

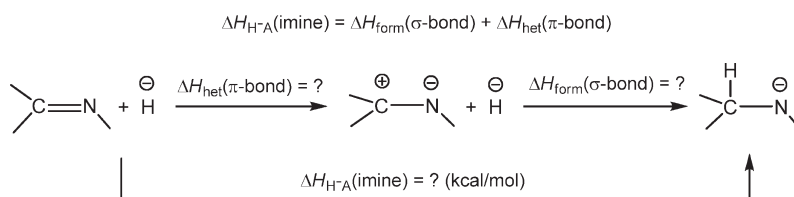
Hydride, Hydrogen, Proton, and Electron Affinities of Imines and Their Reaction Intermediates in Acetonitrile and Construction of Thermodynamic Characteristic Graphs (TCGs) of Imines as a “Molecule ID Card”

Xiao-Qing Zhu,* Qiao-Yun Liu, Qiang Chen, and Lian-Rui Mei

State Key Laboratory of Elemento-Organic Chemistry, Department of Chemistry, Nankai University, Tianjin 300071, China

xqzhu@nankai.edu.cn

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A series of 61 imines with various typical structures were synthesized, and the thermodynamic affinities (defined as enthalpy changes or redox potentials in this work) of the imines to abstract hydride anions, hydrogen atoms, and electrons, the thermodynamic affinities of the radical anions of the imines to abstract hydrogen atoms and protons, and the thermodynamic affinities of the hydrogen adducts of the imines to abstract electrons in acetonitrile were determined by using titration calorimetry and electrochemical methods. The pure heterolytic and homolytic dissociation energies of the C=N π -bond in the imines were estimated. The polarity of the C=N double bond in the imines was examined using a linear free-energy relationship. The idea of a thermodynamic characteristic graph (TCG) of imines as an efficient “Molecule ID Card” was introduced. The TCG can be used to quantitatively diagnose and predict the characteristic chemical properties of imines and their various reaction intermediates as well as the reduction mechanism of the imines. The information disclosed in this work could not only supply a gap of thermodynamics for the chemistry of imines but also strongly promote the fast development of the applications of imines.

Introduction

Imines are one class of the most important and fundamental unsaturated organic compounds with a C=N double bond as their characteristic chemical bond and are extensively present in natural products and many drugs.¹ Since imines have many interesting biological activities^{2–7} and roles⁸ and can be converted into various very useful amines, imines have received much intense attention of chemists for a long time.⁹ Especially, in recent years, the reductions and

additions of imines by various chemical agents, such as reducing agents,^{10–17} nucleophilic agents,^{18–21} neutral radicals,²² and many other agents,^{23–26} to yield various desired amines are increasingly drawing the attention of many researchers, especially synthesis chemists. Since reductions of imines with hydride agents are the most important reactions and thermodynamics and kinetics of the reductions are not only dependent on the hydride-donating ability

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(hydricity) of hydride agents²⁷ but also directly dependent on the hydride-obtaining ability (hydride affinity) of imines, the hydride affinities of imines in solution can provide a very useful thermodynamic clue for chemists to diagnose chemical activities of imines²⁸ and select suitable reducing agents to

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reduce imines. However, systematic examination of the past publications on the chemistry of imines shows that, although there are many chemists who have devoted much time to the study of imines, the main attention was limited to the preparation, reactions, and application of imines. Rather scant attention has been paid to the study on the fundamental thermodynamics of the characteristic reactions of imines, especially to the determination of hydride affinities of imines in solution by using experimental method. It is evident that the terrible lack of the knowledge about the hydride affinities of imines in solution makes it difficult to understand the characteristic reactions of imines and to further develop the applications of imines. In addition, since the reductions of imines by hydride agents could involve a multistep hydride transfer mechanism, such as $e^- - H^+ - e^-$, $e^- - H$, and $H - e^-$, etc. (Scheme 1), it is evident that, besides the hydride affinity of imines, hydrogen affinity of imines (X), hydrogen affinity and proton affinity of the radical anions of imines ($X^{\cdot-}$), reduction potentials of imines (X), and the hydrogen adducts of imines (XH) as well as the heterolytic and homolytic C=N π -bond dissociation energies of imines are also very important and desired thermodynamic parameters for chemists to thoroughly elucidate the reduction mechanism of imines and quantitatively diagnose the chemical reactivity of imines and their various reaction intermediates in solution. Therefore, determination of the hydride affinity, hydrogen affinity, proton affinity, and electron affinity of imines and their various reaction intermediates in solution has been a strategic goal in our research program for a long time. In this paper, the following eight contributions are provided: (1) 61 typical imines (X) (X = 1–11 in Scheme 2) were designed and synthesized according to the convenient synthetic strategies. (2) Hydride affinities of the 61 imines in acetonitrile were determined by using

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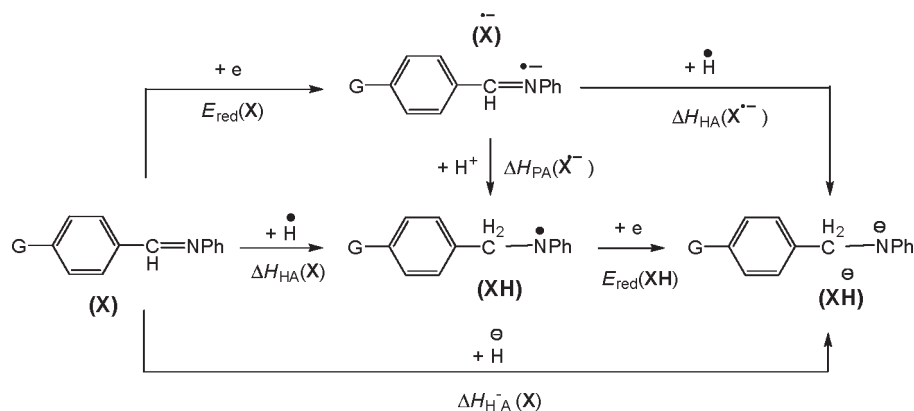
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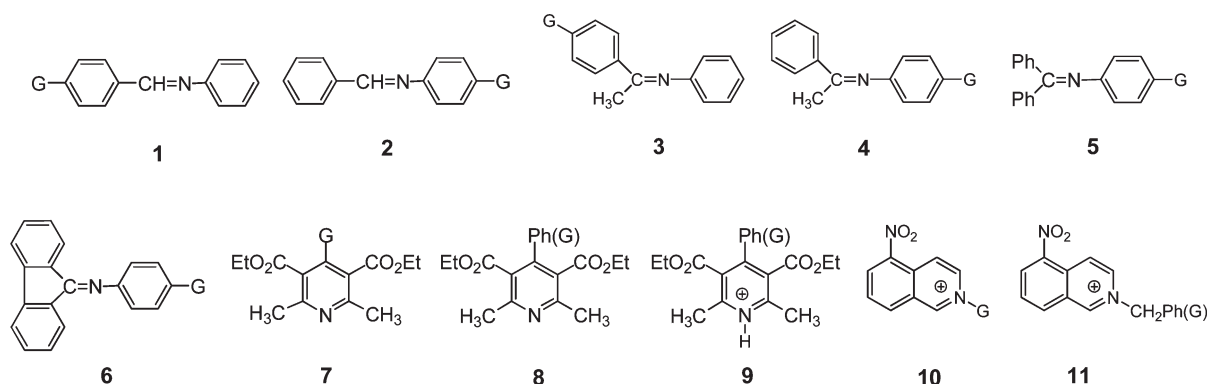
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(28) Since the most special characteristic reactions of imines are all involved in reduction or nucleophilic additions of the C=N double bond, the hydride affinities of imines should be the most intrinsic thermodynamic scale to measure their chemical activities and reactivities (hydride anion is the size-smallest nucleophilic agent).

SCHEME 1. Possible Pathways of Reduction of Imines (X) by Hydride Anion



SCHEME 2. Chemical Structures of Examined Imines (X = 1–11)



1: G = CH₃O (a), CH₃ (b), H (c), Cl (d), Br (e), CF₃ (f), NO₂ (g); 2: G = CH₃O (a), CH₃ (b), Cl (c), Br (d), CF₃ (e); 3: G = CH₃O (a), CH₃ (b), H (c), Cl (d), NO₂ (e); 4: G = CH₃O (a), CH₃ (b), Cl (c), Br (d), CF₃ (e); 5: G = CH₃O (a), CH₃ (b), H (c), Cl (d), Br (e), CF₃ (f); 6: G = CH₃O (a), CH₃ (b), H (c), Cl (d), Br (e), CF₃ (f); 7: G = H (a), *i*-C₃H₇ (b); 8: G = *p*-CH₃O (a), *p*-CH₃ (b), *p*-H (c), *p*-Cl (d), *p*-Br (e), *p*-CF₃ (f), *p*-NO₂ (g); 9: G = *p*-CH₃O (a), *p*-CH₃ (b), *p*-H (c), *p*-Cl (d), *p*-NO₂ (e), *m*-NO₂ (f); 10: G = CH₃ (a), C₂H₅ (b), *n*-C₃H₇ (c); 11: G = *p*-CH₃O (a), *p*-CH₃ (b), *p*-H (c), *p*-Cl (d), *p*-Br (e), *p*-CF₃ (f), *p*-NO₂ (g)

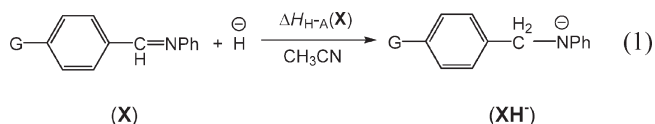
titration calorimetry. (3) Standard reduction potentials of the 61 imines (X) and their hydrogen adducts (XH) were determined by using the electrochemical methods of CV (cyclic voltammetry) and OSWV (Osteryoung square wave voltammetry), respectively. (4) Hydrogen affinities of the 61 imines in acetonitrile as well as hydrogen affinities and proton affinities of the 61 X^{•-} in acetonitrile were estimated quantitatively by using thermodynamic cycle method according to Hess's law. (5) Heterolytic and homolytic C=N π-bond dissociation energies of some typical imines in acetonitrile were safely estimated. (6) Polarity of C=N double bond in some typical imines were rationally examined according to the effect of remote substituents on the hydride affinities. (7) Effects of charge and protonation of imines on the hydride affinities, on the hydrogen affinities, on the proton affinities, and on the electron affinities of imines and their various reaction intermediates were examined quantitatively. (8) Thermodynamic characteristic graphs (TCGs) of imines in acetonitrile as a "Molecule ID Card" was proposed, which can be used to quantitatively diagnose the characteristic chemical properties of imines and their various reaction intermediates. It is clear that all of these important experimental results not only supply a gap of the chemical

thermodynamics of imines to satisfy chemists' growing need for the thermodynamic parameters but also strongly promote the fast development of the chemistry and applications of imines.

Results

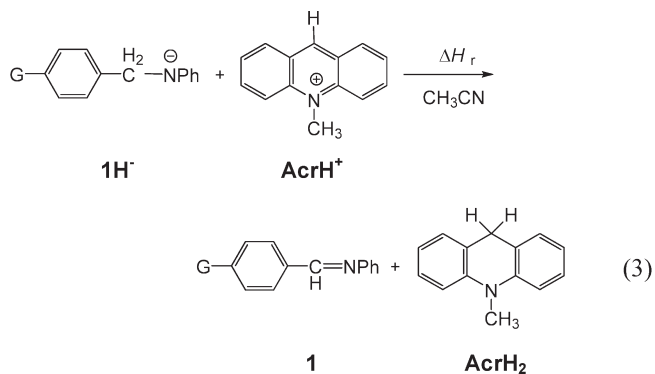
The hydride affinity of imines (X) [$\Delta H_{H-A}(X)$] in this work is defined as the enthalpy change of the reaction of imines X with a free hydride anion in acetonitrile to form the corresponding nitranions XH⁻ (eqs 1 and 2) at 298 K. The determinations of the enthalpy changes of the 61 imines to gain hydride anions in acetonitrile were performed according to three different experimental strategies: (i) For the imines which have weak ability to accept a hydride anion (1–8), the hydride affinities can be obtained according to eq 4, which were formed from hydride exchange reaction of the corresponding nitranions of imines (1H⁻–8H⁻) with the strong hydride acceptor *N*-methylacridinium (AcrH⁺ClO₄⁻) in acetonitrile (eq 3). In eq 4, ΔH_r is the reaction enthalpy change of eq 3, which can be determined by using titration calorimetry (Figure 1); $\Delta H_{H-A}(\text{AcrH}^+)$ is the hydride affinity of AcrH⁺ in acetonitrile, which is available from our

previous work.²⁹ (ii) For the protonated imines (**9**), the hydride affinities can be obtained according to eq 6. In eq 6, ΔH_r is the reaction enthalpy change of eq 5 in acetonitrile, which can be determined by using titration calorimetry; $\Delta H_{H-A}(\text{PhXn}^+)$ is the hydride affinity of PhXn^+ in acetonitrile, which is available from our previous work.³⁰ (iii) For the salts of imines (**10** and **11**), the hydride affinities can be obtained according to eq 8. In eq 8, ΔH_r is the reaction enthalpy changes of eq 7 in acetonitrile, which can be determined by using titration calorimetry; $\Delta H_{H-A}(\mathbf{1})$ is the hydride affinity of **1** ($G = \text{Cl}$) in acetonitrile, which is available from this work. The detailed hydride affinities of the 61 imines in acetonitrile are summarized in Table 2.



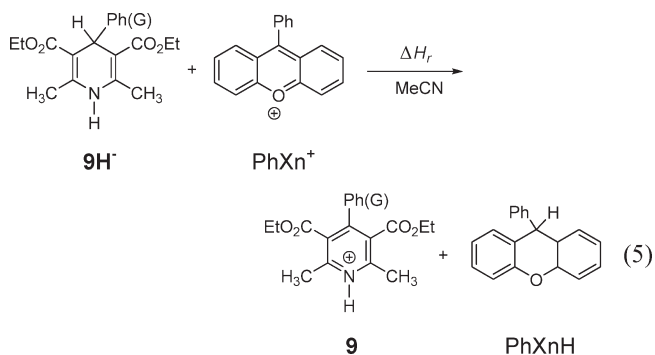
$$\Delta H_{H-A}(\text{X}) = H_f(\text{XH}^-) - [H_f(\text{X}) + H_f(\text{H}^-)] \quad (2)$$

Strategy (i) for **1–8**:



$$\Delta H_{H-A}(\text{X}) = \Delta H_{H-A}(\text{AcrH}^+) - \Delta H_r \quad (4)$$

Strategy (ii) for **9**:



$$\Delta H_{H-A}(\mathbf{9}) = \Delta H_{H-A}(\text{PhXn}^+) - \Delta H_r \quad (6)$$

Strategy (iii) for **10** and **11**:

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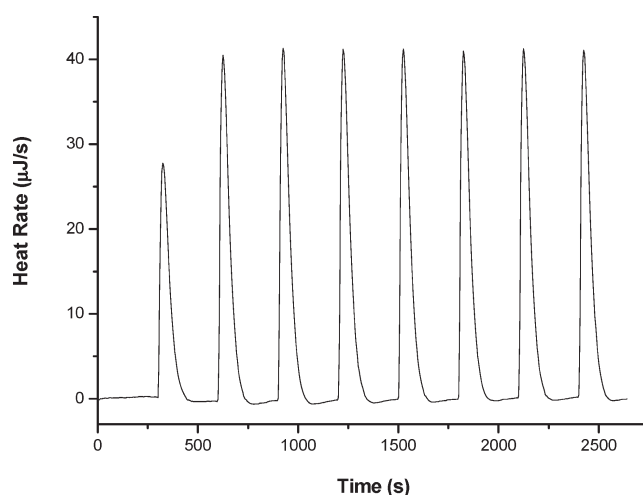
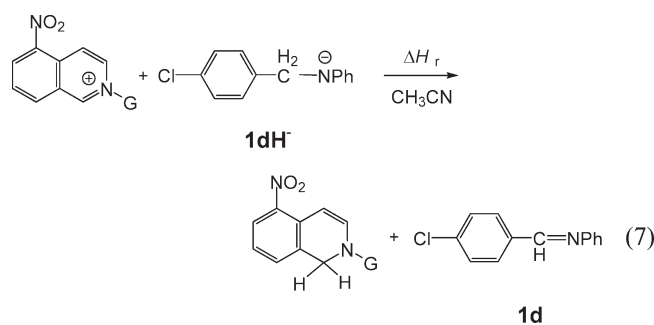


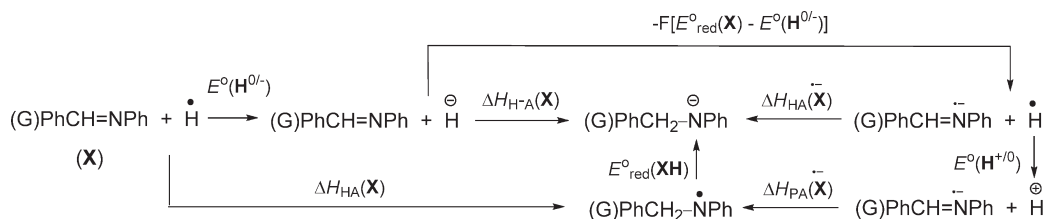
FIGURE 1. Isothermal titration calorimetry (ITC) for the reaction heat of carbanion **1dH⁻** with *N*-methylacridinium ($\text{AcrH}^+\text{ClO}_4^-$) in acetonitrile solution at 298 K. Titration was conducted by adding 5 μL of $\text{AcrH}^+\text{ClO}_4^-$ (2.0 mM) every 300 s into the acetonitrile solution containing the carbanion **1dH⁻** (15 mM), which was obtained in situ from the reactions of the corresponding saturated neutral compounds of imines **1dH₂** with KH.



$$\Delta H_{H-A}(\text{X}) = \Delta H_{H-A}(\mathbf{1}, G = \text{Cl}) + \Delta H_r \quad (8)$$

Hydrogen affinities of the imines (**X**) and hydrogen affinities and proton affinities of the radical anions of imines ($\text{X}^{\bullet-}$), in this work, are also defined as the enthalpy changes of the imines (**X**) to gain a neutral hydrogen atom in acetonitrile and the enthalpy changes of the radical anions ($\text{X}^{\bullet-}$) to gain a neutral hydrogen atom or to gain a proton in acetonitrile, which can be used to measure hydrogen-obtaining abilities of **X**, hydrogen-obtaining abilities of $\text{X}^{\bullet-}$ and proton-obtaining abilities of $\text{X}^{\bullet-}$, respectively. In order to obtain the enthalpy change values of the 61 imines to obtain hydrogen atom in acetonitrile and the enthalpy change values of the 61 $\text{X}^{\bullet-}$ to obtain hydrogen atom and to obtain proton in acetonitrile, three thermodynamic cycles were constructed according to the chemical process of **X** to obtain a hydride anion in acetonitrile (Scheme 3). From the three thermodynamic cycles, eqs 9–11,³¹ were formed according to Hess's law. In eqs 9–11, $\Delta H_{H-A}(\text{X})$ and $\Delta H_{\text{HA}}(\text{X})$ are the

(31) It should be pointed out here that we used the term free-energy change ΔG_{et} to replace the enthalpy change ΔH_{et} in eqs 9–11 for the electron transfer processes. The validation of this treatment is that entropies associated with electron transfer are negligible, which has been verified by the previous papers: (a) Arnett, E. M.; Amarnath, K.; Harvey, N. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1990**, *112*, 344. (b) Li, X.; Zhu, X.-Q.; Zhang, F.; Wang, X.-X.; Cheng, J.-P. *J. Org. Chem.* **2008**, *130*, 2501.

SCHEME 3. Three Thermodynamic Cycles Were Constructed on the Basis of the Reaction of Imines (X) by Hydride Anion (H^-)

hydride affinities and hydrogen affinities of X in acetonitrile, respectively; $\Delta H_{HA}(X^{\bullet-})$ and $\Delta H_{PA}(X^{\bullet-})$ are the hydrogen affinities and proton affinities of $X^{\bullet-}$ in acetonitrile, respectively; $E^{\circ}_{red}(XH)$, $E^{\circ}_{red}(X)$, $E^{\circ}(H^{0/-})$, and $E^{\circ}(H^{+/0})$ are the standard redox potentials of XH, X, H^+ , and H^- in acetonitrile, respectively. Evidently, it is not difficult to obtain the hydrogen affinities of X in acetonitrile and the hydrogen affinities and proton affinities of $X^{\bullet-}$ in acetonitrile, if only $\Delta H_{H-A}(X)$, $E^{\circ}_{red}(XH)$, $E^{\circ}_{red}(X)$, $E^{\circ}(H^{0/-})$, and $E^{\circ}(H^{+/0})$ are available. In fact, $\Delta H_{H-A}(X)$ can be available from the above work (Table 1), the standard redox potentials of $E^{\circ}(H^{0/-})$ and $E^{\circ}(H^{+/0})$ can be obtained from literature,³² $E^{\circ}_{red}(XH)$, $E^{\circ}_{red}(X)$ can be obtained from direct experimental measurements (Table 1, Figures 2 and 3). The detailed values of $\Delta H_{HA}(X)$, $\Delta H_{HA}(X^{\bullet-})$, and $\Delta H_{PA}(X^{\bullet-})$ for the 61 imines in acetonitrile are also summarized in Table 2.

$$\Delta H_{HA}(X) = \Delta H_{H-A}(X) - F[E^{\circ}(H^{0/-}) - E^{\circ}_{red}(XH)] \quad (9)$$

$$\Delta H_{HA}(X^{\bullet-}) = \Delta H_{H-A}(X) - F[E^{\circ}(H^{0/-}) - E^{\circ}_{red}(X)] \quad (10)$$

$$\Delta H_{PA}(X^{\bullet-}) = \Delta H_{HA}(X^{\bullet-}) - F[E^{\circ}(H^{+/0}) - E^{\circ}_{red}(XH)] \quad (11)$$

Discussion

Hydride Affinities of the Imines in Acetonitrile. The second column in Table 2 shows that the hydride affinity scale of the 61 imines (**1–11**) in acetonitrile ranges from -39.0 to -45.8 kcal for **1**, from -37.2 to -45.4 kcal for **2**, from -37.4 to -40.3 kcal for **3**, from -35.6 to -43.7 kcal for **4**, from -35.7 to -42.1 kcal for **5**, from -45.9 to -51.5 kcal for **6**, from -39.2 to -39.8 kcal for **7**, from -37.2 to -42.8 kcal for **8**, from -68.8 to -74.7 kcal for **9**, from -73.9 to -73.6 kcal for **10**, and from -72.9 to -75.5 kcal for **11**. By simply comparing the hydride affinities of the imines (**1–11**) with the same substituent (e.g., G = H in Figure 4), it is found that the hydride affinity of the imines decreases in the following order: **10a** (-73.9 kcal, G = CH_3 rather than H) > **11c** (-73.5 kcal) > **9c** (-70.9 kcal) > **6c** (-47.5 kcal) > **1c** (-40.8 kcal) = **2c** (-40.8 kcal) > **7a** (-39.2 kcal) > **3c** (-38.9 kcal) = **4c** (-38.9 kcal) > **8c** (-38.1 kcal) > **5c** (-37.1 kcal), that is, the hydride-obtaining abilities of the imines are decreased in the order: **10a** > **11c** > **9c** > **6c** > **1c** (**2c**) > **7a** > **3c** (**4c**) > **8c** > **5c**.³³ If the neutral imines (**1–8**) are examined, it is found that the hydride affinities are generally smaller (i.e., more positive) than -50 kcal, which indicates that the neutral imines generally belong to very weak hydride acceptors, and in living body, these neutral imines generally could not be

directly reduced into the corresponding amines by some well-known natural reducing agents, such as NADH, Vitamin C, etc.; the reason is that these natural reducing agents generally need at least 50 kcal energy to release hydride anion in water (e.g., 53.6 kcal for NADH to release hydride anion in water).³⁴ However, when the positively charged imines (**9–11**) are examined, it is found that the hydride affinities of the charged imines (**9–11**) are generally larger (i.e., more negative) than -70 kcal, which indicates that these positively charged imines are generally due to strong or good hydride acceptors and generally can be directly reduced into the corresponding amines by some natural reducing agents in living body.

If the hydride affinities of the imines (**1–11**) and some primary benzyl carbonium ions in acetonitrile solution (e.g., -106 , -112 , -118 , and -121 kcal for $4-CH_3OC_6H_4CH_2^+$, $4-MeC_6H_4CH_2^+$, $C_6H_5CH_2^+$, and $4-ClC_6H_4CH_2^+$, respectively)³⁵ are compared, it is found that the hydride affinities of the imines (**1–11**) are much smaller than those of the corresponding primary benzyl carbonium ions in acetonitrile; the reason is that the reduction of the primary benzyl carbonium ions by hydride anion does not involve the heterolytic dissociation of any π -bond.

In order to estimate the C=N π -bond heterolytic dissociation energies of the imines in acetonitrile, the hydride affinities of some benzyl cations in acetonitrile solution can be regarded as the approximations of the releasing energy due to the new C-H σ -bond formation after the C=N π -bond heterolytic dissociation when the imines **1**, **3**, **8**, and **9** were reduced by hydride anion; the reason is that the structure of the benzyl cation is the kindred efficient structure of imines **1**, **3**, **8**, and **9** when the C=N π -bond was broken by heterolytic dissociation.³⁶

(34) Zhu, X.-Q.; Yang, Y.; Zhang, M.; Cheng, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 15298–15299.

(35) Cheng, J.-P.; Handoo, K. L.; Parker, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2655.

(36) Although the structures of the benzylic cations formed from imines by π -bond dissociation of C=N are different from the structures of the corresponding benzyl cations, the relative efficient positive charges on the center carbon atom in the two cases should be quite close to each other, the reason is that the F values (F is inductive parameter) of R(Ph)N⁺ are quite small, which could be close to zero (the F value of H atom).

(32) Wayner, D. D. M.; Parker, V. D. *Acc. Chem. Res.* **1993**, *26*, 287.

(33) Unless specified, the magnitude of the hydride affinities in this paper indicates the absolute value rather than the pure mathematical values (negative values) for the sake of convention.

TABLE 1. Reaction Enthalpy Changes of Equations 3, 5, and 7 in Acetonitrile at 298 K (kcal) and Reduction Potentials of X and XH in Acetonitrile at 298 K (V vs Fc^{+/0})

imines (X)	ΔH_r^a	$E_{red}(X)^b$		$E_{red}(XH)^b$		imines (X)	ΔH_r^a	$E_{red}(X)^b$		$E_{red}(XH)^b$	
		CV	OSWV	CV	OSWV			CV	OSWV	CV	OSWV
1(a-g)						6(a-f)					
CH ₃ O (a)	-35.2	-1.974	-1.933	-0.821	-0.790	H (c)	-33.6	-1.905	-1.864	-0.766	-0.735
CH ₃ (b)	-34.6	-1.949	-1.908	-0.801	-0.771	Cl (d)	-31.5	-1.852	-1.811	-0.731	-0.700
CH ₃ O (a)	-42.1	-2.444	-2.406	-0.529	-0.572	Br (e)	-31.8	-1.850	-1.809	-0.730	-0.699
CH ₃ (b)	-41.2	-2.415	-2.377	-0.519	-0.562	CF ₃ (f)	-29.6	-1.751	-1.710	-0.706	-0.677
H (c)	-40.3	-2.363	-2.325	-0.488	-0.531	7(a,b)					
Cl (d)	-38.5	-2.295	-2.257	-0.432	-0.475	H (a)	-41.9	-2.480	-2.446	-0.670	-0.695
Br (e)	-39.0	-2.290	-2.252	-0.430	-0.473	<i>i</i> -C ₃ H ₇ (b)	-41.3	-2.490	-2.450	-0.566	-0.595
CF ₃ (f)	-36.8	-2.152	-2.114	-0.354	-0.397	8(a-g)					
NO ₂ (g)	-35.3	-2.021	-1.983	-0.292	-0.335	<i>p</i> -CH ₃ O (a)	-44.4	-2.663	-2.611	-0.469	-0.497
2(a-f)						<i>p</i> -CH ₃ (b)	-44.0	-2.632	-2.580	-0.463	-0.491
CH ₃ O (a)	-43.9	-2.451	-2.413	-0.554	-0.597	H (c)	-43.0	-2.580	-2.528	-0.449	-0.479
CH ₃ (b)	-42.9	-2.425	-2.387	-0.542	-0.585	<i>p</i> -Cl (d)	-41.6	-2.505	-2.453	-0.416	-0.444
H (c)	-40.3	-2.363	-2.325	-0.488	-0.531	<i>p</i> -Br (e)	-41.5	-2.507	-2.455	-0.417	-0.445
Cl (d)	-38.2	-2.301	-2.263	-0.396	-0.439	<i>p</i> -CF ₃ (f)	-39.9	-2.422	-2.370	-0.382	-0.411
Br (e)	-38.4	-2.282	-2.244	-0.395	-0.438	<i>p</i> -NO ₂ (g)	-38.3	-2.341	-2.289	-0.354	-0.382
CF ₃ (f)	-35.7	-2.144	-2.106	-0.300	-0.343	9(a-f)					
3(a-e)						<i>p</i> -CH ₃ O (a)	-28.0	-1.011	-0.980	0.741	0.712
CH ₃ O (a)	-43.7	-2.654	-2.606	-0.667	-0.713	<i>p</i> -CH ₃ (b)	-27.2	-0.964	-0.932	0.750	0.721
CH ₃ (b)	-42.9	-2.634	-2.586	-0.647	-0.687	H (c)	-25.9	-0.885	-0.856	0.762	0.731
H (c)	-42.2	-2.576	-2.530	-0.611	-0.659	<i>p</i> -Cl (d)	-25.0	-0.806	-0.775	0.776	0.745
Cl (d)	-40.8	-2.447	-2.394	-0.564	-0.607	<i>m</i> -NO ₂ (e)	-22.9	-0.683	-0.655	0.806	0.776
NO ₂ (e)	-37.2	-2.095	-2.018	-0.472	-0.514	<i>p</i> -NO ₂ (f)	-22.1	-0.665	-0.634	0.810	0.781
4(a-f)						10(a-c)					
CH ₃ O (a)	-45.5	-2.674	-2.624	-0.711	-0.760	CH ₃ (a)	-31.3	-0.959	-0.924	0.150	0.115
CH ₃ (b)	-44.4	-2.638	-2.596	-0.672	-0.712	C ₂ H ₅ (b)	-31.1	-0.963	-0.928	0.131	0.095
H (c)	-42.2	-2.576	-2.530	-0.611	-0.659	<i>n</i> -C ₃ H ₇ (c)	-31.0	-0.965	-0.930	0.158	0.119
Cl (d)	-40.7	-2.444	-2.394	-0.550	-0.596	11(a-g)					
Br (e)	-40.4	-2.434	-2.384	-0.546	-0.592	<i>p</i> -CH ₃ O (a)	-30.3	-0.953	-0.927	0.237	0.204
CF ₃ (f)	-37.4	-2.331	-2.285	-0.468	-0.512	<i>p</i> -CH ₃ (b)	-30.5	-0.949	-0.923	0.243	0.210
5(a-f)						H (c)	-30.9	-0.944	-0.918	0.257	0.224
CH ₃ O (a)	-45.4	-2.406	-2.371	-0.563	-0.603	<i>p</i> -Cl (d)	-31.5	-0.938	-0.912	0.276	0.243
CH ₃ (b)	-45.0	-2.385	-2.350	-0.541	-0.581	<i>p</i> -Br (e)	-31.6	-0.936	-0.910	0.278	0.245
H (c)	-44.1	-2.344	-2.309	-0.509	-0.549	<i>p</i> -CF ₃ (f)	-32.2	-0.926	-0.900	0.303	0.270
Cl (d)	-43.1	-2.300	-2.265	-0.476	-0.516	<i>p</i> -NO ₂ (g)	-32.9	-0.919	-0.893	0.325	0.292
Br (e)	-43.6	-2.295	-2.260	-0.475	-0.515						
CF ₃ (f)	-41.0	-2.215	-2.180	-0.395	-0.435						

^a ΔH_r obtained from the reaction heats of eqs 3, 5, and 7 by switching the sign; the latter were measured by titration calorimetry in acetonitrile at 298 K. The data given in kcal were average values of at least three independent runs. The reproducibility is ± 0.5 kcal. ^bMeasured by CV and OSWV methods in acetonitrile at 298 K, the unit in volts vs Fc^{+/0} and reproducible to 5 mV or better.

Thus, the C=N π -bond heterolytic dissociation enthalpies of **1**, **3**, **8**, and **9** in acetonitrile solution can be estimated according to the difference in the hydride affinities of the imines and the corresponding benzyl cations. The detailed C=N π -bond heterolytic dissociation enthalpies of imines **1**, **3**, **8**, and **9** in acetonitrile are listed in Table 3. By using the similar method, the homolytic C=N π -bond dissociation enthalpies of **1**, **3**, **8**, and **9** and (C=N)^{•-} π -bond dissociation enthalpies of **1**^{•-}, **3**^{•-}, **8**^{•-}, and **9**^{•-} can also be estimated;³⁷ the detailed results are also listed in Table 3. From Table 3, it is clear that the heterolytic C=N π -bond dissociation enthalpies of imines **1**, **3**, **8**, and **9** range from 68.0 to 83.2 kcal for **1**, from 69.6 to 85.1 kcal

for **3**, from 70.3 to 86.2 kcal for **8**, and from 38.2 to 54.3 kcal for **9**; the homolytic C=N π -bond dissociation enthalpies of imines **1**, **3**, **8**, and **9** range from 62.6 to 61.3 kcal for **1**, from 61.0 to 59.0 kcal for **3**, from 66.8 to 63.4 kcal for **8**, and from 62.3 to 58.0 kcal for **9**. Since the heterolytic C=N π -bond dissociation enthalpies of the neutral imines (**1**, **3**, and **8**) are quite large, it is not difficult to understand why the hydride affinities of the neutral imines are generally quite smaller. However, if the hydride affinities and the heterolytic C=N π -bond dissociation enthalpies of imines **1a** and **1g** are examined together (see Figure 5), an illegitimate result can be surprisingly found that, for the neutral imines, the larger the heterolytic C=N π -bond dissociation energy of the imines, the larger the hydride affinity of the imines. The reason could be that the large C=N π -bond heterolytic dissociation energy can result in the larger releasing energy to form the new C-H σ -bond.

From Table 3, if the heterolytic C=N π -bond dissociation energies and the corresponding homolytic C=N π -bond dissociation energies are compared, it is found that, when the imine is neutral, the heterolytic C=N π -bond

(37) The hydrogen affinity of benzylic cation in acetonitrile is 88.0 kcal/mol. See: Berkowitz, J. Ellison, G. B.; Gutman, D. *J. Phys. Chem.* 1994, 98, 2744–2765. Since the remote substituent effect on the hydrogen affinity of benzyl cation is quite small (Luo, Y.-R. *Handbook of Bond Dissociation Energies*, 3rd ed.; Science Press, ISBN: 7-03-014707-3; pp 35–36 (Chinese Version, 2005), hydrogen affinity of benzyl cation in acetonitrile herein is used to replace the hydrogen affinities of the other remote substituted benzylic cations to estimate the C=N π -bond homolytic dissociation energies of the other remote substituted imines in acetonitrile.

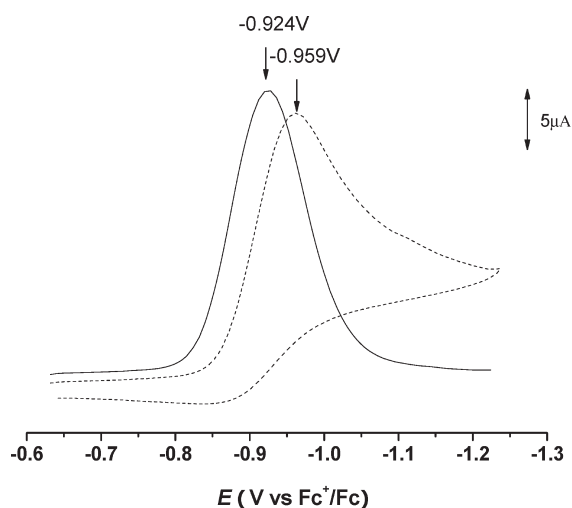


FIGURE 2. Cyclic voltammetry (CV) and Osteryoung square wave voltammetry (OSWV) of **10a** in deaerated acetonitrile containing 0.1 M *n*-Bu₄NPF₆ as supporting electrolyte. Dashed line: CV graph (sweep rate = 0.1 V/s). Solid line: OSWV graph.

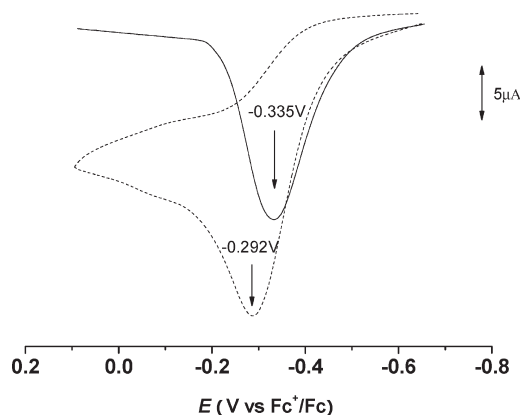


FIGURE 3. Cyclic voltammetry (CV) and Osteryoung square wave voltammetry (OSWV) of **10aH⁻** in deaerated acetonitrile containing 0.1 M *n*-Bu₄NPF₆ as supporting electrolyte. Dashed line: CV graph (sweep rate = 0.1 V/s). Solid line: OSWV graph.

dissociation enthalpy is quite greater than the corresponding homolytic C=N π -bond dissociation enthalpy, but when the imine is positively charged, the heterolytic C=N π -bond dissociation enthalpy is remarkably smaller than the corresponding homolytic C=N π -bond dissociation enthalpy. This result indicates that, in the addition reaction of C=N double bond of imines, the radical mechanism is preferable to the ionic mechanism for the neutral imines, but for the positively charged imines, the case is just reverse.

In addition, from Figure 4, if the hydride affinities of Hantzsch pyridine **8** and the protonated Hantzsch pyridine **9** are compared, it is found that the hydride affinity of protonated Hantzsch pyridine **9** is greater than that of the corresponding neutral Hantzsch pyridine by about 32 kcal, which means that the protonation of Hantzsch pyridine can greatly promote its hydride-obtaining ability. This result can be used to reply why in most cases the reduction of neutral imines needs catalysts of protonic acids.

Hydrogen Affinities of the Imines in Acetonitrile. The third column in Table 2 shows that the hydrogen affinity scale of

the 61 imines (**1–11**) in acetonitrile ranges from -26.0 to -27.4 kcal for **1**, from -24.8 to -27.1 kcal for **2**, from -27.6 to -29.6 kcal for **3**, from -26.9 to -29.3 kcal for **4**, from -23.2 to -25.9 kcal for **5**, from -37.9 to -40.9 kcal for **6**, from -27.3 to -29.0 kcal for **7**, from -22.0 to -25.4 kcal for **8**, from -26.2 to -30.5 kcal for **9**, from -44.7 to -45.3 kcal for **10**, and from -42.0 to -42.6 kcal for **11**. If the hydrogen affinities of the 11 types of the imines (**1–11**) are compared, it is found that when the substituent is same (e.g., G = H) the hydrogen affinities of the imines decrease in the following order: **10a** (-45.1 kcal, G = CH₃) > **11c** (-42.2 kcal) > **6c** (-38.2 kcal) > Hantzsch pyridine **7c** (-29.0 kcal) > **3c** (-27.9 kcal) > protonated Hantzsch pyridine **9c** (-27.8 kcal) > **1c** (-26.8 kcal) > **5c** (-23.6 kcal) > 4-phenyl Hantzsch pyridine **8c** (-22.9 kcal) (see Figure 6). Since the hydrogen affinities of the 61 imines all are quite small, generally much smaller than the corresponding hydride affinities, the imines whether charged or not should belong to very weak hydrogen atom acceptors. This result suggests that, when the imines are reduced by a hydride anion, it is unlikely that the hydride transfer was initiated by hydrogen atom transfer. If hydrogen affinity of Hantzsch pyridine **8c** (-22.9 kcal) and the corresponding protonated species **9c** (**9c** = **8cH⁺**) (-27.8 kcal) are compared, it is interesting to find that, unlike the large difference of the two hydride affinities, the difference of the corresponding hydrogen affinities is small; that is, the protonation effect on the hydrogen affinities of imines is not remarkable, and the main reason could be that the hydrogen atom does not carry charge. This finding can be used to diagnose the mechanism for the reduction of imines by altering the acidity of reaction medium; that is, if the reductions of imines are initiated by hydrogen atom transfer, the effect of the acidity of reaction medium on the reaction rate should not be quite large, but if the reductions of imines are reduced by hydride anion in one step, the effect of the acidity of reaction medium on the reaction rate should be quite large.

Hydrogen Affinities and Proton Affinities of Neutral and Charged Radical Intermediates of Imines in Acetonitrile. As stated in the Introduction, if reductions of imines (X) by hydride donors were initiated by single-electron transfer, the corresponding charged or uncharged radicals (X^{•-}) as incipient reaction intermediates could be formed. Since hydrogen affinities and proton affinities of the reaction intermediates (X^{•-}) as very important thermodynamic parameters both can be used to diagnose the chemical activities of the reaction intermediates and predict the second step reaction for the reductions of imines, it is necessary to examine and compare the hydrogen affinities and proton affinities of the reaction intermediates in acetonitrile. From columns 4 and 5 in Table 2, we found that the hydrogen affinity scale and proton affinity scale of the reaction intermediates (X^{•-}) range from -62.8 to -71.6 kcal and from 8.3 to -34.5 kcal, respectively. If the hydrogen affinities of the reaction intermediates X^{•-} are examined in detail, it is found that, when the substituent is same (such as, G = H), the hydrogen affinities of the reaction intermediates decrease in the order **4c^{•-}** (-71.0 kcal) > **8c^{•-}** (-70.1 kcal) > **7c^{•-}** (-69.3 kcal) > **10a^{•-}** (-69.0 kcal, G = CH₃) > **11c^{•-}** (-68.5 kcal) > **1c^{•-}** (-68.2 kcal) > **9c^{•-}** (-64.4 kcal) > **6c^{•-}** (-64.2 kcal) > **5c^{•-}** (-64.1 kcal) (see Figure 7). From Figure 7, it is clear that whether the reaction intermediates X^{•-} are charged (X = **1–8**) or uncharged (X = **9–11**), the hydrogen

TABLE 2. Hydride and Hydrogen Affinities of Imines (X), Hydrogen, and Proton Affinities of X^{-•} (kcal) and Reduction Potentials of X and XH (V vs Fe^{+/0}) and Activation Coefficients of the C=N π-Bond by Electron Addition (A_e%) in Acetonitrile

imines (X)	$\Delta H_{H-A}(X)^a$	$\Delta H_{HA}(X)^b$	$\Delta H_{HA}(X^{•-})^b$	$\Delta H_{PA}(X^{•-})^b$	$E_{red}^o(X)^c$	$E_{red}^o(XH)^c$	$A_e\%^d$
1(a-g)							
CH ₃ O (a)	-39.0	-26.0	-68.2	-28.3	-2.406	-0.572	61.88
CH ₃ (b)	-39.9	-26.7	-68.5	-28.3	-2.377	-0.562	61.02
H (c)	-40.8	-26.8	-68.2	-27.3	-2.325	-0.531	60.70
Cl (d)	-42.6	-27.4	-68.4	-26.2	-2.257	-0.475	59.94
Br (e)	-42.1	-26.8	-67.8	-25.5	-2.252	-0.473	60.47
CF ₃ (f)	-44.3	-27.3	-66.8	-22.8	-2.114	-0.397	59.13
NO ₂ (g)	-45.8	-27.3	-65.3	-19.9	-1.983	-0.335	58.19
2(a-f)							
CH ₃ O (a)	-37.2	-24.8	-66.6	-27.2	-2.413	-0.597	62.76
CH ₃ (b)	-38.2	-25.5	-67.0	-27.3	-2.387	-0.585	61.94
H (c)	-40.8	-26.8	-68.2	-27.3	-2.325	-0.531	60.70
Cl (d)	-42.9	-26.6	-68.8	-25.8	-2.263	-0.439	61.34
Br (e)	-42.7	-26.6	-68.2	-25.2	-2.244	-0.438	61.00
CF ₃ (f)	-45.4	-27.1	-67.7	-22.5	-2.106	-0.343	59.97
3(a-e)							
CH ₃ O (a)	-37.4	-27.6	-71.2	-34.5	-2.606	-0.713	61.23
CH ₃ (b)	-38.2	-27.8	-71.6	-34.3	-2.586	-0.687	61.17
H (c)	-38.9	-27.9	-71.0	-33.0	-2.530	-0.659	60.70
Cl (d)	-40.3	-28.1	-69.2	-30.1	-2.394	-0.607	59.39
NO ₂ (e)	-43.9	-29.6	-64.2	-22.9	-2.018	-0.514	53.89
4(a-f)							
CH ₃ O (a)	-35.6	-26.9	-69.8	-34.2	-2.624	-0.760	61.46
CH ₃ (b)	-36.7	-26.9	-70.3	-33.6	-2.596	-0.712	61.73
H (c)	-38.9	-27.9	-71.0	-33.0	-2.530	-0.659	60.70
Cl (d)	-40.4	-27.9	-69.3	-29.9	-2.394	-0.596	59.74
Br (e)	-40.7	-28.1	-69.4	-29.9	-2.384	-0.592	59.51
CF ₃ (f)	-43.7	-29.3	-70.1	-28.8	-2.285	-0.512	58.20
5(a-f)							
CH ₃ O (a)	-35.7	-23.4	-64.1	-24.9	-2.371	-0.603	63.49
CH ₃ (b)	-36.1	-23.3	-64.0	-24.3	-2.350	-0.581	63.59
H (c)	-37.1	-23.6	-64.1	-23.6	-2.309	-0.549	63.18
Cl (d)	-38.0	-23.7	-64.0	-22.7	-2.265	-0.516	62.97
Br (e)	-37.5	-23.2	-63.4	-22.1	-2.260	-0.515	63.41
CF ₃ (f)	-42.1	-25.9	-66.1	-23.0	-2.180	-0.435	60.81
6(a-f)							
CH ₃ O (a)	-45.9	-37.9	-64.2	-29.3	-1.933	-0.790	40.97
CH ₃ (b)	-46.5	-38.1	-64.3	-28.9	-1.908	-0.771	40.74
H (c)	-47.5	-38.2	-64.2	-28.0	-1.864	-0.735	40.50
Cl (d)	-49.6	-39.5	-65.1	-28.1	-1.811	-0.700	39.32
Br (e)	-49.3	-39.2	-64.8	-27.7	-1.809	-0.699	39.51
CF ₃ (f)	-51.5	-40.9	-64.7	-27.2	-1.710	-0.677	36.79
7(a,b)							
H (a)	-39.2	-29.0	-69.3	-32.2	-2.446	-0.695	58.15
<i>i</i> -C ₃ H ₇ (b)	-39.8	-27.3	-70.0	-30.6	-2.450	-0.595	61.00
8(a-g)							
<i>p</i> -CH ₃ O (a)	-36.7	-22.0	-70.6	-29.0	-2.611	-0.497	68.84
<i>p</i> -CH ₃ (b)	-37.1	-22.2	-70.3	-28.5	-2.580	-0.491	68.42
<i>p</i> -H (c)	-38.1	-22.9	-70.1	-28.0	-2.528	-0.479	67.33
<i>p</i> -Cl (d)	-39.5	-23.5	-69.8	-26.9	-2.453	-0.444	66.33
<i>p</i> -Br (e)	-39.6	-23.7	-70.0	-27.1	-2.455	-0.445	66.14
<i>p</i> -CF ₃ (f)	-41.2	-24.5	-69.6	-25.9	-2.370	-0.411	64.80
<i>p</i> -NO ₂ (g)	-42.8	-25.4	-69.3	-25.0	-2.289	-0.382	63.35
9(a-f)							
<i>p</i> -CH ₃ O (a)	-68.8	-26.2	-65.2	4.4	-0.980	0.712	59.82
<i>p</i> -CH ₃ (b)	-69.6	-26.8	-64.9	5.0	-0.932	0.721	58.71
<i>p</i> -H (c)	-70.9	-27.8	-64.4	5.6	-0.856	0.731	56.83
<i>p</i> -Cl (d)	-71.8	-28.4	-63.5	6.9	-0.775	0.745	55.28
<i>m</i> -NO ₂ (e)	-74.7	-30.5	-63.1	8.1	-0.634	0.776	52.55
<i>p</i> -NO ₂ (f)	-73.9	-29.8	-62.8	8.3	-0.655	0.781	51.66
10(a-c)							
CH ₃ (a)	-73.9	-45.1	-69.0	-13.2	-0.924	0.115	34.63
C ₂ H ₅ (b)	-73.7	-45.3	-68.9	-13.6	-0.928	0.095	34.25
<i>n</i> -C ₃ H ₇ (c)	-73.6	-44.7	-68.8	-13.0	-0.930	0.119	35.03

TABLE 2. Continued

imines (X)	$\Delta H_{H-A}(X)^a$	$\Delta H_{HA}(X)^b$	$\Delta H_{HA}(X^{\bullet-})^b$	$\Delta H_{PA}(X^{\bullet-})^b$	$E^{\circ}_{red}(X)^c$	$E^{\circ}_{red}(XH)^c$	$A_c\%$ ^d
11(a-g)							
<i>p</i> -CH ₃ O (a)	-72.9	-42.0	-68.1	-10.2	-0.927	0.204	38.33
<i>p</i> -CH ₃ (b)	-73.1	-42.1	-68.2	-10.2	-0.923	0.210	38.27
<i>p</i> -H (c)	-73.5	-42.2	-68.5	-10.2	-0.918	0.224	38.39
<i>p</i> -Cl (d)	-74.1	-42.3	-68.9	-10.2	-0.912	0.243	38.61
<i>p</i> -Br (e)	-74.2	-42.4	-69.0	-10.2	-0.910	0.245	38.55
<i>p</i> -CF ₃ (f)	-74.8	-42.4	-69.3	-10.0	-0.900	0.270	38.82
<i>p</i> -NO ₂ (g)	-75.5	-42.6	-69.9	-10.0	-0.893	0.292	39.06

^a $\Delta H_{H-A}(X)$ values of imines **1–8** were estimated from eq 4, taking $\Delta H_{H-A}(\text{AcrH}^+) = -81.1$ kcal from ref 29; $\Delta H_{H-A}(X)$ values of imines **9** were estimated from eq 6, taking $\Delta H_{H-A}(\text{PhXn}^+) = -96.8$ kcal;³⁰ $\Delta H_{H-A}(X)$ values of imines **10** and **11** were estimated from eq 8, taking $\Delta H_{H-A}(\mathbf{1}, \text{G}=\text{Cl}) = -42.6$ kcal. ^b $\Delta H_{HA}(X)$, $\Delta H_{HA}(X^{\bullet-})$ and $\Delta H_{PA}(X^{\bullet-})$ were estimated from eqs 9–11, respectively, taking $E^{\circ}(\text{H}^{+/0}) = -2.307$ (V vs $\text{Fc}^{+/0}$), $E^{\circ}(\text{H}^{0/-}) = -1.137$ V (V vs $\text{Fc}^{+/0}$) (Fc = ferrocene),²³ and choosing the reduction potentials of **X** and **XH** measured by OSWV method (Table 1) as $E^{\circ}(X^{0/-})$ and $E^{\circ}(XH^{0/-})$, since the values from OSWV were identified to be closer to the corresponding standard redox potentials than the values from CV.²⁹ ^cThe values derived by OSWV were chosen as the standard reduction potentials of **X** and **XH**. ^dDerived from eq 12.

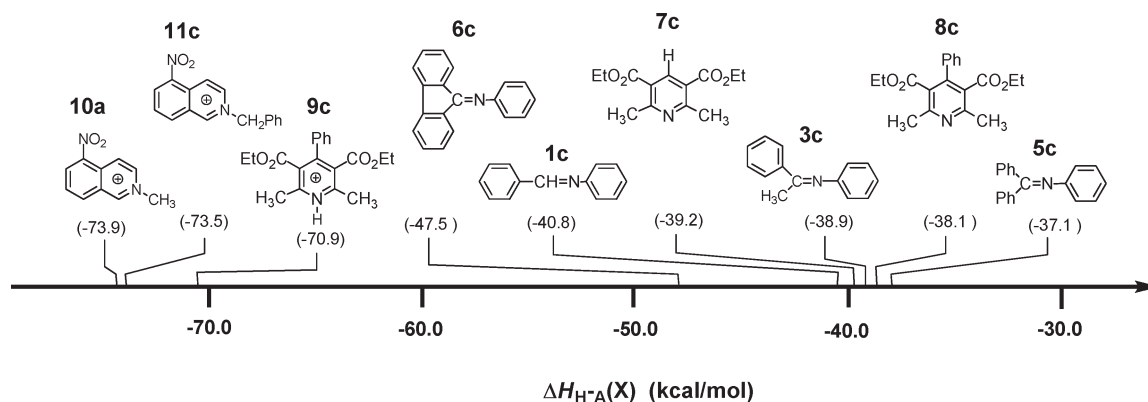


FIGURE 4. Comparison of hydride affinities of some typical neutral and charged imines in acetonitrile.

affinities of $X^{\bullet-}$ all are quite large (generally more negative than -62 kcal), which means that whether the reaction intermediates $X^{\bullet-}$ are charged or not, they all belong to strong hydrogen acceptors. When the proton affinities of the reaction intermediates $X^{\bullet-}$ are examined in detail, it is found that, when the substituent is the same (such as, $\text{G} = \text{H}$), the proton affinities of the reaction intermediates $X^{\bullet-}$ decrease in the order $4^{\bullet-}$ (-33.0 kcal) $>$ $7^{\bullet-}$ (-32.2 kcal) $>$ $6^{\bullet-}$ (-28.0 kcal) \sim $8^{\bullet-}$ (-28.0 kcal) $>$ $1^{\bullet-}$ (-27.3 kcal) $>$ $5^{\bullet-}$ (-23.6 kcal) $>$ $10^{\bullet-}$ (-13.2 kcal, $\text{G} = \text{CH}_3$) $>$ $11^{\bullet-}$ (-10.2 kcal) $>$ $9^{\bullet-}$ (5.6 kcal) (see Figure 8), and from Figure 8, it is found that when the reaction intermediates $X^{\bullet-}$ are charged ($\text{X} = \mathbf{1-8}$) the proton affinities are quite large (generally more negative than -19.0 kcal), indicating that the negatively charged radicals of imines are ascribed to strong bases; however, when the reaction intermediates $X^{\bullet-}$ are uncharged ($\text{X} = \mathbf{9-11}$), the proton affinities all are quite small (generally more positive than -13.0 kcal); even more, some of them become positive values (such as 8.3 kcal for $\text{X} = \mathbf{9}$, when $\text{G} = m\text{-NO}_2$), indicating that the uncharged radicals $X^{\bullet-}$ ($\text{X} = \mathbf{9-11}$) are generally ascribed to very weak bases, and the basicities of some uncharged reaction intermediates $X^{\bullet-}$, such as $\text{X} = \mathbf{9}$ are weaker than that of acetonitrile. These results indicate that the charge effect on proton affinities of the reaction intermediates $X^{\bullet-}$ is markedly larger than that on the corresponding hydrogen affinities.

Since the hydrogen affinities of the reaction intermediates $X^{\bullet-}$ are larger than the corresponding proton affinities by more than 34.9 kcal for the negatively charged radicals $X^{\bullet-}$ ($\text{X} = \mathbf{1-8}$) and by more than 55.3 kcal for the uncharged radicals $X^{\bullet-}$ ($\text{X} = \mathbf{9-11}$), respectively, it is conceived that when the imines

(**X**), especially the protonated or positively charged imines (**9–11**), are reduced by organic hydride donors, such as NADH or its models, the hydrogen-atom transfer should be much more favorable than the corresponding proton transfer in the second step reaction when the reductions of imines were initiated by electron transfer. As a consequence, we can suggest that the $e^- - \text{H}^{\bullet}$ sequence hydride transfer should be most likely among the possible multistep mechanisms for the reductions of imines, especially for the imines with positive charge by organic reducing agents (Scheme 1), if the hydride transfer were initiated by single-electron transfer.

If the hydrogen affinities of the reaction intermediates $X^{\bullet-}$ and their corresponding parent imines (**X**) were compared (see columns 3 and 4 in Table 2 or Figures 6 and 7), it is clear that the hydrogen affinities of the reaction intermediates $X^{\bullet-}$ are generally much larger than those of the corresponding parent imines (**X**). Since the value of the hydrogen affinity is dependent not only on the formation energy of new C–H σ -bond but also on the breaking energy of the old C=N π -bond, the term that the differences of the two hydrogen affinities of $X^{\bullet-}$ and **X** is divided by the hydrogen affinities of the reaction intermediates $X^{\bullet-}$ (eq 12) can be used to scale the activation degree (or the weaken degree) of the C=N π -bond in the imines by electron addition. This term, in this work, may be defined as activation coefficients of C=N π -bond by electron ($A_c\%$ in eq 12). The detailed activation coefficients of the 61 imines in acetonitrile are summarized in Table 2. From Table 2, it is clear that when the imines are **1–5** and **8**, the activation coefficients ($A_c\%$) are generally larger than 50% but smaller than 60% ; when the imines are **9**, the

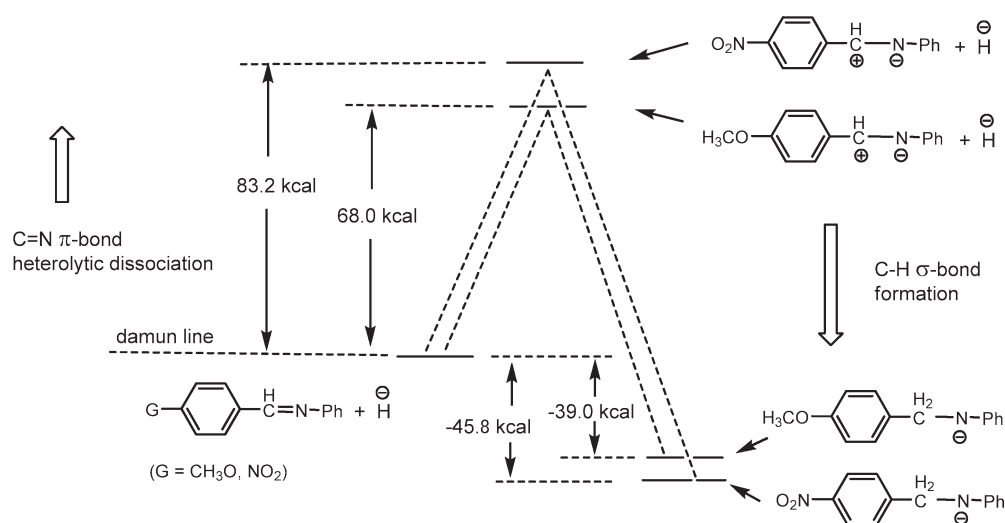


FIGURE 5. Comparison of potential energy changes for the reductions of imine **1a** ($G = \text{CH}_3\text{O}$) and imine **1g** ($G = \text{NO}_2$) by hydride anion in acetonitrile.

TABLE 3. Heterolytic and Homolytic Dissociation Energies of C=N π -Bond in the Imines (kcal)

imines (X)	$\Delta H_{\text{het}}(\pi\text{-bond})^a$	$\Delta H_{\text{homo}}(\pi\text{-bond})^b$	$\Delta H_{\text{homo}}(\pi\text{-bond})^{*-c}$	$\Delta\Delta H^d$	$\Delta\Delta H^{*e}$
1(a-g)					
CH_3O (a)	68.0	62.5	20.3	5.5	42.2
CH_3 (b)	72.1	61.8	20.0	10.3	41.8
H (c)	77.2	61.7	20.3	15.5	41.4
Cl (d)	76.4	61.1	20.1	15.3	41.0
Br (e)	77.4	61.7	20.7	15.7	41.0
CF_3 (f)	81.5	61.2	21.7	20.3	39.5
NO_2 (g)	83.2	61.2	23.2	22.0	38.0
3(a-e)					
CH_3O (a)	69.6	60.9	17.3	8.7	43.6
CH_3 (b)	76.8	60.7	16.9	16.1	43.8
H (c)	79.1	60.6	17.5	18.5	43.1
Cl (d)	78.7	60.4	19.3	18.3	41.1
NO_2 (e)	85.1	58.9	24.3	26.2	34.6
8(a-g)					
<i>p</i> - CH_3O (a)	70.3	66.5	17.9	3.8	48.6
<i>p</i> - CH_3 (b)	74.9	66.3	18.2	8.6	48.1
<i>p</i> -H (c)	79.9	65.6	18.4	14.3	47.2
<i>p</i> -Cl (d)	79.5	65.0	18.7	14.5	46.3
<i>p</i> -Br (e)	79.9	64.8	18.5	15.1	46.3
CF_3 (f)	84.6	64.0	18.9	20.6	45.1
<i>p</i> - NO_2 (g)	86.2	63.1	19.2	23.1	43.9
9(a-e)					
<i>p</i> - CH_3O (a)	38.2	62.3	23.3	-24.1	39.0
<i>p</i> - CH_3 (b)	42.4	61.7	23.6	-19.3	38.1
<i>p</i> -H (c)	47.1	60.7	24.1	-13.6	36.6
<i>p</i> -Cl (d)	47.2	60.1	25.0	-12.9	35.1
<i>p</i> - NO_2 (e)	54.3	58.0	25.4	-3.7	32.6

^aDerived from the eq: $\Delta H_{\text{het}}(\pi\text{-bond}) = \Delta H_{\text{H-A}}(\text{X}) - \Delta H_{\text{H-A}}[(\text{G})\text{-PhCH}_2^+]$.³⁵ ^b $\Delta H_{\text{homo}}(\pi\text{-bond}) = \Delta H_{\text{H-A}}(\text{X}) - \Delta H_{\text{H-A}}(\text{PhCH}_2^*)$.³⁷ ^c $\Delta H_{\text{homo}}(\pi\text{-bond})^{*-} = \Delta H_{\text{H-A}}(\text{X}^{*-}) - \Delta H_{\text{H-A}}(\text{PhCH}_2^*)$.³⁷ ^d $\Delta\Delta H = \Delta H_{\text{het}}(\pi\text{-bond}) - \Delta H_{\text{homo}}(\pi\text{-bond})$. ^e $\Delta\Delta H^* = \Delta H_{\text{homo}}(\pi\text{-bond}) - \Delta H_{\text{homo}}(\pi\text{-bond})^{*-}$.

activation coefficients ($A_c\%$) are generally larger than 40% but smaller than 50%; when the imines are **6**, **10**, and **11**, the

π -bond activation coefficients ($A_c\%$) are generally larger than 30% but smaller than 40%. According to the molecular structure resonance of view,³⁸ the objective (or natural) structure of X^{*-} could be expressed by several different subjective (or theoretical) resonance structures, such as the idealized Lewis-type structure with the C=N π -bond retained (**I**), the idealized Lewis-type resonance structure with C=N π -bond broken (**II**), and some others. Since the resonance structure (**II**) is merely one efficient (or allowable) Lewis-type structure of X^{*-} among the resonance structures of X^{*-} with C=N π -bond broken to accept hydrogen atom or proton,³⁹ it is conceivable that the activation coefficient ($A_c\%$) can scale the percent of the resonance structure (**II**) of X^{*-} in the total of the all resonance structures of X^{*-} .

Since the idealized Lewis-type structure with C=N π -bond broken (**II**) directly express the localized state of single electron and negative charge in reaction intermediates X^{*-} , $A_c\%$ can be used to measure the relative effective spin intensity on the molecular spin center atom or to measure the relative effective negative charge on the molecular negatively charged center atom. Figures 9 and 10 show the relative effective spin density and the relative effective negative charge on the center atom in the reaction intermediates X^{*-} , respectively. From Table 2, it is clear that the relative effective spin density on the molecular center atom increases in the order $10\text{a}^{*-} < 11\text{c}^{*-} < 6\text{c}^{*-} < 7\text{c}^{*-} < 9\text{c}^{*-} < 1\text{c}^{*-} (2\text{c}^{*-}) < 3\text{c}^{*-} (4\text{c}^{*-}) < 5\text{c}^{*-} < 8\text{c}^{*-}$. Evidently, for the radical reaction intermediates of imines (X^{*-}), the activation coefficients of C=N π -bond by electron ($A_c\%$) can be used to predict the kinetic driving force of the radicals for dimerization or polymerization with other radicals since the dimerization or polymerization rates of the radicals should be directly dependent on the effective spin density on the molecular center atom. Meanwhile, for the charged radicals of imines (see Figure 10), since the effective spin density on

(38) (a) Pauling, L.; Wheland, G. W. *J. Chem. Phys.* **1933**, *1*, 362. (b) Wheland, G. W.; Pauling, L. *J. Am. Chem. Soc.* **1935**, *57*, 2086. (c) Wheland, G. W. *The Theory of Resonance and Its Application to Organic Chemistry*; John Wiley: New York, 1955. (d) Pauling, L. *Nature of the Chemical Bond*, 3rd ed.; Cornell University Press: Ithaca, NY, 1960.

(39) Although the protonated Hantzsch ester **9** still has some other resonance structures with two π -bonds in the pyridine ring, such as the resonance structures with positive charge on the 2-position carbon, these resonance structures all are regarded as inefficient resonance structures because they cannot be converted into 1,4-dihydropyridine esters.

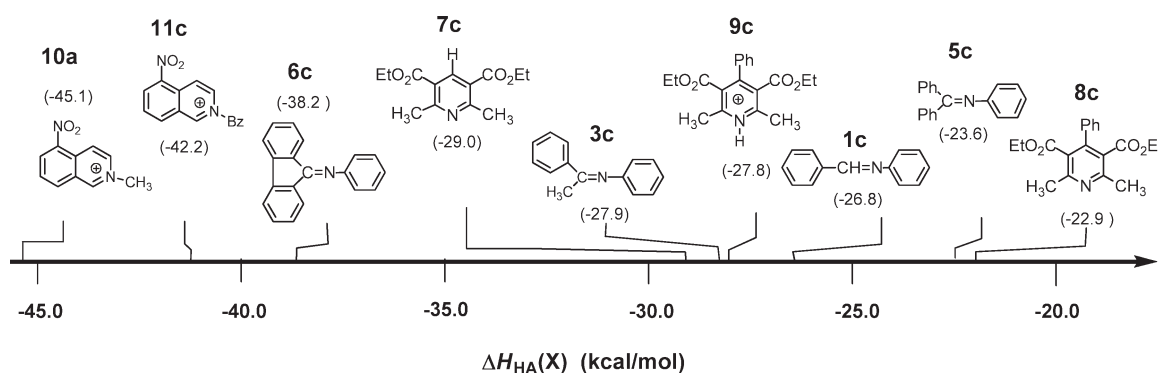


FIGURE 6. Comparison of hydrogen affinities of some typical neutral and charged imines in acetonitrile.

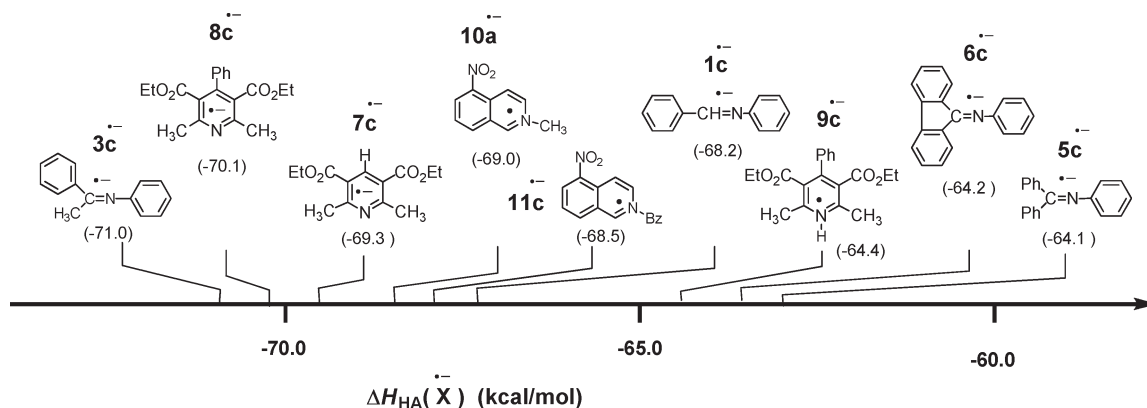


FIGURE 7. Comparison of hydrogen affinities of some typical neutral and negatively charged radicals of imines in acetonitrile.

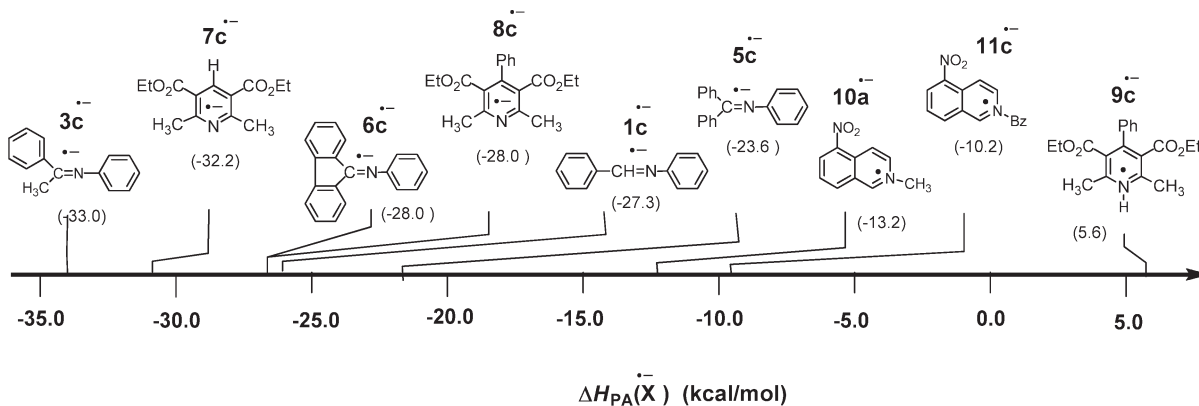


FIGURE 8. Comparison of proton affinities of the corresponding neutral or negatively charged radicals of some typical imines ($X^{\bullet-}$) in acetonitrile.

the molecular spin center atom is equal to effective negative charge density on the molecular negative charge center atom, the activation coefficients of C=N π -bond by electron ($A_c\%$) can be also used to measure the kinetic driving force of the radical anions of imines for nucleophilic additions or nucleophilic substitutions. In fact, these predictions have been

well supported by some experimental observations.^{40–43}

$$A_c\% = \frac{\Delta H_{HA}(X^{\bullet-}) - \Delta H_{HA}(X)}{\Delta H_{HA}(X^{\bullet-})} \quad (12)$$

Electron Affinities of the Imines (X) and Their Reaction Intermediate XH in Acetonitrile. As well-known, the standard reduction potentials of imines and their reaction intermediates XH are very important electrochemical parameters, which can be used as an indicator of the electron-obtaining ability of X and XH in thermodynamics. From column 6 in Table 2, it is found that the one-electron reduction potentials of the imines (1–11) [$E^0(X^{0/-})$] range from -1.710 to -2.624 (V vs

(40) (a) Marquet, J.; Moreno-Manas, M.; Pacheco, P.; Prat, M.; Katritzky, A. R.; Brycki, B. *Tetrahedron* **1990**, *46*, 5333–5346.

(41) (a) Kano, K.; Matsuo, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3269–3273. (b) Kano, K.; Matsuo, T. *Tetrahedron Lett.* **1975**, *16*, 1389–1392.

(42) Sato, T.; Inoue, T.; Mukaiyama, T. *Chem. Lett.* **1975**, 637–640.

(43) (a) Khan, N. H.; Zuberi, R. H.; Siddiqui, A. A. *Synth. Commun.* **1980**, *10*, 363–371. (b) Zuberi, R. H. *Sci. Environ.* **1982**, *4*, 71–76.

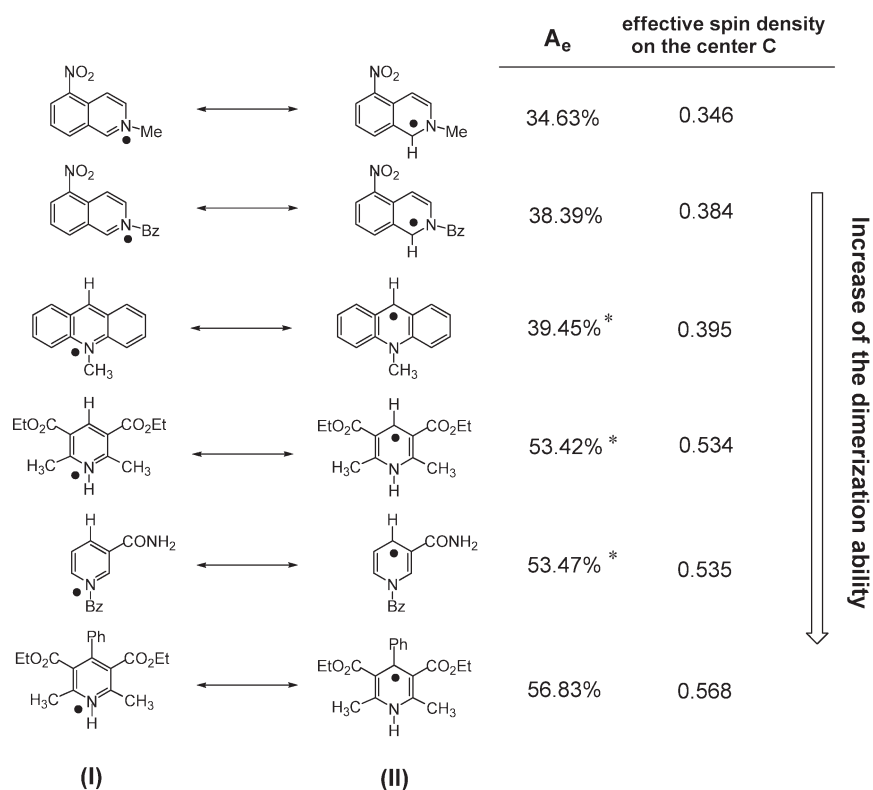


FIGURE 9. Relative effective spin density on the center carbon atom for some neutral radicals of imines (* the values are derived from ref 29).

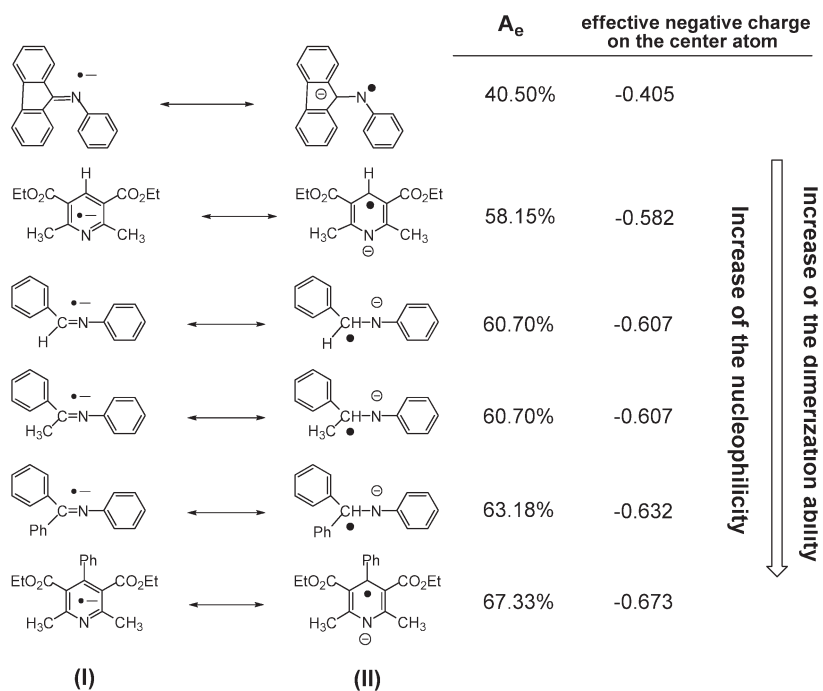


FIGURE 10. Relative effective negative charge on the center atom for some typical radical anions of imines, the effective negative charge on the atoms in the delocalized molecular resonance structure herein was defined as zero.

$Fc^{+/0}$ for the neutral imines (1–8) and from -0.634 to -0.980 (V vs $Fc^{+/0}$) for the positively charged imines (9–11). Since the one-electron reduction potentials of the neutral imines are quite negative values, generally more negative than -1.7 V relative to ferrocene, the neutral imines (1–8), especially

attached by electron-donating groups, should belong to very weak one-electron acceptors, but the positively charged imines (9–11), especially attached by electron-withdrawing groups, should belong to good electron acceptors. This result suggests that, in living body, when the neutral imines were reduced by

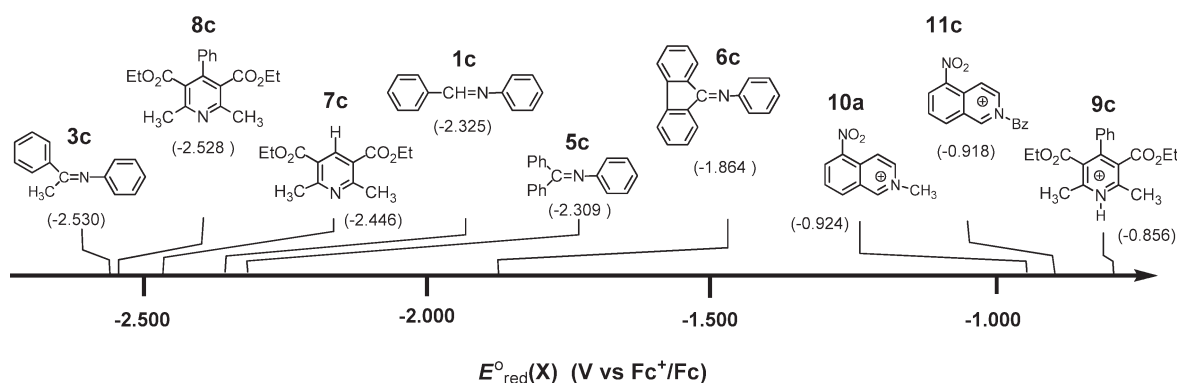


FIGURE 11. Comparison of reduction potentials of some typical neutral and charged imines in acetonitrile.

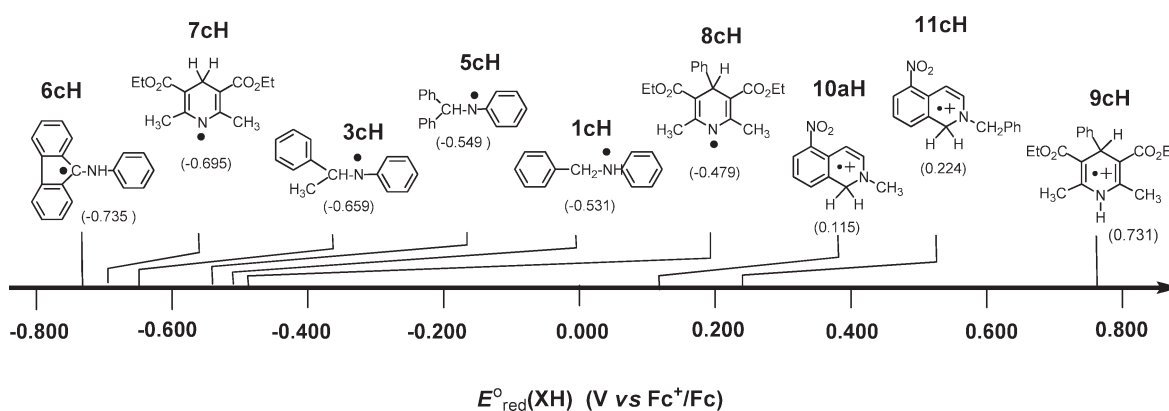


FIGURE 12. Comparison of electron affinities of some typical neutral and charged radicals of imines in acetonitrile.

natural organic reducing agents (NADH and Vitamin C), the mechanism initiated by one-electron transfer is impossible because the oxidation potentials of NADH and Vitamin C in pH = 7 aqueous solution are 0.280 and -0.276 (V vs $\text{Fc}^{+/0}$), respectively, and electron transfer to the neutral imines takes at least 46 and 33 kcal heat (or other energy) from NADH and from Vitamin C, respectively. However, for the positively charged imines especially attached by one or multiple strong electron-withdrawing groups, it is likely that the reduction was initiated by electron transfer, especially when vitamin C was used as the hydride donor.

In order to more intuitively disclose the effect of structure, charge, and protonation of imines on the electron-obtaining abilities of the imines, the 11 imines (**1–11**, G = H) were ranked in a row according to their one-electron reduction potentials from negative (left) to positive (right) (Figure 11). From Figure 11, it is clear that the electron-obtaining abilities of 11 imines (**1–11**, G = H) increase in the order **3c(4c)** < **8c** < **7c** < **1c(2c)** < **5c** < **6c** < **10a** < **11c** < **9c**. Comparison of imine **8c** and its protonated imine **9c** shows that the reduction potential of **9c** is more positive than that of **8c** by about 1.672 V, which means that protonation of imines can increase the electron-obtaining ability of imines by about 1.672 V (equivalent to 38.6 kcal), which is not only much larger than the effect of the protonation on the hydrogen-obtaining ability of the imine (5.1 kcal) but also markedly larger than the effect of the protonation on the hydride-obtaining ability of the imine (32.8 kcal). This result suggests that the protonation of imines is more propitious to the

reduction of imines by electron transfer than by hydrogen atom or by hydride anion.

From column 7 in Table 2, it is found that the one-electron reduction potentials of the reaction intermediates of imines (XH) [$E^\circ(\text{XH}^{0/-})$] range from -0.790 (V vs $\text{Fc}^{+/0}$) for **6aH** to 0.781 (V vs $\text{Fc}^{+/0}$) for **9fH**. Figure 12 shows an intuitive comparison of some representative reduction potentials of XH. From Figure 12, it is clear that the reduction potentials of the positively charged XH (X = **9–11**) are much more positive than those of the neutral XH (X = **1–8**), which suggests that the positive charge on the reaction intermediates of imines (XH) can markedly promote their electron-obtaining abilities. If the reduction potentials of **8H** and their corresponding protonated species (**9H**) are compared, it is found that protonation can promote the reduction potentials of XH by about 1.2 V (equivalent to 27.7 kcal), which means that the effect of protonation on the reduction potentials of XH is smaller than that on the reduction potentials of the corresponding parent imine (X) (about 1.7 V).

Effects of the Remote Substituents on the Chemical Affinities of Imines and Their Various Reaction Intermediates. From Table 2, it is clear that the hydride affinities, hydrogen affinities, and proton affinities as well as redox potentials of imines and their various reduction intermediates are not only strongly dependent on the structure and charge of imines but also largely dependent on the nature of the remote substituents on the benzene ring. In order to elucidate the relations of the nature of substituents with the chemical affinities and the redox potentials, the remote substituent (G) effects on

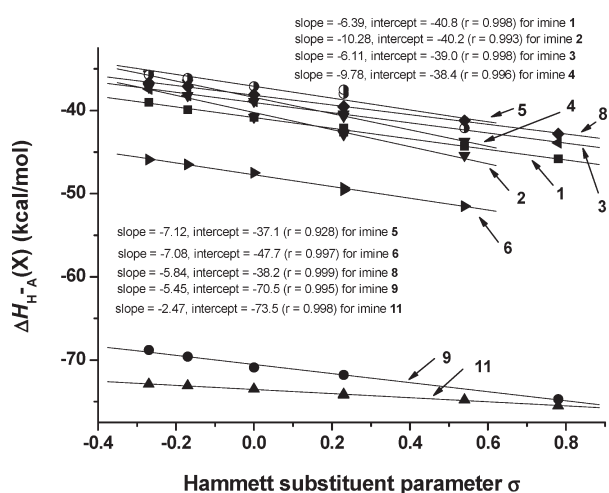


FIGURE 13. Plot of $\Delta H_{H-A}(X)$ against Hammett substituent parameters σ .

the $\Delta H_{H-A}(X)$, $\Delta H_{HA}(X)$, $\Delta H_{PA}(X^{\bullet-})$, and $\Delta H_{HA}(X^{\bullet-})$ as well as on the $E^{\circ}_{red}(X)$ and $E^{\circ}_{red}(XH)$ were examined, and the results show that $\Delta H_{H-A}(X)$, $\Delta H_{HA}(X)$, and $\Delta H_{PA}(X^{\bullet-})$ as well as $E^{\circ}_{red}(X)$ and $E^{\circ}_{red}(XH)$ of the 45 chemical and electrochemical processes all are linearly dependent on the Hammett substituent parameters σ with very good correlation coefficients (see Figure 13 and Figures S1–S4 in Supporting Information), which indicates that the Hammett linear free-energy relationships all hold in the 45 chemical and electrochemical processes. From the slopes and the intercepts of the 45 straight lines in Figure 13 and Figures S1–S4 in the Supporting Information, the corresponding 45 mathematical formulas (eqs 13–57) can be easily derived. Evidently, for any substituted imines X (1–6, 8, 9, and 11) at the *para*- and/or *meta*-position on the benzene ring, it is not difficult to safely estimate the values of $\Delta H_{H-A}(X)$, $\Delta H_{HA}(X)$, and $\Delta H_{PA}(X^{\bullet-})$ according to eqs 13–39 as long as the corresponding Hammett substituent parameters (σ) are available and the standard deviation of the estimations is less than ± 0.50 kcal. In the same way, for any substitution at *para*- and/or *meta*-position imines X (1–6, 8, 9, and 11) and their corresponding reduction intermediates XH, the redox potentials $E^{\circ}_{red}(X)$ and $E^{\circ}_{red}(XH)$ can also be reliably estimated from eqs 40–57 if only the corresponding Hammett substituent parameters are available and the standard deviation of the estimations is less than 30 mV. Since the family of the substituent groups is very large, and the Hammett parameters of most substituents located at the *para*- and *meta*-position can be easily obtained from literature,⁴⁴ it is evident that the 45 formulas should have very extensive application in the prediction of the related chemical potency of the imines and their various reaction intermediates to capture hydride, hydrogen atom, proton, and electron.

$$\Delta H_{H-A}(X) = -6.39\sigma_p - 40.8 \quad \text{for } \mathbf{1} \quad (13)$$

$$\Delta H_{H-A}(X) = -10.28\sigma_p - 40.2 \quad \text{for } \mathbf{2} \quad (14)$$

$$\Delta H_{H-A}(X) = -6.11\sigma_p - 39.0 \quad \text{for } \mathbf{3} \quad (15)$$

$$\Delta H_{H-A}(X) = -9.78\sigma_p - 38.4 \quad \text{for } \mathbf{4} \quad (16)$$

$$\Delta H_{H-A}(X) = -7.12\sigma_p - 37.1 \quad \text{for } \mathbf{5} \quad (17)$$

$$\Delta H_{H-A}(X) = -7.08\sigma_p - 47.7 \quad \text{for } \mathbf{6} \quad (18)$$

$$\Delta H_{H-A}(X) = -5.84\sigma_p - 38.2 \quad \text{for } \mathbf{8} \quad (19)$$

$$\Delta H_{H-A}(X) = -5.45\sigma_p - 70.5 \quad \text{for } \mathbf{9} \quad (20)$$

$$\Delta H_{H-A}(X) = -2.47\sigma_p - 73.5 \quad \text{for } \mathbf{11} \quad (21)$$

$$\Delta H_{HA}(X) = -1.05\sigma_p - 26.7 \quad \text{for } \mathbf{1} \quad (22)$$

$$\Delta H_{HA}(X) = -2.57\sigma_p - 26.0 \quad \text{for } \mathbf{2} \quad (23)$$

$$\Delta H_{HA}(X) = -1.86\sigma_p - 28.0 \quad \text{for } \mathbf{3} \quad (24)$$

$$\Delta H_{HA}(X) = -2.86\sigma_p - 27.6 \quad \text{for } \mathbf{4} \quad (25)$$

$$\Delta H_{HA}(X) = -2.55\sigma_p - 23.6 \quad \text{for } \mathbf{5} \quad (26)$$

$$\Delta H_{HA}(X) = -3.70\sigma_p - 38.6 \quad \text{for } \mathbf{6} \quad (27)$$

$$\Delta H_{HA}(X) = -3.23\sigma_p - 22.8 \quad \text{for } \mathbf{8} \quad (28)$$

$$\Delta H_{HA}(X) = -3.96\sigma_p - 27.5 \quad \text{for } \mathbf{9} \quad (29)$$

$$\Delta H_{HA}(X) = -0.52\sigma_p - 42.2 \quad \text{for } \mathbf{11} \quad (30)$$

$$\Delta H_{PA}(X^{\bullet-}) = 8.06\sigma_p - 27.1 \quad \text{for } \mathbf{1}^{\bullet-} \quad (31)$$

$$\Delta H_{PA}(X^{\bullet-}) = 5.82\sigma_p - 26.4 \quad \text{for } \mathbf{2}^{\bullet-} \quad (32)$$

$$\Delta H_{PA}(X^{\bullet-}) = 11.47\sigma_p - 32.3 \quad \text{for } \mathbf{3}^{\bullet-} \quad (33)$$

$$\Delta H_{PA}(X^{\bullet-}) = 7.42\sigma_p - 32.3 \quad \text{for } \mathbf{4}^{\bullet-} \quad (34)$$

$$\Delta H_{PA}(X^{\bullet-}) = 2.80\sigma_p - 23.7 \quad \text{for } \mathbf{5}^{\bullet-} \quad (35)$$

$$\Delta H_{PA}(X^{\bullet-}) = 2.45\sigma_p - 28.4 \quad \text{for } \mathbf{6}^{\bullet-} \quad (36)$$

$$\Delta H_{PA}(X^{\bullet-}) = 3.78\sigma_p - 27.9 \quad \text{for } \mathbf{8}^{\bullet-} \quad (37)$$

$$\Delta H_{PA}(X^{\bullet-}) = 3.51\sigma_p + 5.6 \quad \text{for } \mathbf{9}^{\bullet-} \quad (38)$$

$$\Delta H_{PA}(X^{\bullet-}) = 0.22\sigma_p - 10.2 \quad \text{for } \mathbf{11}^{\bullet-} \quad (39)$$

$$E^{\circ}_{red}(X) = 0.395\sigma_p - 2.321 \quad \text{for } \mathbf{1} \quad (40)$$

$$E^{\circ}_{red}(X) = 0.371\sigma_p - 2.324 \quad \text{for } \mathbf{2} \quad (41)$$

$$E^{\circ}_{red}(X) = 0.576\sigma_p - 2.492 \quad \text{for } \mathbf{3} \quad (42)$$

$$E^{\circ}_{red}(X) = 0.446\sigma_p - 2.511 \quad \text{for } \mathbf{4} \quad (43)$$

$$E^{\circ}_{red}(X) = 0.232\sigma_p - 2.311 \quad \text{for } \mathbf{5} \quad (44)$$

$$E^{\circ}_{red}(X) = 0.269\sigma_p - 1.864 \quad \text{for } \mathbf{6} \quad (45)$$

$$E^{\circ}_{red}(X) = 0.304\sigma_p - 2.528 \quad \text{for } \mathbf{8} \quad (46)$$

$$E^{\circ}_{red}(X) = 0.324\sigma_p - 0.872 \quad \text{for } \mathbf{9} \quad (47)$$

$$E^{\circ}_{red}(X) = 0.032\sigma_p - 0.918 \quad \text{for } \mathbf{11} \quad (48)$$

(44) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.

$$E^{\circ}_{\text{red}}(\text{XH}) = 0.231\sigma_{\text{p}} - 0.522 \quad \text{for } \mathbf{1H} \quad (49)$$

$$E^{\circ}_{\text{red}}(\text{XH}) = 0.330\sigma_{\text{p}} - 0.520 \quad \text{for } \mathbf{2H} \quad (50)$$

$$E^{\circ}_{\text{red}}(\text{XH}) = 0.188\sigma_{\text{p}} - 0.657 \quad \text{for } \mathbf{3H} \quad (51)$$

$$E^{\circ}_{\text{red}}(\text{XH}) = 0.300\sigma_{\text{p}} - 0.667 \quad \text{for } \mathbf{4H} \quad (52)$$

$$E^{\circ}_{\text{red}}(\text{XH}) = 0.197\sigma_{\text{p}} - 0.552 \quad \text{for } \mathbf{5H} \quad (53)$$

$$E^{\circ}_{\text{red}}(\text{XH}) = 0.146\sigma_{\text{p}} - 0.742 \quad \text{for } \mathbf{6H} \quad (54)$$

$$E^{\circ}_{\text{red}}(\text{XH}) = 0.113\sigma_{\text{p}} - 0.472 \quad \text{for } \mathbf{8H} \quad (55)$$

$$E^{\circ}_{\text{red}}(\text{XH}) = 0.065\sigma_{\text{p}} - 0.731 \quad \text{for } \mathbf{9H} \quad (56)$$

$$E^{\circ}_{\text{red}}(\text{XH}) = 0.084\sigma_{\text{p}} - 0.225 \quad \text{for } \mathbf{11H} \quad (57)$$

In addition, from the line slopes in Figure 13 and Figures S1–S4 in the Supporting Information, it is clear that electron-withdrawing groups (G) not only can increase the hydride-accepting ability and electron-obtaining ability of the imines but also can increase the hydrogen-obtaining ability of the imines, which can support the viewpoint that the neutral hydrogen atom has significant nucleophilicity in the organic reaction system.²⁹

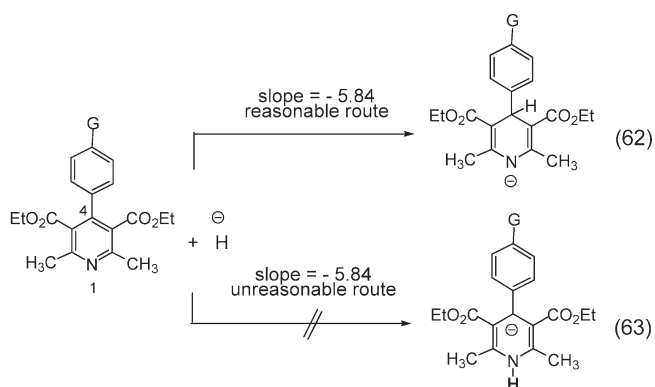
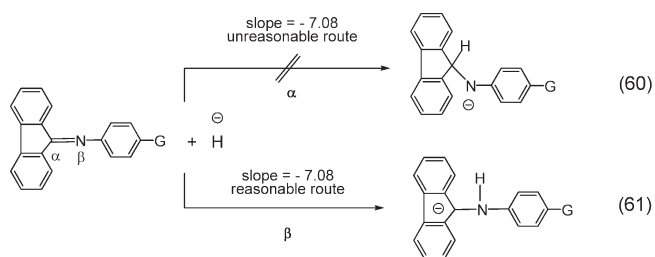
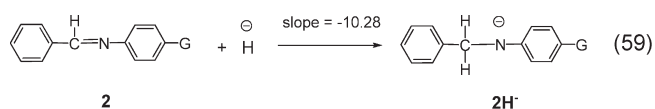
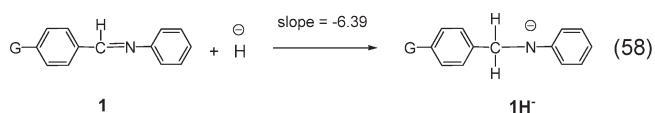
Determination of Polar Direction of C=N Double Bond in the Imines. As is well-known, C=N double bond is an eigen bond of imines. Since the electronegativity of the carbon atom (2.5) is smaller than that of nitrogen atom (3.0),⁴⁵ a common credendum has been accepted by many chemists that C=N double bonds of imines are regarded as a polar chemical bond and the terminal of carbon carries partial positive charge. According to this viewpoint, the following conclusions can be drawn: (i) when imines are reduced by hydride anion, the terminal carbon atom of C=N double bond should be a privileged atom to accept the hydride anion; (ii) for the amines formed from the corresponding imines, acidity of the hydrogen atom contacted with the nitrogen atom should always be larger than that of hydrogen atom contacted with the adjacent carbon atom. However, since the difference in the electronegativities between the carbon atom (2.5) and nitrogen atom (3.0) are not great, this credendum is not always appropriate for all imines. So, it is necessary to develop an efficient method to determine the polar direction of C=N double bond for some well-known and important imines. From our previous papers,⁴⁶ it has been found that Hammett linear free-energy analysis of the remote substituents effect on thermodynamics and/or kinetics of reaction has been verified to be able to provide a very efficient method to estimate the distance between the molecular charge center and the substituent location. If Hammett linear free-energy relationship analysis method were applied in the reduction process of imines by hydride anions, one efficient access could be available to diagnose the polar direction of C=N double bond in the imines. In order to clearly show how to use of the method to diagnose the polar direction of C=N double bond in imines, the effects of

the remote substituent on the hydride affinities of imines **1** and **2** were examined together for comparison. From Figure 13, it is clear that the enthalpy changes for **1** and **2** to accept hydride anions all are excellently linearly dependent on the Hammett substituent parameters σ_{p} with line slopes of -6.39 and -10.28 . According to the root cause of the Hammett substituent effect, it is conceived that the negative sign of the line slope values reflects increase of negative charge density on the reaction center atom during the reduction process of the imines, and the magnitude of the line slope values reflects the sensitivity of the two reductions of imines to the effects of the substituent G changes; that is, the magnitude of the line slope values is a measure of the distance between the molecular negative center and the location of the substituents G in XH^- . Since the absolute value of the line slope for the reduction of imines **2** (-10.28) is much larger than that of the line slope for the reduction of imines **1** (-6.39), it is evident that the negative center atom in $\mathbf{1H}^-$ should be farther away from the substituent G than that in $\mathbf{2H}^-$. Since both $\mathbf{1H}^-$ and $\mathbf{2H}^-$ have the same parent structure, which allows us to safely make a reasonable proposal that the negative center atom in $\mathbf{1H}^-$ and $\mathbf{2H}^-$ should be the nitrogen atom rather than the carbon atom (see eqs 58 and 59), that is, the terminal carbon atom of C=N double bond in **1** and **2** carries partial positive charge and the acidity of hydrogen atom attached at the carbon atom in $\mathbf{1H}_2$ and $\mathbf{2H}_2$ is weaker than that of the hydrogen atom at the nitrogen atom (see Scheme 4). By the same way, if the imines **3** and **4** were examined, the case is just the same as in **1** and **2**; that is, the terminal carbon atoms of C=N double bond in **3** and **4** carry partial positive charge and the acidity of hydrogen atom attached at the carbon atom in $\mathbf{3H}_2$ and $\mathbf{4H}_2$ is also weaker than that of the hydrogen atom at the nitrogen atom. However, if **6** is examined, it is found that the line slope for the reduction of **6** is -7.08 . This value is markedly smaller than that of the line slope for the reduction of **2** (-10.28) but quite close to that of the line slope for the reduction of **1** (-6.39). This result means that the reduction route of imines **6** shown in eq 60 is unreasonable, but the route in eq 61 is reasonable; that is, the terminal carbon atom of C=N double bond in **6** carries partial negative charge and the acidity of hydrogen atom attached at the carbon atom in $\mathbf{6H}_2$ is stronger than that of the hydrogen atom at the nitrogen atom (see Scheme 4). If **5** is examined, it is found that the line slope for the reduction of **5** is -7.12 , which seems to show that the polarity of C=N double bond in **5** is the same as the case of the C=N double bond in **6**. However, if the r values of the line slopes in Figure 13 are examined carefully, it is found that the r value for **5** is not good (0.928) (see Figure 13), which means that only according to the line slope (-7.12), the prediction of polarity of C=N in imine **5** is in lack of safety. However, if the effects of the substituents (G) on the $\Delta H_{\text{H-A}}(\mathbf{5})$ were examined in detail, it is found that, when G is electron-withdrawing groups, the line slope is more negative than -10 (see Figure S5 in Supporting Information), which means that the polarity of C=N double bond in **5** is like the case of C=N double bond in **1** rather than in **6**, but when G is electron-donating groups, the line slope is -5.26 ($r = 0.996$), which means that, in these cases, the polarity of C=N double bond in **5** is like the case in **6**. Here, we were interested to find that, when G changes from electron-withdrawing groups to electron-donating groups, the polarity of C=N in **5** has a reversion

(45) Umland, J. B.; Bellama, J. M. *General Chemistry*, EISBN: 0-534-35872-1, a division of Thomson Learning Asia Pte Ltd. 2001.

(46) (a) Zhu, X.-Q.; Liu, Y.; Zhao, B.-J.; Cheng, J.-P. *J. Org. Chem.* 2001, 66, 370–375. (b) Zhu, X.-Q.; Dai, Z.; Yu, A.; Wu, S.; Cheng, J.-P. *J. Phys. Chem. B* 2008, 112, 11694–11707. (c) Page, M.; Williams, A. *Organic and Bioorganic Mechanisms*; Longman, 1997; Chapter 3, pp 52–79.

(see Scheme 4); the reason could be that the acidities of aniline and diphenylmethane are quite close to each other.⁴⁷ For imine **8** and the corresponding protonated derivative **9**, since the line slopes for the reductions of **8** (−5.84) and **9** (−5.45) are close to the line slope for the reductions of **1** (−6.39), the reduction route of **8** or **9** in eq 62 should be reasonable, but the reduction route in eq 63 should be incorrect; that is, the terminal nitrogen atoms of C=N double bond in **8** could carry partial negative charge, and the acidity of hydrogen atom at the 4-position in **8H₂** should be weaker than that of the hydrogen atom at the 1-position (see Scheme 4).



Thermodynamic Characteristic Graphs (TCGs) of Imines as a “Molecule ID Card”. It is well-known that the structure of an organic compound (such as an imine) can be safely diagnosed or determined according to its characteristic spectra, such as NMR spectrum, IR spectrum, and MS, but the chemical properties of an organic molecule (such as an imine) and its various reaction intermediates could not be directly diagnosed or determined only according to a certain spectrum or graph of the molecule until now. If a certain

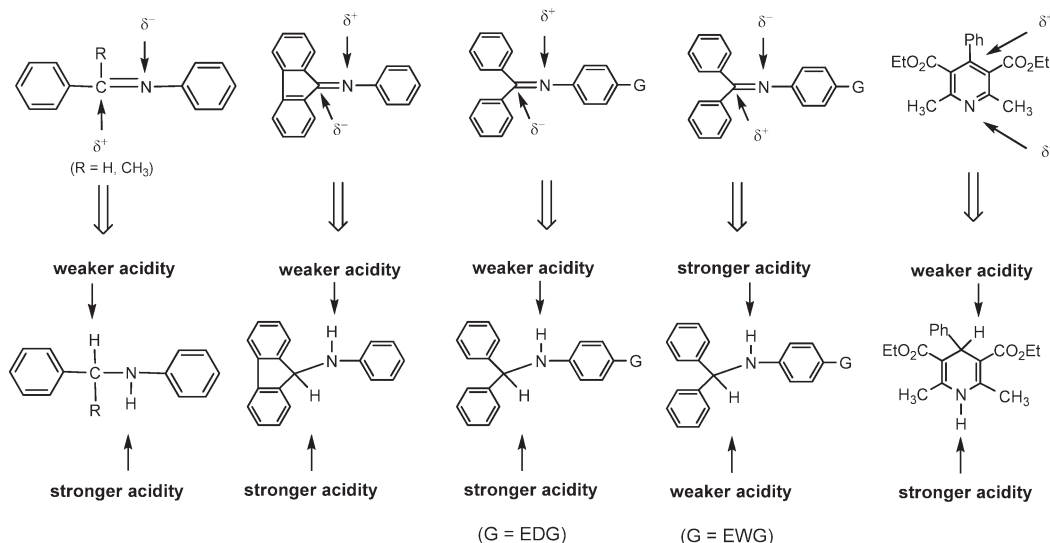
characteristic chemical information graph of a molecule can be produced and can be efficiently used to quantitatively diagnose or scale the characteristic chemical properties of the molecule and its various reaction intermediates, which is like the case of the NMR spectrum and IR spectrum of a molecule, where it can be used to determine the molecular structure, the chemists’ dream for a long time could become reality in that the characteristic graphs of molecules could be reliably designed with various new chemical reactions, safely predicting the possible products of reactions and exactly parse the reaction mechanism. Therefore, developing a characteristic graph of molecule as its “Molecule ID Card”, which contains the essential information about the chemical properties of molecule and its various reaction intermediates, has been my ambition for a long time.

In Table 2, it is found that there are six primary thermodynamic parameters about the characteristic chemical or electrochemical properties of imines (**X**) and their reaction intermediates (**X^{−•}** and **XH**), which have been obtained by using experimental methods in this work. Since the sizes of proton, hydride anion, hydrogen atom, and electron all are quite small, it is conceived that the hydride affinity, hydrogen affinity, proton affinity, and electron affinity of imines and their various reaction intermediates should be the most intrinsic thermodynamic parameters to quantitatively scale the characteristic chemical properties of imines and their various reaction intermediates, such as acidity, basicity, nucleophilicity, electrophilicity, reducibility, oxidizability, and so on, which gives us one efficient access to quantitatively scale the chemical properties of imines and their various reaction intermediates. If the six thermodynamic parameters scaling the different chemical characters of imine and its various reaction intermediates are gathered together according to their mutual conversion to build a graph, it is clear that, for any species among the imines and their various reaction intermediates, one can obtain three characteristic thermodynamic parameters from the graph to quantitatively diagnose the characteristic chemical properties of the species. Since this graph only consists of thermodynamic parameters of imine and its reaction intermediates, this graph, in this work, is defined as the thermodynamic characteristic graph (TCG) of imine, which can be used as a “Molecule ID Card” of the imine to quantitatively diagnose the characteristic chemical properties of the imines and their various reaction intermediates in acetonitrile solution.

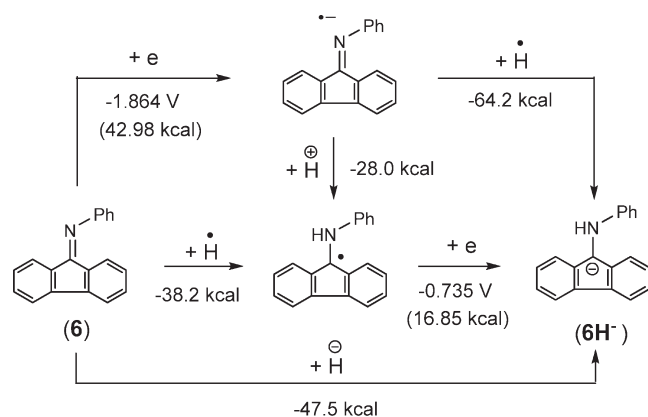
Schemes 5 and 6 are the thermodynamic characteristic graphs of imines **6c** and **7c**. From the TCGs of **6c** and **7c**, the characteristic chemical properties of **6c** and **7c** as well as their various reaction intermediates in acetonitrile can be easily and quantitatively diagnosed (see Tables 4 and 5). In addition, if the reaction system of imines **6c** and **7cH[−]** is examined or diagnosed according to the TCGs of **6c** and **7c**, the following predictions can be safely made (Scheme 7): (i) when **6c** and **7cH[−]** are mixed in acetonitrile, hydride anion transfer is allowed from **7cH[−]** to **6c** to yield **7c** and **6cH[−]**, but hydrogen atom transfer and electron transfer are both forbidden; (ii) when radical anion **6c^{−•}** and neutral radical **7cH** contacted each other in acetonitrile, **6cH[−]** and **7c** as well as **6c** and **7cH[−]** can be formed by hydrogen atom transfer and electron transfer, respectively, but **7c^{−•}** and **6cH[•]** cannot be formed by proton transfer; (iii) when **6cH** and **7c^{−•}** met together in acetonitrile, **6c** and **7cH[−]**, **6c^{−•}** and **7cH**, as well as

(47) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.

SCHEME 4. Polar Direction of C=N Double Bond of the Imines and Relative Acidity of the Two Hydrogen Atoms Attached at the Carbon Atom and the Nitrogen Atom in the Corresponding 2H Adduct of Imines



SCHEME 5. Thermodynamic Characteristic Graph (TCG) of 6c



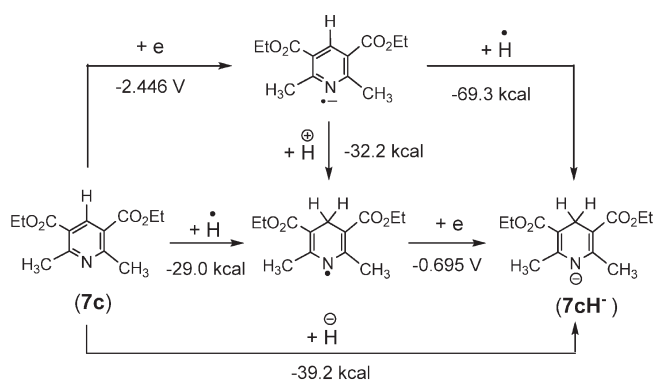
"Molecule ID Card" of Imine 6c

6cH⁻ and 7c all can be formed by hydrogen atom transfer, proton transfer, and electron transfer, respectively, which means that the couple of 7c^{•+} and 6cH is the most active couple of the species in the reaction system; (iv) when imines 7c and 6cH⁻ were mixed in acetonitrile, no reaction was found, which means that the couple of 7c and 6cH⁻ is the most stable couple of the species in this reaction system. Evidently, the thermodynamic characteristic graph (TCG) of the molecule is a very useful chemical information memorizer of molecules, which not only can be used to diagnose the chemical characters of molecules and their various reaction intermediates but also can be used to construct a thermodynamic analysis platform to predict reaction products and analyze the reaction mechanism.

Conclusions

In this work, 61 typical neutral and positively charged imines (X) as a class of very important unsaturated organic compounds were synthesized. Enthalpy changes of the 61

SCHEME 6. Thermodynamic Characteristic Graph (TCG) of Imine 7c







"Molecule ID Card" of Imine 7c

imines to accept a hydride anion and to accept a neutral hydrogen atom as well as the enthalpy changes of their corresponding reaction intermediate (X^{•+}) to accept a hydrogen atom and to accept a proton in acetonitrile were estimated by using experimental method. The standard reduction potentials of the 61 imines (X) and their corresponding radicals (XH) were examined by using CV and OSWV methods, respectively. After detailed examination of the determined enthalpy changes and redox potentials as well as the remote substituent effects on the enthalpy changes and the redox potentials, the following conclusions can be made:

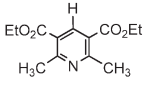
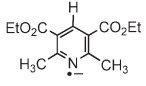
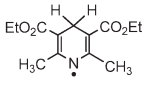
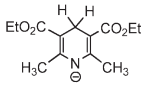
- (1) The neutral imines, especially attached by strong electron-donating groups, belong to very weak hydride acceptors; they cannot directly be reduced by some organic reducing agents, such as NADH and its model BNAH. However, if the neutral imines are positively charged or protonated, especially carrying strong electron-withdrawing groups, they become strong or midstrong hydride acceptors and can be directly reduced by some natural reducing agents and many man-made models without any aid. These results

TABLE 4. Chemical Properties of Imine 6c and Its Various Reaction Intermediates Are Diagnosed According to the TCG of 6c (Scheme 5)

species	parameters*	diagnoses of the characteristic properties
	$\Delta H_{H-A}(6c) = -47.5$ kcal $\Delta H_{HA}(6c) = -38.2$ kcal $E_{red}(6c) = -1.864$ V	mild hydride acceptor, mild electrophilic agent mild hydrogen acceptor, small dimerizability weak one-e oxidant
	$\Delta H_{PA}(6c^{\bullet-}) = -28.0$ kcal $\Delta H_{HA}(6c^{\bullet-}) = -64.2$ kcal $E_{ox}(6c^{\bullet-}) = -1.864$ V	strong base strong hydrogen acceptor, large dimerizability strong one-e reductant
	$\Delta H_{PD}(6cH) = 28.0$ kcal $\Delta H_{HD}(6cH) = 38.2$ kcal $E_{red}(6cH) = -0.735$ V	weak acid strong hydrogen donor good one-e oxidant
	$\Delta H_{H-D}(6cH^{\ominus}) = 47.5$ kcal $\Delta H_{HD}(6cH^{\ominus}) = 64.2$ kcal $E_{ox}(6cH^{\ominus}) = -0.735$ V	strong hydride donor, strong nucleophilic agent good hydrogen donor, mild-strong antioxidant strong one-e reductant

*Note: $\Delta H_{PD}(6cH)$, $\Delta H_{HD}(6cH)$, $\Delta H_{H-D}(6cH^{\ominus})$, and $\Delta H_{HD}(6cH^{\ominus})$ are defined as the enthalpy changes of $6cH$ to release proton, to release hydrogen atom, and the enthalpy changes of $6cH^{\ominus}$ to release hydride anion and to release in acetonitrile, respectively. The values are equal to the enthalpy changes of the corresponding opposite species to capture proton, to capture hydrogen atom, or to capture hydride anion in acetonitrile by switch the signs.

TABLE 5. Chemical Properties of Imine 7c and Its Various Reaction Intermediates Are Diagnosed According to the TCG of 7c (Scheme 6)

species	parameters*	diagnoses of the characteristic properties
	$\Delta H_{H-A}(7c) = -39.2$ kcal $\Delta H_{HA}(7c) = -29.0$ kcal $E_{red}(7c) = -2.446$ V	weak hydride acceptor, weak electrophilic agent weak hydrogen acceptor, small dimerizability very weak one-e oxidant
	$\Delta H_{PA}(7c^{\bullet-}) = -32.2$ kcal $\Delta H_{HA}(7c^{\bullet-}) = -69.3$ kcal $E_{ox}(7c^{\bullet-}) = -2.446$ V	strong base strong hydrogen acceptor, large dimerizability very strong one-e reductant
	$\Delta H_{PD}(7cH) = 32.2$ kcal $\Delta H_{HD}(7cH) = 28.0$ kcal $E_{red}(7cH) = -0.695$ V	weak acid strong hydrogen donor, strong anti-oxidant mild-strong one-e oxidant
	$\Delta H_{H-D}(7cH^{\ominus}) = 39.2$ kcal $\Delta H_{HD}(7cH^{\ominus}) = 69.3$ kcal $E_{ox}(7cH^{\ominus}) = -0.695$ V	very strong hydride donor, strong nucleophilic agent mild-strong hydrogen donor, good antioxidant strong one-e reductant

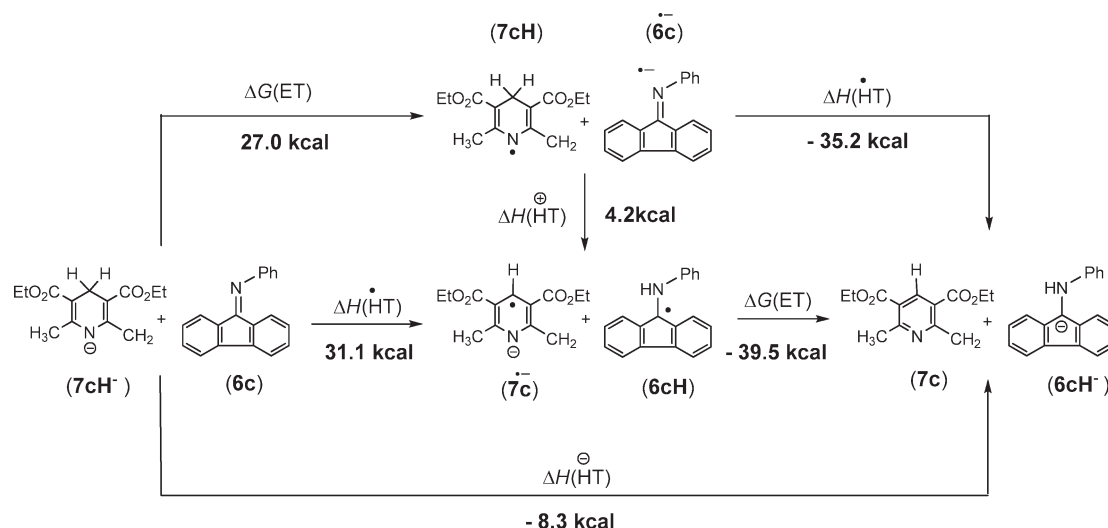
*Note: $\Delta H_{PD}(7cH)$, $\Delta H_{HD}(7cH)$, $\Delta H_{H-D}(7cH^{\ominus})$, and $\Delta H_{HD}(7cH^{\ominus})$ are defined as the enthalpy changes of $7cH$ to release proton, to release hydrogen atom, and the enthalpy changes of $7cH^{\ominus}$ to release hydride anion and to release in acetonitrile, respectively. The values are equal to the enthalpy changes of the corresponding opposite species to capture proton, to capture hydrogen atom, or to capture hydride anion in acetonitrile by switch the signs.

suggest that reduction of neutral imines generally needs promotion by protonation or methylation at the nitrogen atom in advance.

- (2) Since the hydrogen atom affinities of imines, whether charged or not, all are quite small (generally close to or more positive than -45 kcal), all of the imines should belong to very weak hydrogen atom acceptors. The hydrogen atom-obtaining abilities are smaller than that of O_2 (the hydrogen affinity of O_2 is estimated to be -48.2 kcal).⁴⁸ As the hydrogen affinities of imines are quite smaller (or much more positive) than the corresponding hydride affinities, it is conceived that the reduction of imines is much more favorable by hydride anion over the neutral hydrogen atom.

- (3) The one-electron reduction potentials of neutral imines are generally close to or more negative than -2.000 (V vs $Fc^{+/0}$), which suggests that neutral imines should be very poor one-electron acceptors; that is, reduction of the neutral imines should be difficult with general single-electron reducing agents. However, for the positively charged imines, it is possible that the reductions take place with general single-electron reducing agents because the one-electron reduction potentials of the positively charged imines are not quite negative (generally, more positive than -1.000 V vs $Fc^{+/0}$).
- (4) For the radicals of imines (X^{\bullet}), since the enthalpy changes of the radicals, whether charged or not, to accept a hydrogen atom all are quite negative, generally much more negative than -60.0 kcal/mol, the radicals whether charged or not should belong to strong or midstrong hydrogen atom acceptors, which indicates that the radicals of imines (X^{\bullet}), especially

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SCHEME 7. Thermodynamic Diagnoses of Possible Hydride Transfer Mechanisms between $7cH^-$ and $6c$ 

without charge ($X = 9-10$), are easy to form dimers.⁴⁹ With the proton-accepting ability of the radicals, if the radical is neutral, the radicals belong to weak proton acceptors (weak base), but if the radical is negatively charged, the radical becomes a strong proton acceptor (strong base). Since the oxidation potentials of the charged radicals of imines are generally negative at -2.000 (V vs $Fc^{+/0}$), it should be very difficult to directly detect the charged radicals of imines in the lab because trace oxygen is enough to oxidize them (the reduction potential of O_2 is about -1.200 (V vs $Fc^{+/0}$) in 1 atm). However, for the neutral radicals of imines, since the oxidation potentials are generally more positive than -1.000 (V vs $Fc^{+/0}$), it should not be very difficult to directly detect them by using conventional experimental methods in the lab.

- (5) The hydrogen adduct of the imine (XH) is the good one-electron oxidizing agent, especially with positive charge. Among the 11 classes of imines, **9H** is the most strong one-electron oxidation agent; the one-electron oxidizing power is close to that of NO^+ ($E_{1/2} = 0.8265$ V vs $Fc^{+/0}$)⁵⁰ and NO_2^+ ($E_{1/2} = 0.91$ V vs $Fc^{+/0}$).⁵¹ Since the electron-accepting ability of XH is much larger than that of the corresponding parent imines (X), it is conceived that, if the reduction of the imines was initiated by electron transfer from a two-electron reducing agent, the second electron transfer could not be the rate-determining step.
- (6) The substituent effects have excellent Hammett linear free-energy relationships on the enthalpy changes of X to accept hydride and to accept a hydrogen atom and on the enthalpy changes of $X^{\cdot-}$ to accept a proton as well as on the reduction potentials of X and XH, respectively, which means that $\Delta H_{H-A}(X)$, $\Delta H_{HA^-}(X)$, and $\Delta H_{PA}(X^{\cdot-})$ as well as $E_{red}^{\circ}(X)$ and $E_{red}^{\circ}(XH)$

of any substituted imines X all can be safely estimated from the corresponding Hammett linear free-energy relationship formulas (eqs 13–57) if only the Hammett substituent parameters (σ) are available and the standard derivation of the estimations is less than 0.50 kcal and 30 mV for the enthalpy changes and for the redox potentials, respectively.

- (7) For the neutral imines, protonation not only increases their ability to accept a hydride anion and electron but also promotes their ability to accept a hydrogen atom. However, for the radical anions of the imines ($X^{\cdot-}$), protonation not only greatly decreases their proton-accepting ability but also markedly decreases their hydrogen-accepting ability. In addition, the protonation of XH can markedly enhance their electron-accepting ability. These results can be used to examine the reduction mechanism of imines catalyzed by protonic acids.
- (8) The polarity of the $C=N$ bond in the imines has been examined according to Hammett substituent effect, and the results show that, if the imines are **5** (diphenyl imines) with electron-donating groups and **6** (fluorenyl imines), the nitrogen terminal of the $C=N$ bond should carry partial positive charge, but if the imine is the others, the carbon terminal carries partial positive charge.
- (9) The $C=N$ π -bond heterolytic and homolytic dissociation energies of imines **1**, **3**, **8**, and **9** were estimated for the first time. The results show that, when the imines are neutral, the $C=N$ π -bond heterolytic dissociation energies are larger than that corresponding π -bond homolytic dissociation energies, but if the imines are positively charged, the $C=N$ π -bond heterolytic dissociation energies become much smaller than the corresponding π -bond homolytic dissociation energies.
- (10) Thermodynamic characteristic graphs of imines as a novel chemical term were proposed for the first time, which not only quantitatively diagnoses the chemical properties of imines and their various reaction intermediates but also predicts the most likely products and reaction mechanisms.

(49) The radicals with like charge can repel.

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It is evident that these important and hard-to-get hydride affinities, hydrogen affinities, proton affinities, and electron affinities of imines and their various reaction intermediates in acetonitrile, and the conclusions drawn from the effects of substitute, structure of imines, protonation, and the charge on the hydride affinities, hydrogen atom affinities, proton affinities, and electron affinities can provide very important clues to examine the electron structure of imines, design the reduction route of imines, analyze the reaction mechanism, capture the reaction intermediates, predict the reaction direction and tendency, and develop the applications of imines. Especially, the thermodynamic characteristic graphs (TCGs) of imines as an efficient "Molecule ID Card" are proposed for the first time, which can be used to quantitatively diagnose reactivities of organic compounds and their various reaction intermediates.

Experimental Section

Materials. All reagents were commercial quality from freshly opened containers or were purified before use.⁵² 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 (Bu_4NPF_6 , Aldrich) was recrystallized from CH_2Cl_2 and was vacuum-dried at 110°C overnight before preparation of supporting electrolyte solution. 9-Phenylxanthylum ($\text{PhXn}^+\text{ClO}_4^-$) was synthesized according to literature methods.⁵³ *N*-Methylacridinium ($\text{AcrH}^+\text{ClO}_4^-$) was obtained from the exchange of $\text{Na}^+\text{ClO}_4^-$ with AcrH^+I^- in hot water; the latter was prepared according to literature methods.⁵⁴ The 61 imines (X in Scheme 1) were synthesized according to conventional synthetic strategies from the corresponding ketones or aldehydes with primary amines by condensations.⁵⁵ Compounds XH_2 were obtained from the reductions of the corresponding parent imines by NaBH_4 in THF or by Zn in alkalized $\text{C}_2\text{H}_5\text{OH}$, and the final products were identified by ^1H NMR and MS. The hydride adducts of imines (XH^-) were prepared according to Arnett's method.⁵⁶ The anion precursor (XH_2^-) was

dissolved in dry acetonitrile, and then a slightly excess amount of KH was added. The mixture was stirred at room temperature for about 20 min and then filtered directly into the reaction vessel. All operations were carried out in an argon-filled glovebox.

Measurement of Redox Potentials. The electrochemical experiments were carried out by cyclic voltammetry (CV) and Osteryoung square wave voltammetry (OSWV) using a BAS-100B electrochemical apparatus in deaerated acetonitrile under argon atmosphere at 298 K as described previously.⁵⁰ *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 a counter electrode, and 0.1 M AgNO_3/Ag (in 0.1 M *n*- $\text{Bu}_4\text{NPF}_6/\text{acetonitrile}$) as reference electrode. The ferrocenium/ferrocene redox couple ($\text{Fc}^{+/0}$) was taken as the internal standard. The reproducibilities of the potentials were usually ≤ 5 mV for ionic species and ≤ 10 mV for neutral species.

Isothermal Titration Calorimetry (ITC). The titration experiments were performed on a CSC4200 isothermal titration calorimeter in acetonitrile at 298 K as described previously.⁵⁷ The performance of the calorimeter was checked by measuring the standard heat of neutralization of an aqueous solution of sodium hydroxide with a standard aqueous HCl solution. Data points were collected every 2 s. The heat of reaction was determined following eight automatic injections from a $250\ \mu\text{L}$ injection syringe containing a standard solution (≈ 2 mM) into the reaction cell (1.30 mL) containing 1 mL of other concentrated reactant (≈ 15 mM). Injection volume ($5\ \mu\text{L}$) was delivered at 0.5 s time interval with 300 s between every two injections. The reaction heat was obtained by integration of each peak except the first.⁵⁸

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Supporting Information Available: Plots of $\Delta H_{\text{HA}}(\text{X})$, $\Delta H_{\text{PA}}(\text{X}^-)$, $\Delta H_{\text{HA}}(\text{X}^{\bullet-})$, and $\Delta H_{\text{H}^-}(\text{S})$ as well as $E_{\text{red}}(\text{X})$ and $E_{\text{red}}(\text{XH})$ against Hammett substituent parameters σ_p . This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(58) Typically, the first injection shows less heat than expected. This is due to diffusion across the tip of the needle.