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ARTICLE

Elemental Step Thermodynamics of Dihydropyrimidine: a New Class of Organic Hydride Donors†

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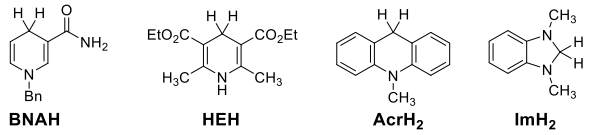
Fan-kun Meng* and Xiao-qing Zhu*

25 dihydropyrimidine derivatives, a new class of organo-hydrides, were designed and synthesized by the Biginelli reaction. For the first time, thermodynamic driving forces of their six elemental steps to obtain a hydride in acetonitrile were determined by an isothermal titration and electrochemical methods, respectively. The effects of molecular structures and substituents on those thermodynamic parameters were examined, uncovering some interesting structure-reactivity relationships. Both the thermodynamic and kinetic studies show that the hydride transfer from dihydropyrimidines to 9-phenylxanthylium ($PhXn^+ClO_4^-$) prefers a concerted mechanism.

Introduction

Inspired by the functions of organic hydride cofactors in vivo such as coenzyme NAD(P)H[1-6] and F420[7-11], organo-hydrides have received significant attentions from the fields of chemistry, biology, pharmaceuticals and energy science, *etc*. In recent years, biomimetic organo-hydrides, represented by N-benzyl-1,4-dihydronicotinamide (BNAH)[12-16], Hantzsch esters (HEH)[17-23] and dihydrobenzoimidazole (ImH_2)[24-28] (Scheme 1) have been widespreadly applied in the hydrogenation of C=C, C=O, C=N double bonds to afford versatile building blocks, owing to their advantages of excellent reactivity, mild experimental conditions, good functional group tolerance, readily available and environmental-friendly. The redox potentials of organic-hydrides and bond dissociation energies to release a hydride or a hydrogen atom are vital to measure their hydrogenation abilities and judge the hydrogenation mechanisms in both organic synthesis and the living metabolism. Consequently, those basic parameters and reaction mechanisms related with organo-hydrides were extensively studied through thermodynamic and kinetic methods during the past half century. T. C. Bruice[29-33], L. L. Miller[34-37], S. Fukuzumi[38-42], J. M. Mayer[43-46], H. Mayr[47, 48], Y, Lu[49-51] and other groups[52-58] have figured out the detailed hydride transfer mechanisms from NADH models to various substrates using integrated approaches, including the intermediate capture, spectrum detection and kinetic analysis. J.-M. Savéant and others[59-63] devoted a lot to the mechanistic



Scheme 1 Conventional organic hydride donors widely employed in synthesis.

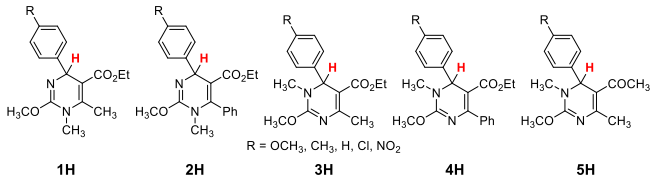
studies of multi-step oxidation of NADH models in acetonitrile through electrochemical kinetics. The structure-reactivity relationships of NADH and ImH_2 models were extensively investigated by M. M. Kreevoy and I. S. H. Lee[64-69] via investigating the location of the substitution and the tightness of the transition state as well as the resemblence of the transition state to reactants and products. Combined with the thermodynamic cycles from Hess's law, our group have systematically determined the thermodynamic parameters in each elemental step for various organic hydride donors and corresponding intermediates by experimental techniques, and further established the thermodynamic driving-force database for hundreds of biomimetic organic hydrides in acetonitrile solution.[70-74] Through our thermodynamic analytic platform, the most possible pathway of the hydride transfer from NADH analogues to olefin, imine, carbonyl compounds and some carbocations can be well diagnosed.[75-78] Besides, a classical but new kinetic equation was established to estimate the rate constants of hydride transfer reactions in acetonitrile by two available parameters related to bond energies.[79]

Although great advance has been achieved in the mechanistic studies and their synthetic application, almost all the existed organo-hydrides have been limited to the skeleton of the dihydropyridine, complementary by few benzimidazole derivatives (Scheme 1). The paucity of the species diversity has seriously restricted the further development of organic hydride chemistry. Therefore, design and synthesis of a new class of organo-hydrides, and determination of their reducing capacity are challenging and urgently needed to respond the

The State Key Laboratory of Elemento-Organic Chemistry, Department of Chemistry, Collaborative Innovation Center of Chemical Science and Engineering, Nankai University, Tianjin 300071, China.
E-mail: mfk_823@163.com, xqzhu@nankai.edu.cn

† Electronic Supplementary Information (ESI) available: Detailed NMR, CV, OSWV and ITC spectrums of dihydropyrimidine derivatives; the plots of thermodynamic parameters against the Hammett substituent parameter. See DOI: 10.1039/x0xx00000x

booming development of organic hydride chemistry. Similar to the structure of pyridine, pyrimidine is another ubiquitous heterocyclic moiety as a privileged structure in various drugs and natural products.[80-84] Naturally, we wonder whether dihydropyrimidine can act as a good hydride donor. Is the hydride-donating ability influenced by incorporation of two N atoms into benzene ring? What's the difference between the reduction ability of 1,2- and 1,4-dihydropyrimidine? Fortunately, we found that the Biginelli reaction[85-89], a generally accepted method to synthesize various dihydropyrimidines, supplied us a good opportunity to design and synthesize some dihydropyrimidine-type organo-hydrides with a novel skeleton. In present work, we have synthesized 25 dihydropyrimidine derivatives (Scheme 2) and determined their thermodynamic parameters for hydride-donating abilities (defined as the enthalpy changes to release a hydride). Considering that the electron-donating ability is also one of the basic parameters to measure the reducing capacity, and the hydride transfer is often initiated by the electron transfer, the redox potential was also determined. Through thermodynamic cycles, the thermodynamic driving forces of their six elemental steps to release a hydride in acetonitrile were obtained. The mechanism of hydride transfer from dihydropyrimidine to 9-phenylxanthylium ($PhXn^+ClO_4^-$) was diagnosed through both thermodynamic and kinetic experiments.



Scheme 2 Structures of dihydropyrimidine derivatives (**XH**) examined in this work.

Results

The target dihydropyrimidine derivatives were synthesized through the Biginelli reaction[90-96] and identified by H NMR.[79, 97-104] Oxidation potentials of the 25 dihydropyrimidines (**XH**) and reduction potentials of their corresponding cations ($\mathbf{X}^+$) were determined using BAS-100B electrochemical workstations by cyclic voltammetry (CV) and Osteryoung square wave voltammetry (OSWV) methods in acetonitrile at 298 K. All the potential values are calibrated to $Fc^{+/0}$ (Fig. 1). The results are summarized in Table 1. The kinetic of the hydride transfer from **1H**(R = OCH_3) (4.8 x 10^{-3} mol/L) to $PhXn^+ClO_4^-$ (cal. 2 x 10^{-4} mol/L) in acetonitrile at 298 K was determined by UV spectrum under a pseudo-first-order condition (details seeing Experimental Section) (Fig. 2).

The thermodynamic driving forces in this work was defined as the enthalpy changes (ΔH_{H^-D}(**XH**)) of **XH** to release a hydride anion in acetonitrile (Eqs. 1 and 2), which can be obtained from the reaction enthalpy changes (ΔH_r) of hydride transfers from **XH** to 9-phenylxanthylium perclorate ($PhXn^+ClO_4^-$) in acetonitrile (Eqs. 3 and 4). In Eq. 4, ΔH_r is the enthalpy change of the reaction of Eq. 3 in acetonitrile, which can be determined using isothermal titration calorimetry (ITC); ΔH_{H^-} $_A$($PhXn^+$) is the hydride affinity of $PhXn^+$ in acetonitrile, which is available from our previous work (-96.8 kcal/mol).[105] The molar enthalpy changes (ΔH_r) of the hydride transfer from dihydropyrimidine derivatives **XH** to $PhXn^+ClO_4^-$ (Eq. 3) were measured using titration calorimetry in acetonitrile (Fig. 3 and ESI†). The detailed enthalpy changes and thermodynamic driving force of 25 **XH** to release hydride anion in acetonitrile are summarized in Table 1.

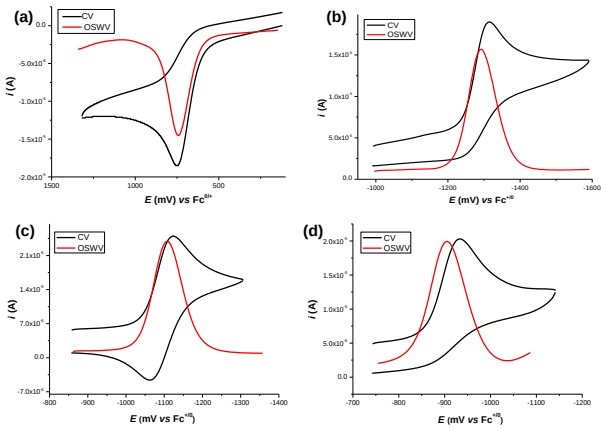


Figure 1 CV and OSWV for the oxidation of **1H**(R = H) (a), the reduction of $\mathbf{1}^+$(R = H) (b), $\mathbf{2}^+$(R = Cl) (c) and $\mathbf{2}^+$(R = NO_2) (d) (about 1 mol/L) in deaerated acetonitrile containing 0.1 M n-Bu_4NPF_6 as supporting electrolyte (sweep rate = 0.1 V s^{-1}), respectively.

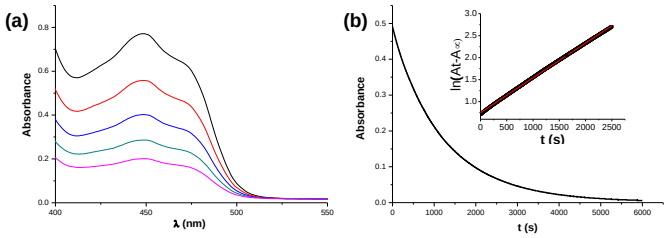


Figure 2 (a) Profiles of the hydride transfer from **1H**(R = OCH_3) to $PhXn^+ClO_4^-$ in acetonitrile at 298 K. (b) Decrease of the absorbance at 450 nm during the reaction of $PhXn^+ClO_4^-$ (cal. 2 x 10^{-4} mol/L) with **1H**(R = OCH_3) (4.8 x 10^{-3} mol/L); insert: fit to a single exponential decay function.

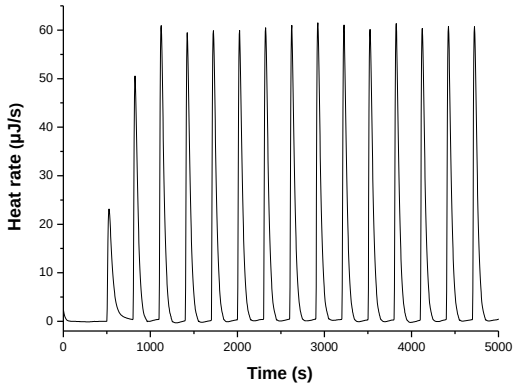
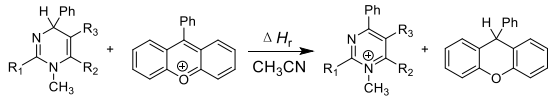


Figure 3 Isothermal titration calorimetry (ITC) for the reaction heat of **1H**(R = OCH_3) with 9-phenylxanthylium perclorate ($PhXn^+ClO4^-$) in acetonitrile at 298 K. Titration was conducted by adding 10 μL of **1H**(R = OCH_3) (3.03 mM) every 300 s into the acetonitrile containing $PhXn^+ClO4^-$ (ca. 30 mM).



(1)

$$\Delta H_{H^-D}(\mathbf{XH}) = \Delta H_f(\mathbf{X}^+) + \Delta H_f(H^-) - \Delta H_f(\mathbf{XH}) \quad (2)$$

(3)

$$\Delta H_{H^-D}(\mathbf{XH}) = \Delta H_r - \Delta H_{H^-A}(PhXn^+) \quad (4)$$

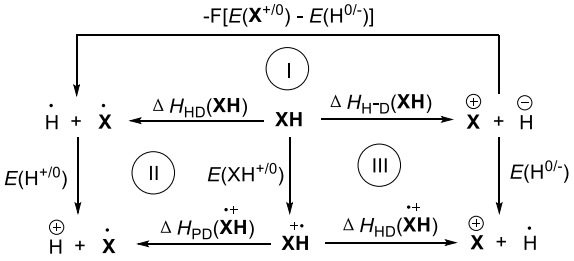
Table 1 Reaction enthalpy changes of **XH** with $PhXn^+$ as well as the redox potentials of relative species in acetonitrile at 298 K.

XH	R	ΔH_r[a]	$E(\mathbf{XH}^{+/0})$[b]		$E(\mathbf{X}^{+/0})$[b]	
			CV	OSWV	CV	OSWV
	OCH_3	-21.8	0.736	0.719	-1.373	-1.358
	CH_3	-21.7	0.743	0.730	-1.342	-1.318
1H	H	-21.4	0.763	0.745	-1.267	-1.249
	Cl	-21.1	0.792	0.766	-1.204	-1.170
	NO_2	-20.3	0.843	0.818	-0.973	-0.950
	OCH_3	-21.0	0.772	0.756	-1.298	-1.278
	CH_3	-20.8	0.786	0.768	-1.254	-1.240
2H	H	-20.6	0.805	0.788	-1.213	-1.190
	Cl	-20.2	0.820	0.800	-1.138	-1.115
	NO_2	-19.4	0.872	0.844	-0.933	-0.908
	OCH_3	-20.1	0.626	0.606	-1.453	-1.438
	CH_3	-20.0	0.634	0.612	-1.424	-1.408
3H	H	-19.9	0.656	0.630	-1.386	-1.360
	Cl	-19.8	0.670	0.648	-1.307	-1.285
	NO_2	-19.4	0.713	0.692	-1.098	-1.080
	OCH_3	-18.8	0.627	0.608	-1.270	-1.248
	CH_3	-18.7	0.642	0.620	-1.248	-1.228
4H	H	-18.5	0.650	0.632	-1.217	-1.199
	Cl	-18.4	0.674	0.652	-1.172	-1.150
	NO_2	-17.8	0.725	0.700	-1.046	-1.028
	OCH_3	-19.9	0.604	0.585	-1.440	-1.422
	CH_3	-19.9	0.619	0.596	-1.409	-1.388
5H	H	-19.7	0.632	0.612	-1.341	-1.324
	Cl	-19.5	0.652	0.636	1.253	-1.236
	NO_2	-19.1	0.727	0.694	-1.074	-1.052

[a] ΔH_r was obtained from the reaction heats of Eq. 3 by ITC in acetonitrile at 298 K. The data, given in kcal/mol, were average values of at least three independent runs, each of which was an average value of more than ten consecutive titrations. The reproducible is ± 0.05 kcal/mol. [b] Measured by CV and OSWV methods in acetonitrile at 298 K, the unit is V *vs* $Fc^{+/0}$ and reproducible to 5 mV or better.

$\Delta H_{HD}(\mathbf{XH})$ is the enthalpy change of **XH** to release hydrogen atoms. $\Delta H_{DP}(\mathbf{XH}^{\bullet+})$ and $\Delta H_{HD}(\mathbf{XH}^{\bullet+})$ are the enthalpy changes of the intermediate $\mathbf{XH}^{\bullet+}$ to release protons and hydrogen atoms, respectively. Evidently, it is difficult to directly determine the enthalpy changes of **XH** to release a hydrogen and that of $\mathbf{XH}^{\bullet+}$ to release protons or hydrogen atoms in acetonitrile, experimentally. In order to obtain their enthalpy changes in acetonitrile, three thermodynamic cycles were constructed according to the chemical process of **XH** to release hydride anion (Scheme 3). [24]

From three thermodynamic cycles, Eqs. 5-7 were derived according to Hess's law. In Eqs. 5-7, $E(\mathbf{X}^{+/0})$, $E(\mathbf{XH}^{+/0})$, $E(H^{0/-})$, and $E(H^{+/0})$ are the standard redox potentials of $\mathbf{X}^+$, **XH**, H^+ and H^- in acetonitrile, respectively. Obviously, $\Delta H_{HD}(\mathbf{XH})$, $\Delta H_{PD}(\mathbf{XH}^{\bullet+})$ and $\Delta H_{HD}(\mathbf{XH}^{\bullet+})$ are easy to obtain if $\Delta H_{H^-D}(\mathbf{XH})$, $E(\mathbf{X}^{+/0})$, $E(\mathbf{XH}^{+/0})$, $E(H^{0/-})$ and $E(H^{+/0})$ are available. In fact, $\Delta H_{H^-D}(\mathbf{XH})$, $E(\mathbf{X}^{+/0})$ and $E(\mathbf{XH}^{+/0})$ are available from above work (Table 1). $E(H^{0/-})$ and $E(H^{+/0})$ can also be obtained from literature.[106] The detailed values of $\Delta H_{HD}(\mathbf{XH})$, $\Delta H_{PD}(\mathbf{XH}^{\bullet+})$ and $\Delta H_{HD}(\mathbf{XH}^{\bullet+})$ of 25 dihydropyrimidine derivatives (**XH**) in acetonitrile are summarized in Table 2.



Scheme 3 Thermodynamic cycles of **XH** constructed on the basis of Hess's law.

$$\Delta H_{HD}(\mathbf{XH}) = \Delta H_{H^-D}(\mathbf{XH}) - F[E(\mathbf{X}^{+/0}) - E(H^{0/-})] \quad (5)$$

$$\Delta H_{PD}(\mathbf{XH}^{\bullet+}) = \Delta H_{HD}(\mathbf{XH}) - F[E(\mathbf{XH}^{+/0}) - E(H^{+/0})] \quad (6)$$

$$\Delta H_{HD}(\mathbf{XH}^{\bullet+}) = \Delta H_{H^-D}(\mathbf{XH}) - F[E(\mathbf{XH}^{+/0}) - E(H^{0/-})] \quad (7)$$

Discussion

Thermodynamic driving forces of dihydropyrimidine derivatives (XH) and related intermediates ($\mathbf{XH}^{\bullet+}$) in acetonitrile. The enthalpy change ($\Delta H_{H^-D}(\mathbf{XH})$) is a very important thermodynamic parameter of **XH** to scale the ability of **XH** to donate hydride anion. Overall, the enthalpy changes of 25 **XH** range from 75.0 kcal/mol for **1H** (R = OCH_3) to 79.0 kcal/mol for **4H** (R = NO_2). The relative small span (about 4 kcal/mol) indicates an insensitivity of the hydride-donating ability to remote substituent effects and structural variants. That is, the substituent at *para* position of benzene ring plays a small part of roles in the hydride-donating ability of the dihydropyrimidine derivatives. Electron-donating groups at *para* position of benzene ring, such as methyl and methoxyl groups, can slightly increase the hydride-donating ability; while electron-withdrawing groups, such as chlorine atom and -NO_2, decrease it.

The elaborate variants of core structures allowed a close investigation of the structure-reactivity relationship for the process of dihydropyrimidine derivatives to release hydrides. A relative energy scale was established in Fig. 4, with **1H**(R = H) as a reference. Intriguingly, the hydride donor abilities of 1,2-isomers are undoubtedly 1.5 kcal/mol weaker than those of 1,4-ones, which completely depart from previous observations in all dihydropyridine-type hydrides, such as BNAH, HEH, $AcrH_2$. The contradiction is probably attributed to the electron-withdrawing abilities of two incorporated nitrogen atoms compared with carbon atoms, as well as the resonance of the methoxyl group *ortho* to two nitrogen atoms. The resonance should be more significant to the conjugated dienes in the 1,2-isomers than the separated dienes in the 1,4-isomers and naturally, stabilized the former better. Replacement of methyl

by phenyl group resulted in a 0.8 kcal/mol decrease of hydride-donating abilities. It's not unexpected since the electron density on the dihydropyrimidine skeleton could delocalize to the benzene ring better. Additionally, change the -CO_2Et group on the 1,2-isomer into -$COCH_3$ increase the enthalpy changes slightly (about 0.2 kcal/mol), because of the slightly stronger electron-withdrawing ability of -$COCH_3$ than -CO_2Et. The quantitative analysis of the dependence of the hydride-donating abilities on the structural variants could supply us a theoretical guidance and a practical tool to rationally modify and design new hydride donors.

In order to intuitively compare the hydride-donating abilities of dihydropyrimidine derivatives (**XH**) with some other conventional hydride donors, a thermodynamic scale was established according to their enthalpy changes to release hydride anion in acetonitrile (Fig. 5). From Fig. 5, it is clear that the enthalpy changes of the 25 **XH** lie in the middle of the scale, indicating their moderate hydride-donating abilities. In other words, their corresponding cations generated by release hydride anion, can also be moderate hydride acceptors. The enthalpy changes are larger than some typically strong hydrides which are widely employed as hydride reductants, such as $LiAlH_4$ (48 kcal/mol)[107, 108], $NaBH_4$ (55 kcal/mol)[107, 108], BNAH (64.2 kcal/mol), Hantzsch (69.3 kcal/mol) and so on; but smaller than 9-phenyl-9H-xanthene (96.8 kcal/mol), TEMPOH (105.6 kcal/mol), toluene (118.0 kcal/mol), whose corresponding cations are always used as the hydride acceptors in organic synthesis. Actually, their values are close to 9,10-dihydro-10-methylacridine ($AcrH_2$ 81.1 kcal/mol). Therefore, the moderate hydride-donating abilities of dihydropyrimidine derivatives perform a well balance of their stabilities and reactivities as hydride donors, and make them be potentially used as ideal reductants and in some case, their corresponding cations as good oxidants.

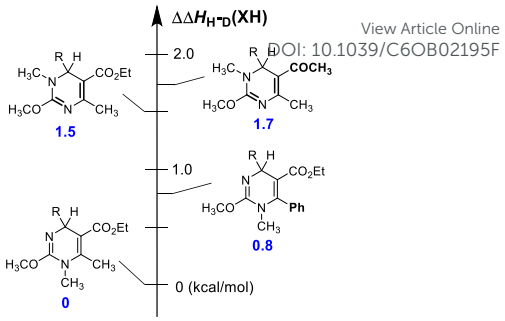


Figure 4 Effects of structural variants on hydride-donating abilities of dihydropyrimidine derivatives in acetonitrile (**1H**(R = H) as a reference).

Table 2 Enthalpy changes of **XH** to release hydride anion and hydrogen atoms as well as those of $\mathbf{XH}^{\bullet+}$ to release protons and hydrogen atoms in acetonitrile at 298 K (in kcal/mol).

XH	R	ΔH_{H^-D}(XH)[a]	ΔH_{HD}(XH)[b]	ΔH_{PD}($XH^{\bullet+}$)	ΔH_{HD}($XH^{\bullet+}$)
	OCH	75.0	80.1	10.3	32.2
	CH_3	75.1	79.3	9.3	32.1
1H	H	75.4	77.9	7.6	31.9
	Cl	75.7	76.4	5.6	31.8
	NO_2	76.5	72.2	0.1	31.4
	OCH	75.8	79.0	8.41	32.1
	CH_3	76.0	78.4	7.46	32.1
2H	H	76.2	77.5	6.15	31.8
	Cl	76.6	76.1	4.41	31.9
	NO_2	77.4	72.1	-0.55	31.7
	OCH	76.7	83.6	16.5	36.5
	CH_3	76.8	83.0	15.7	36.4
3H	H	76.9	82.0	14.3	36.1
	Cl	77.0	80.4	12.3	35.9
	NO_2	77.4	76.1	7.0	35.2
	OCH	78.0	80.6	13.4	37.8
	CH_3	78.1	80.2	12.7	37.6
4H	H	78.3	79.7	11.9	37.5
	Cl	78.4	78.8	10.5	37.2
	NO_2	79.0	76.5	7.1	36.6
	OCH	76.9	83.9	17.2	37.2
	CH_3	76.9	82.7	15.8	37.0
5H	H	77.1	81.4	14.1	36.8
	Cl	77.3	79.6	11.7	36.4
	NO_2	77.8	75.8	6.6	35.5

[a]ΔH_{H^-D}(**XH**) were derived from Eq. 4, taking $\Delta H_{H^-A}(PhXn^+)$ = -96.8 kcal/mol in acetonitrile, the uncertainties are all smaller than 1 kcal/mol. [b]ΔH_{HD}(**XH**), ΔH_{PD}($\mathbf{XH}^{\bullet+}$) and ΔH_{HD}($\mathbf{XH}^{\bullet+}$) were estimated from Eqs. 5-7, respectively, taking $E(H^{+/0})$ = -2.307 V, $E(H^{0/-})$ = -1.137 V, which were derived from Parker's work adjusted to versus $Fc^{+/0}$ by adding -0.357 V.[106] Relative uncertainties were estimated to be smaller than or close to 1 kcal/mol in each case. The standard oxidation potential values of **XH** and $\mathbf{X}^{\bullet}$ in acetonitrile were all derived from the experimental results using OSWV method, because OSWV has been verified to be a more exact electrochemical method for evaluating the standard one-electron redox potentials of analyte with irreversible electrochemical processes than CV.

The hydrogen-donating ability of dihydropyrimidine derivatives (**XH**) is defined by the enthalpy changes (ΔH_{HD}(**XH**)) of **XH** to release a hydrogen atom. From Table 2, it shows that ΔH_{HD}(**XH**) spans a range of about 12 kcal/mol, from the most stronger hydrogen donor **2H**(R = NO_2) 72.1 kcal/mol to the weakest one **5H**(R = OCH_3) 83.9 kcal/mol. Those values are comparable to the common antioxidants[109] $(CH_3)_3SnH$ 68.8 kcal/mol, PhSH 78.6 kcal/mol, *i*-C_3H_7OOH 80.3 kcal/mol, PhOH, 81.7 kcal/mol, HOOH 83.4 kcal/mol, indicating it's a good alternative to be used in the antioxidant process. The higher hydrogen-donating abilities of **XH** with electron-withdrawing groups than those with electron-donating groups implies that the electron-donating group can improve the stability of the resulted carbon radical ($\mathbf{X}^{\bullet}$) better, which further hints that those radicals have some positive charge densities on the radical carbon atom and tend to be electron-deficient. Similar to the tendency observed in the hydride-donating ability, the enthalpy changes of 1,2-isomers to release hydrogen atoms are averagely 2 kcal/mol larger than those of 1,4-isomers. That's to say, the separated dienes in the 1,4-isomers can delocalize the single electron in resulted carbon radicals more effectively than the conjugated dienes in the 1,2-isomers and therefore, lead to a better stability for the radicals of 1,4-isomers.

The radical cation is one of the most important reactive intermediates in both the academic research and the industrial production. Due to their high reactivities, their thermodynamic parameters are generally unavailable and thus, invaluable. Through our thermodynamic cycles, the enthalpy changes of

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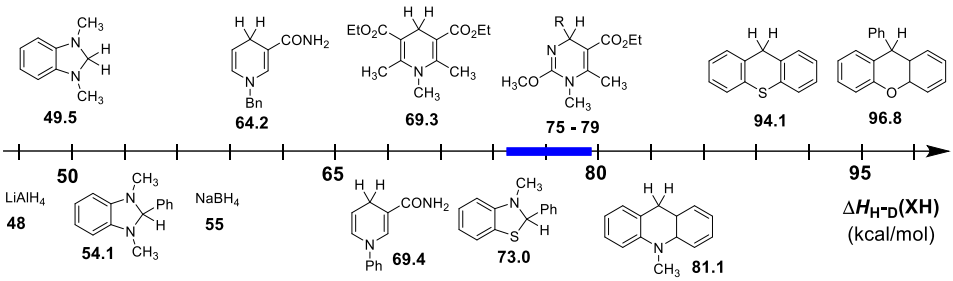

Figure 5 Comparison of hydride dissociation energies of some typical organic hydrides (**XH**) in acetonitrile.

XH$^{\bullet+}$ to release protons ΔH_{PD}(**XH**$^{\bullet+}$) and hydrogen atoms ΔH_{HD}(**XH**$^{\bullet+}$) could be derived, which are two vital parameters to measure the stabilities of corresponding radical cations. Those parameters range from -0.6 kcal/ mol **2H**(R = NO_2) to 17.2 kcal/mol **5H**(R = OCH_3) for ΔH_{PD}(**XH**$^{\bullet+}$), and from 31.4 kcal/mol **1H**(R = NO_2) to 37.8 kcal/mol **4H**(R = OCH_3) for ΔH_{HD}(**XH**$^{\bullet+}$), respectively. The relative small ΔH_{PD}(**XH**$^{\bullet+}$) values show that the resulted radical cations should be extremely strong organic acids, compared with $PhCO_2H$ 32.5 kcal/mol [110] and CF_3CO_2H 22.4 kcal/mol[111] in acetonitrile. If there are basic substrates in reaction system or even in neutral system, the degradation of radical cations (**XH**$^{\bullet+}$) through the acid-base neutralization could proceed, preferentially and smoothly. Considering the larger values of ΔH_{HD}(**XH**$^{\bullet+}$), their degradation mechanisms through the hydrogen transfer pathway seem inhibited, unless there is a strong hydrogen acceptor in reaction system or under an acidic reaction condition. Therefore, the high instabilities of **XH**$^{\bullet+}$ are mainly originated from their strong proton-donating abilities, in other terminology "their stronger acidities", which can be further verified by the irreversibility of the electrochemical measurements in following sections.

Electrochemical behaviors for the redox of dihydropyrimidine (XH) and related X$^+$ in acetonitrile. The redox potential is a basic thermodynamic parameter to measure the single-electron redox capacity of organic compounds. In present work, the oxidation potentials of dihydropyrimidine derivatives and the reduction potentials of their corresponding cations (**X**$^+$) were determined by cyclic voltammetry (CV) and Osteryoung square wave voltammetry (OSWV) methods in acetonitrile at 298 K. All the hydride donors exhibit an irreversible oxidation peak with a range of 0.604 V *vs* $Fc^{+/0}$ for **5H**(R = OCH_3) to 0.872 V for **2H**(R = NO_2) as shown in Fig. 1 and ESI†. The irreversibility of the electrochemical oxidation process is ascribed to the rapid degradation of the resulted radical cations (**XH**$^{\bullet+}$), mainly through a deprotonation process to the solution or another substrates, to generate neutral radicals (**X**$^\bullet$), as described above[112]. The effect of bases or acids on the deprotonation process of the radical cations (**XH**$^{\bullet+}$), produced in situ by electrochemical oxidation, have detailedly been analyzed in some previous work.[59-62, 97] Those oxidation potentials are remarkably larger than conventional dihydropyridine hydride donors[70], 0.219 V for BNAH, 0.460 V for $AcrH_2$ and 0.479 V for HEH, corresponding to their very weaker single-electron reductants. It is noteworthy that the radicals (**X**$^\bullet$), generated through the deprotonation of **XH**$^{\bullet+}$, should be very strong single-electron reducing agents, which were immediately oxidized at the oxidation potential of parent **XH**. Hence, the CV peaks of the parent **XH** likely correspond to a two-electron transfer process.

Because of the inaccessibility of the high reactive radicals **X**$^\bullet$ in our experimental conditions, their oxidation potentials are determined by the reduction process of **X**$^+$, instead. The reduction potentials of related cations **X**$^+$ distribute between -1.440 for **5H**(R = OCH_3) and -0.933 for **2H**(R = NO_2), implying them very weak oxidants. Conversely, their corresponding neutral radicals **X**$^\bullet$ are extremely strong single-electron reduction reagents. Additionally, cyclic voltammetry (CV) technology can be employed to test the relative stabilities of resulted radicals according to the reversibility of the CV peaks. For serials **1H**, **3H** and **5H**, which have a methyl group at 6 position of the pyrimidine, the reduction of **X**$^+$ is an irreversible process, indicating the resulted **X**$^\bullet$ is too reactive to be captured under present electrochemical conditions. However, when the methyl at 6 position of the benzene was replaced by the phenyl, the CV behave nearly reversible for serials **2H** and **4H**, except those with a strong withdrawing group NO_2 (Fig. 1c and 1d). It is directly indicated that the produced radicals **2**$^\bullet$ and **4**$^\bullet$ are more stable than **1**$^\bullet$, **3**$^\bullet$ and **5**$^\bullet$. The different reversibility between the reduction of serial **1**$^+$ and **2**$^+$ shows that the phenyl at 6 position of the pyrimidine stabilizes the **X**$^\bullet$ better than the methyl group, through its delocalization. Additionally, for **2H** and **4H,** the radicals **X**$^\bullet$ with R = OCH_3, CH_3,

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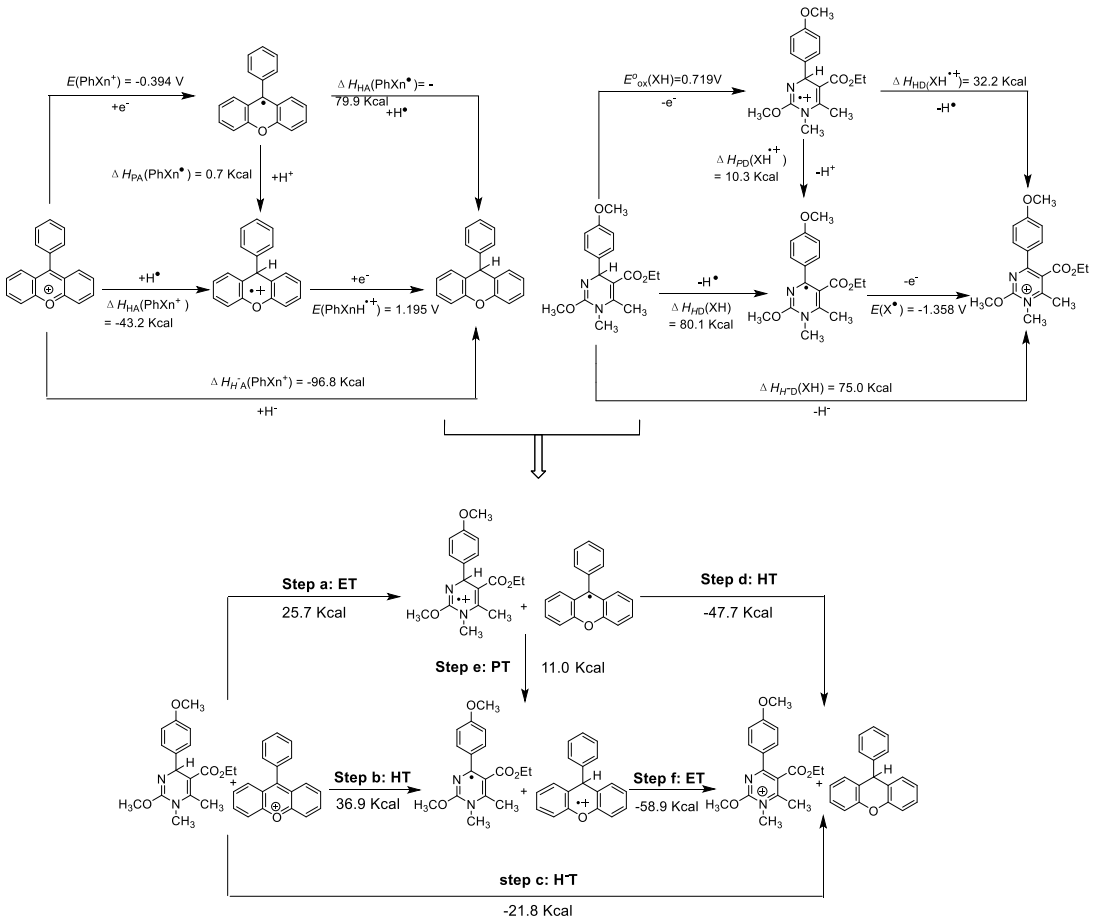
H, and Cl are more stable than R = NO_2, from which we can safely speculate that the radicals **X**$^{\bullet}$ are somewhat electron deficiency and an electron-donating substituent can significantly stabilize the reactive **X**$^{\bullet}$.

Interestingly, as a hydride reductant, the 1,4-isomer (75.35 kcal/mol for **1H**(R = H)) is stronger than the 1,2-isomer (76.88 kcal/mol for **3H**(R = H)). While used as an electron reductant, it is just the opposite, 0.656 V for **3H**(R = H) *vs* 0.763 V for **1H**(R = H). Such a rare discrepancy offered an alternative mechanistic probe to diagnose whether dihydropyrimidine derivatives are oxidized through a concerted hydride transfer or electron transfer initiated multi-step pathway, if the suitable reaction system could be well-designed.

From Tables 1 and 2, it is clear that all the enthalpy changes of **XH** and their intermediates **XH**$^{\bullet+}$ depend on the nature of substituents at the *para* position of the phenyl ring, as well as the redox potentials of **XH** and **X**$^{+}$. To elucidate the relationship of substituents with those parameters, the effects of remote substituents are examined, respectively.[113, 114] The results in Fig. s40-s41 (ESI†) show that all these values are linearly dependent on Hammett substituent parameters σ_p with good correlation coefficients, implying that the linear free energy relationship holds well in these chemical and electrochemical processes. With the slopes and the intercepts of these linear correlations, mathematical formulae are derived [Fig. s40-s41 in ESI†]. Evidently, for any *para* or *meta* position of the phenyl, it is easy to estimate the enthalpy changes and redox potentials, as long as the corresponding σ value is available. Hence, these formulae might quantitatively guide us to modify dihydropyrimidine analogues with suitable substituents for a special use.

Diagnoses mechanistic possibilities for the hydride transfer from dihydropyrimidines XH to PhXn^{+}. Possible reactions between **XH** and hydride acceptors should include the hydride transfer, hydrogen transfer, and electron transfer, which could be assigned to the possible elemental steps of hydride transfer reactions (Scheme 4). Since thermodynamics could offer intrinsic criteria in diagnosing the possibilities of reactions, it might be efficient and comprehensive to elucidate the possibilities of all the elemental steps of hydride transfer. With all the six thermodynamic parameters, the thermodynamic analytic platform for the hydride donor **XH** can be constructed. The same does for the hydride acceptor PhXn^{+}, whose parameters were available from our previous work[76] (Scheme 4). According to Hess's law, it is easy to access the thermodynamic driving forces of all possible elemental steps of the hydride transfer from **XH** to PhXn^{+}, as shown in Scheme 4. Herein, the reaction of **1H**(R = OCH_3) with PhXn^{+} was taken as an example to diagnose the detailed mechanisms of hydride transfers according to the thermodynamic analytic platform.



Scheme 4 Thermodynamic diagnosis of possible hydride transfer mechanisms between **1H**(R = OCH_3) and PhXn^{+} in acetonitrile.

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From Scheme 4, it is obvious that among three initial steps (steps a, b and c) of the four possible pathways, hydride transfer (step c) from **XH** to $PhXn^+$ should be spontaneous, since it's thermodynamically favorable by 21.8 kcal/mol. While the electron transfer (step a) and hydrogen atom transfer (step b) are thermodynamically forbidden by more than 25.7 kcal/mol). Even if the electron transfer or hydrogen transfer is triggered, the generated transient ion pairs of $\mathbf{XH}^{\bullet+}$ and $PhXn^{\bullet}$, or $\mathbf{X}^{\bullet}$ and $PhXnH^{\bullet+}$ would immediately react with each other through the possible stepwise routes (steps b-f, a-e, or a-d-f), until they give the same pair of stable products of $\mathbf{X}^+$ and PhXnH as produced by the concerted hydride transfer (step c). Therefore, it might be concluded that the hydride transfer reaction tends to proceed through a concerted manner, rather than the stepwise hydrogen or electron transfer patterns.

In order to further verify the reaction mechanism of **1H**(R = OCH_3) with $PhXn^+ClO_4^-$, the kinetics of the reaction was examined (Fig. 2) in acetonitrile at 298 K under a pseudo-first-order condition. The reaction rates k_2 were 0.16 L/(mol s) (for details seeing Experimental Section). Activation parameter was obtained from Eyring equation (18.5 kcal/mol), which is much smaller than the enthalpy changes of the initial electron transfer (step a, 25.7 kcal/mol) and hydrogen transfer (step b, 36.89 kcal/mol). On the basis of a general *reaction law*[115] that the activation energy change is always larger than or at least equal to the corresponding standard state energy change for any elemental reaction, it is evident that both the initial steps a and b could be ruled out. Therefore, from the kinetic analysis, the hydride transfer from **XH** to $PhXn^+ClO_4^-$ is also concerted.

Conclusions

In present work, we have developed a serial of readily available dihydropyrimidine organo-hydrides. Thermodynamic driving forces of each elemental step for hydride donors in acetonitrile were obtained for the first time through thermodynamic cycles, as well as those for corresponding reactive intermediates, which allow us to evaluate their reducing capacity quantitatively and elucidate the most accessible hydride transfer mechanism. Thermodynamic parameters indicated that they are moderate reducing reagents in both the hydride and electron redox process, lying between conventional biomimetic hydride donors BNAH and $AcrH_2$. The 1,4-isomers are stronger hydride donors than 1,2-isomers, different from any reported dihydropyridine derivative. The opposite tendency between the electron and hydride reducing ability supplies a potential probe in mechanistic researches. The linear free energy relationships between those thermodynamic parameters and substituent constants are exactly held. The mechanism of hydride transfer from the dihydropyrimidine **XH** to $PhXn^+$ is most probably through a concerted pathway according to both the thermodynamic and kinetic analysis. Those thermodynamic and mechanistic studies are critical to understanding the reducing properties of dihydropyrimidine derivatives, offering a practical guide for the rational design of new organic-hydrides and opening an avenue for the wide application of dihydropyrimidine derivatives in various hydrogenation processes.

Experimental Section

Materials. All reagents were of commercial quality from freshly opened containers or were purified before use. Reagent grade acetonitrile was refluxed over $KMnO_4$ and K_2CO_3 for several hours and was doubly distilled over P_2O_5 under argon before use. The commercial tetrabutylammonium hexafluorophosphate (n-Bu_4NPF_6, Aldrich) was recrystallized from CH_2Cl_2 and dried at 110 °C overnight before preparation of supporting electrolyte solution. 9-Phenylxanthium perclorate ($PhXn^+ClO_4^-$)[70] and dihydropyrimidines (**XH**)[90-96] were obtained according to literature methods, and the final products were identified by ^1H NMR.

Isothermal Titration Calorimetry (ITC). The titration experiments were performed on a CSC4200 isothermal titration calorimeter in acetonitrile at 298 K as described previously. The performance of the calorimeter was checked by measuring the standard heat of neutralization of aqueous solution of sodium hydroxide with standard aqueous HCl solution. The heat of reaction was determined following 10 automatic injections from a 250 µL injection syringe containing standard solution (3mM) into the reaction cell (1.30 mL) containing 1mL concentrated 9-Phenylxanthium perclorate (($PhXn^+ClO_4^-$). Injection volume (10 µL) were delivered 0.5 s time interval with 300-350 s between every two injections. The reaction heat was obtained by integration of each peak except the first.

Measurment of Redox Potentials. The electrochemical experiments were carried out by cyclic voltammetry (CV) and Osteryoung square wave voltammetry (OSWV) using a BAS100B electrochemical apparatus in deaerated acetonitrile under argon atmosphere at 298 K as described previously.[70, 71, 76, 77, 105] n-Bu_4NPF_6 (0.1 M) in acetonitrile was employed as the supporting electrolyte. A standard three-electrode cell consists of a glassy carbon disk as work electrode, a platinum wire as counter electrode, and 0.1 M $AgNO_3$/Ag (in 0.1 M n-Bu_4NPF_6-acetonitrile) as reference electrode. The ferrocenium/ferrocene redox couple ($Fc^{+/0}$) was taken as internal standard.

The reproducibilities of the potentials were usually $\leqslant$ 5 mV for ionic species and $\leqslant$ 10 mV for neutral species.

Kinetic Measurements. Kinetic measurements were carried out in acetonitrile by UV/vis spectrophotometer connected to a super thermostat circulating bath to regulate the temperature of cell compartments. The oxidation rate of **XH** by $PhXn^+ClO_4^-$ was measured at 298 K by monitoring the changes of absorption of $PhXn^+ClO_4^-$ (cal. 2 x 10^{-4} mol/L) at 450 nm under pseudo-first-order conditions (**1H**(R = OCH_3) 4.8 x 10^{-3} mol/L, over 20-fold excess). The pseudo-first-order rate constant was obtained k_{obs} = 7.91 x 10^{-3} s^{-1} from the slope of the work plot, and then converted to k_2. The activation parameters were derived from Eyring equation.

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