. From the deuterium kinetic isotope effect of 4.16, it is clear that direct hydride dissociation from the 4-carbon position must be involved in the rate-limiting step. It is also noted that replacement of a hydrogen at the 4-position of the dihydropyridine ring with a phenyl group (4-phenyl-HEH) has a strong rate-retardation effect (ca. 10<sup>4</sup>

Table 1  
Rate constants and kinetic isotope effect of the reactions of HEH and 4-aryl-HEH with tropylium cation at 298 K

Substrates	$k_2^{\text{app}}, \text{M}^{-1}\text{s}^{-1 \text{ a}}$	$k_2, \text{M}^{-1}\text{s}^{-1 \text{ a}}$	$k_{\text{H}}/k_{\text{D}}$
4-aryl-HEH ( <b>3</b> )			
R=OCH <sub>3</sub> ( <b>3a</b> )	1.79	1.82	
R=CH <sub>3</sub> ( <b>3b</b> )	1.59	1.61	
R=H ( <b>3c</b> )	1.26	1.28	
R=Cl ( <b>3d</b> )	0.57	0.58	
R=CN ( <b>3e</b> )	0.16	0.17	
R=NO <sub>2</sub> ( <b>3f</b> )	0.13	0.13	
HEH ( <b>1</b> )	1.86 <sup>b</sup>	$1.12 \times 10^4$ <sup>c</sup>	
4, 4-d <sub>2</sub> -HEH ( <b>2</b> )	0.45 <sup>b</sup>	$2.70 \times 10^3$ <sup>c</sup>	4.16

<sup>a</sup> Calculated from eq (1) except otherwise noted. Experiment conditions: in 0.1 M ClCH<sub>2</sub>COOH-0.1 M KOH 30% aqueous acetonitrile buffer solution, pH = 3.00, ionic strength 1.0. <sup>b</sup> In 0.25 M K<sub>2</sub>HPO<sub>4</sub>-0.25 M KH<sub>2</sub>PO<sub>4</sub> 30% aqueous acetonitrile buffer solution, pH = 8.54, ionic strength 0.5. <sup>c</sup> Calculated from eq (2).

folds), which, again, suggests that the tropylium cation must have served as a hydride acceptor, but not as an electron acceptor, in its reaction with Hantzsch esters. This is because ET processes are known to show only minimum effect of steric rate-reduction. The above experimental results also clearly eliminate the N–H bond dissociation as the initial step in the oxidation of the HEH derivatives with T<sup>+</sup>.

A Hammett-type free energy analysis on the oxidations of 4-aryl-HEH by T<sup>+</sup> shows a good linear correspondence of  $\log k_2$  against  $\sigma$  constants ( $r=0.9946$ ) with a  $\rho$  value equal to  $-1.16$ . The much poorer linear regression with  $\sigma^+$  ( $r=0.9420$ ) may be understood if one considers that the phenyl ring has to adopt a twist-conformation with respect to the central dihydropyridine ring after removal (or partial removal) of a hydride from the 4-C position, resulting in a much attenuated through-resonance effect compared to that in the normal Brown-model reaction. The negative  $\rho$  value is also consistent with the mechanism proposed above.

On the other hand, distinction between the one-step and the multistep hydride transfer mechanisms may also be made on the basis of the thermodynamic point of view.<sup>19</sup> For this purpose, electrochemical measurements of the respective reactants were performed<sup>25</sup> and showed that the energies of electron transfer from HEH to T<sup>+</sup> and from 4-aryl-HEH to T<sup>+</sup> is 24.6 kcal/mol (i.e., 1.064 V) and 28.4–32.0 kcal/mol (i.e., 1.230–1.384 V), respectively. According to the energetic criteria proposed for differentiating the formal hydride transfer mechanisms of the NADH model-mediated reactions,<sup>19</sup> the electron transfer free energies  $\Delta G(e^-_{\text{T}})$  of the latter reactions fall in the region for the one-step mechanism [i.e.,  $\Delta G(e^-_{\text{T}}) > 1.0$  V], whereas the  $\Delta G(e^-_{\text{T}})$  of the former reactions in the region for a ‘hybrid’ mechanism [i.e.,  $\Delta G(e^-_{\text{T}})$  close to 1.0 V]. And indeed, this is in good accord with the observed KIE of 4.16 which indicates a direct hydride transfer joined with some degree of electron transfer in the rate-limiting step of the HEH oxidation.

To summarize, in the present work, we have presented both the kinetic evidence and preliminary thermodynamic evidence to show that the oxidation of 4-aryl-HEH with the tropylium cation should proceed via an initial one-step hydride removal from the 4-C position of its dihydropyridine ring and that the oxidation of HEH with T<sup>+</sup> should proceed via a hybrid mechanism of hydride transfer and electron transfer. To our knowledge, this appears to be the first work of this kind with regard to the structural variation on the 4-position and to the Hammett-type analysis on the kinetics as effected by the remote substituents in the 4-aryl ring.

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