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Heterolytic and Homolytic N−H Bond Dissociation Energies of 4-Substituted Hantzsch 2,6-Dimethyl-1,4-dihydropyridines and the Effect of One-Electron Transfer on the N−H Bond Activation

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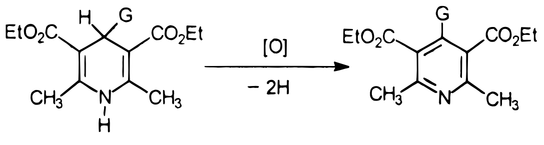
Introduction

Substantial research activities have been devoted in the past to the chemistry and biology of the Hantzsch dihydropyridine derivatives (e.g., Hantzsch esters) because of their wide applications in hot areas such as synthesis of substituted pyridines,[1] serving as effective redox catalysts under mild conditions, modeling the NAD(P)H coenzyme to study its oxidation mechanism in living systems,[2,3] and in seeking new drugs for treating heart vascular diseases,[4,5] and so on.

From the point of view of chemists, the key steps of these biologically related transformations of Hantzsch esters must involve a sequential cleavage of the N−H and C−H bonds of the central dihydropyridine ring (Scheme 1). It is therefore desirable to have knowledge on the energetics of the related bond dissociation in order to understand the currently much-debated mechanisms of the NAD(P)H-mediated formal hydride transfer reactions. Furthermore, because the NAD(P)H model reactions are frequently found to proceed first by a rate-determining one-electron transfer, and followed by a rapid N−H or C−H bond scission of the incipient radical intermediate (e.g., Scheme 2),[1,3,6] it would also be beneficial if the quantitative measures of the dissociation energies of the corresponding electron-transfer activated bonds are available. However, despite the obvious importance and the great need of the bond energy data of the NAD(P)H model compounds, essentially no such information, either for the neutral models, or for their corresponding radical ions, has yet been released in the literature.[7]

We have recently carried out some investigations on the cleavage energies of different types of chemical bonds and on their applications in analyzing various chemical and biological problems,[9] where a mechanistic study of the NAD(P)H-model-mediated reactions on the basis of a detailed energetic analysis was exemplified.[9e] This work is now extended to include the N−H bond energies of NAD(P)H model compounds and the comparisons of the driving forces for the five (out of seven[10]) possible bond scission processes (eqs 1−5). The substituted Hantzcsh esters (**1a**−**g**) were chosen as the representative NAD(P)H-model family because of the above-mentioned importance of this group of compounds. The N−H bond energies obtained in this work, to our best knowledge, constitute the first collection of the bond energetic data for the dihydropyridine systems and would provide a versatile data platform which not only allows a parallel comparison of the dissociation energetics of the same N−H bond under different oxidations states, but will also facilitate derivation of other energetic data in the future on the basis of suitable thermochemical cycles.[11]

Scheme 1



1 **2**

G = H (**a**), *i*-Pr (**b**), Ph (**c**), 4-$MeOC_6H_4$ (**d**), 4-MeC_6H_4 (**e**), 4-ClC_6H_4 (**f**), 4-CNC_6H_4 (**g**)

$$RH \rightarrow R^{\ominus} + H^{\oplus} \tag{1}$$

$$RH \rightarrow R^{\bullet} + H^{\bullet} \tag{2}$$

$$RH^{\bullet +} \rightarrow R^{\bullet} + H^{\oplus} \tag{3}$$

$$RH^{\bullet -} \rightarrow R^{\bullet} + H^{\ominus} \tag{4}$$

$$RH^{\bullet -} \rightarrow R^{\ominus} + H^{\bullet} \tag{5}$$

Results and Discussion

The five N−H bond cleavage reaction routes i−v of Hantzsch esters **1** (HEH) and their radical ions are depicted in Scheme 3, together with the necessary equations and cycles for the evaluations of the energetic data (Table 2).

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[1] Vanden Eynde, J.-J.; D'Orazio, R.; Haverbelze, Van Y. *Tetrahedron* **1994**, *50*, 2479.

[2] (a) Meijer, H. P.; Pandit, U. K. *Tetrahedron* **1985**, *41*, 467. (b) Zhu, X. Q.; Liu, Y. C.; Cheng, J.-P. *J. Org. Chem.* **1999**, *64*, 8980.

[3] Lu, Y.; Cheng, J.-P. *Chin Sci. Bull. (Engl. Ed.)* **1996**, *41*, 1881.

[4] Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223.

[5] Bocker, R. H.; Guengerich, F. P. *J. Med. Chem.* **1986**, *29*, 1596.

[6] Taraban, M. B.; Kruppa, N. I.; Polyakov, N. E. *J. Photochem. Photobiol. A: Chem.* **1993**, *73*, 151.

[7] However, the homolytic bond dissociation energy and pK_a of $ArcH_2$ were estimated by Parker[8a] and this group.[8b]

[8] (a) Cheng, J.-P.; Handoo, K. L.; Xue, J.; Parker, V. D. *J. Org. Chem.* **1993**, *58*, 5050. (b) Cheng, J.-P.; Lu, Y. *J. Phys. Org. Chem.* **1997**, *10*, 577.

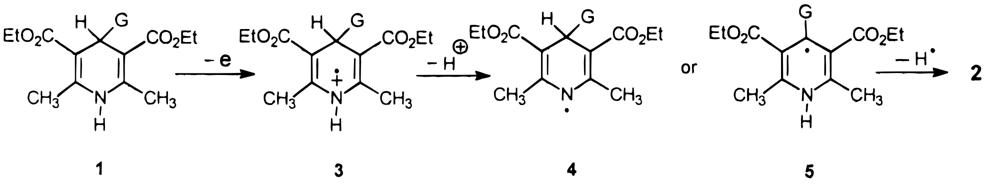
[9] (a) Cheng, J.-P.; Xian, M.; Wang, K.; Zhu, X.-Q.; Yin, Z.; Wang, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10266. (b) Cheng, J.-P.; Wang, K.; Yin, Z.; Zhu, X.-Q.; Lu, Y. *Tetrahedron Lett.* **1998**, *39*, 7925. (c) Cheng, J.-P.; Liu, B.; Zhao, Y.; Zhang, X. M. *J. Org. Chem.* **1998**, *63*, 7072. (d) Cheng, J.-P.; Liu, B.; Zhang, X. M. *J. Org. Chem.* **1998**, *63*, 7475. (e) Cheng, J.-P.; Lu, Y.; Zhu, X.-Q.; Mu, L. J. *J. Org. Chem.* **1998**, *63*, 6108. (f) Cheng, J.-P.; Liu, B.; Zhao, Y.; Sun, Y.; Lu, Y. *J. Org. Chem.* **1999**, *64*, 604. (g) Zhu, X.-Q.; Xian, M.; Wang, K.; Cheng, J.-P. *J. Org. Chem.* **1999**, *64*, 4187.

[10] Because N−H bond is more acidic than C−H bond, it should be first considered and thus was the primary focus of the present work. The inaccessibility of the means for the oxidation potentials of the nitrogen radicals has eliminated an estimation for the other two energetic processes (i.e., the ones produce nitrogen cations) from the present research.

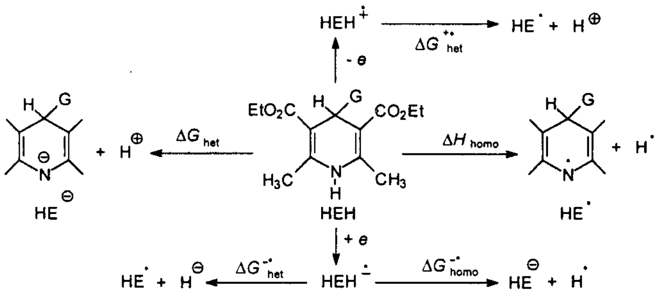
[11] (a) Cheng, J.-P.; Handoo, K. L.; Parker, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2655. (b) Zhang, X. M.; Bordwell, F. G. *J. Org. Chem.* **1992**, *57*, 4163. (c) Zhang, X. M.; Bordwell, F. G. *J. Am. Chem. Soc.* **1992**, *114*, 9787.

10.1021/jo991145v CCC: $19.00

Scheme 2



Scheme 3



route i:

$$\text{N-H} \xrightarrow{\Delta G_{\text{het}}\,(\text{N-H})} \text{N}^{\ominus} + \text{H}^{\oplus}$$

$$\Delta G_{\text{het}}(\text{N-H}) = -\,\text{RT}\ln K_a = 1.364\text{p}K_a \qquad (6)$$

route ii:

$$\begin{tikzcd}\text{NH} \arrow[rrr, bend left, "\Delta H_{\text{homo}}\,(\text{N-H})"] \arrow[r, "\Delta G_{\text{het}}(\text{N-H})"] & \text{N}^{\ominus} + \text{H}^{\oplus} \arrow[r, "E_{\text{ox}}(\text{N}^{\ominus})"] & \text{N}^{\bullet} + \text{H}^{\oplus} \arrow[r, "E(\text{H}^{\oplus}/\text{H})"] & \text{N}^{\bullet} + \text{H}^{\bullet}\end{tikzcd}$$

$$\begin{aligned}\Delta H_{\text{homo}}(\text{N-H}) = \text{BDE} &= \Delta G_{\text{homo}}(\text{N-H}) + \text{F}E_{\text{ox}}(\text{N}^{-}) + \text{C}\\ &= 1.364\text{p}K_a + 23.06\,(\text{N}^{-}) + 73.6\end{aligned} \qquad (7)$$

route iii:

$$\begin{tikzcd}\text{NH}^{+\bullet} \arrow[rrr, bend left, "\Delta G_{\text{het}}\,(\text{NH}^{+\bullet})"] \arrow[r, "-\,E_{\text{ox}}(\text{NH})"] & \text{NH} \arrow[r, "\Delta G_{\text{het}}(\text{N-H})"] & \text{N}^{\ominus} + \text{H}^{\oplus} \arrow[r, "E_{\text{ox}}(\text{N}^{\ominus})"] & \text{N}^{\bullet} + \text{H}^{\oplus}\end{tikzcd}$$

$$\begin{aligned}\Delta G_{\text{het}}(\text{NH}^{+\bullet}) &= \Delta G_{\text{het}} + \text{F}[E_{\text{ox}}(\text{N}^{-}) - E_{\text{ox}}(\text{NH})]\\ &= 1.364\text{p}K_a + 23.06[E_{\text{ox}}(\text{N}^{-}) - E_{\text{ox}}(\text{NH})]\end{aligned} \qquad (8)$$

route iv:

$$\begin{tikzcd}\text{NH}^{-\bullet} \arrow[rrrrr, bend left, "\Delta G_{\text{het}}(\text{NH}^{-\bullet})"] \arrow[r, "E_{\text{rd}}(\text{NH})"] & \text{NH} \arrow[r, "\Delta G_{\text{het}}(\text{N-H})"] & \text{N}^{\ominus} + \text{H}^{\oplus} \arrow[r, "E_{\text{ox}}(\text{N}^{\ominus})"] & \text{N}^{\bullet} + \text{H}^{\oplus} \arrow[r, "E(\text{H}^{\oplus}/\text{H})"] & \text{N}^{\bullet} + \text{H}^{\bullet} \arrow[r, "E(\text{H}/\text{H}^{\ominus})"] & \text{N}^{\bullet} + \text{H}^{\ominus}\end{tikzcd}$$

$$\begin{aligned}\Delta G_{\text{het}}(\text{NH}^{-\bullet}) &= \Delta G_{\text{het}}(\text{N-H}) + \text{F}[E_{\text{ox}}(\text{N}^{-}) + E_{\text{rd}}(\text{NH})] + \text{C}\\ &= 1.364\text{p}K_a + 23.06[E_{\text{ox}}(\text{N}^{-}) + E_{\text{rd}}(\text{NH})] + 94.7\end{aligned} \qquad (9)$$

route v:

$$\begin{tikzcd}\text{NH}^{-\bullet} \arrow[rrr, bend left, "\Delta G_{\text{homo}}(\text{NH}^{-\bullet})"] \arrow[r, "E_{\text{rd}}(\text{NH})"] & \text{NH} \arrow[r, "\Delta G_{\text{het}}(\text{N-H})"] & \text{N}^{\ominus} + \text{H}^{\oplus} \arrow[r, "E_{\text{ox}}(\text{N}^{\ominus})"] & \text{N}^{\ominus} + \text{H}^{\bullet}\end{tikzcd}$$

$$\begin{aligned}\Delta G_{\text{homo}}(\text{NH}^{-\bullet}) &= \Delta G_{\text{het}}(\text{N-H}) + \text{F}E_{\text{rd}}(\text{NH}) + \text{C}\\ &= 1.364\text{p}K_a + 23.06\,E_{\text{rd}}(\text{NH}) + 73.6\end{aligned} \qquad (10)$$

The free energies of the N−H bond heterolysis were derived using eq 6. The pK_a values of the NAD(P)H model compounds in eq 6 were measured in dimethyl sulfoxide solution (DMSO) by Bordwell's indicator method.[12] The energetics of other bond scission processes corresponding to eqs (2−5), i.e., the homolytic bond dissociation energy [ΔH_{homo}(NH), or BDE],[13] the acid dissociation free energy of radical cation [$\Delta G_{\text{het}}(\text{NH}^{+\bullet})$, or p$K(\text{NH}^{+\bullet})$)],[14] the heterolytic dissociation energy of radical anion [$\Delta G_{\text{het}}(\text{NH}^{-\bullet})$)],[11c]

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[12] (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456, and references therein. (b) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006. (c) Zhao, Y.; Huan, Z. W.; Cheng, J.-P. *Chem. J. Chin. Univ.* **1994**, *15*, 207.

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Table 1. Equilibrium Acidities (pK_a's) of Compounds 1a−g and the Relevant Redox Potentials in DMSO at 25 °C

compd, G =	pK_a[a]	$E_{ox}(N^-)$[b]	$E_{ox}(NH)$[c]	$E_{rd}(NH)$[d]
H (**1a**)	19.8	−0.625	0.446	−2.763
i-Pr (**1b**)	20.3	−0.514	0.654	−2.855
C_6H_5 (**1c**)	19.1	−0.384	0.662	−2.742
4-MeOC_6H_4 (**1d**)	19.2	−0.404	0.612	−2.758
4-MeC_6H_4 (**1e**)	19.2	−0.400	0.618	−2.752
4-ClC_6H_4 (**1f**)	18.7	−0.344	0.680	−2.694
4-CNC_6H_4 (**1g**)	18.3	−0.294	0.745	−2.597

[a] Equilibrium acidities (pK_a's) measured in DMSO using Overlapping Indicator method (see Experimental Section). [b] Oxidative E^p values of nitranion in volts versus ferrocium/ferrocene (F_c^+/F_c) redox couple under the conditions as described in Experimental Section. Reproducible to ≤5 mV. [c] Oxidative E^p values of substrate versus F_c^+/F_c. Reproducible to ≤10 mV. [d] Reductive E^p values of versus F_c^+/F_c. Reproducible to ≤10 mV.

Table 2. Bond Cleavage Energies of Processes as Specified in Routes i−v[a]

compd, G =	$\Delta G°_{het}$ (NH)[b]	BDE[c]	$\Delta G°_{het}$ ($NH^{+\bullet}$)[d]	$\Delta G°_{het}$ ($NH^{-\bullet}$)[e]	$\Delta G°_{homo}$ ($NH^{-\bullet}$)[f]
H (**1a**)	27.0	86.2	2.4	44	37
i-Pr (**1b**)	27.7	89.4	0.8	45	35
C_6H_5 (**1c**)	26.1	90.8	2.0	49	36
4-MeOC_6H_4 (**1d**)	26.2	90.5	2.9	48	36
4-MeC_6H_4 (**1e**)	26.2	90.6	2.9	48	36
4-ClC_6H_4 (**1f**)	25.5	91.2	2.0	50	37
4-CNC_6H_4 (**1g**)	25.0	92.8	1.1	53	38

[a] Quantities obtained in DMSO (except otherwise specified) at 25 °C and are expressed in kcal/mol. [b] Derived from eq 6. [c] Gas-phase values calculated using eq 7. [d] Derived from eq 8. [e] Derived from eq 9. [f] Derived from eq 10.

and the homolytic dissociation energy of radical anion [$\Delta G_{homo}(NH^{-\bullet})$][11c] were evaluated using eqs (7−10), respectively. The electrochemical potentials[15] necessary for calculating the respective energetic data are list in Table 1, together with the pK_as determined in the same medium. The minimum energies required for the bond-breaking processes as specified in routes i−v thus derived are presented in Table 2.

Derivations of the quantities for the last four columns in Table 2 require the use of appropriate thermodynamic cycles incorporating the directly determined pK_as with relevant redox data. Similar thermodynamic approaches to derive the otherwise hard-to-get energetic quantities have also been seen frequently in recent literature[16−18] for untackling important chemical problems. A combinative use of various cycles in the present work thus provides an opportunity for parallel comparisons of the relative ease of bond scission processes both within this substituted family and among the different bonding patterns of the same N−H bond. The stabilities of the related reactive intermediates can also be visualized on the basis of the derived energetic data.

Heterolytic and Homolytic N−H Bond Dissociation Energies and the Stabilities of the Corresponding Nitranions and Nitrogen Radicals. An inspection of the pK_a data in Table 1 shows that the secondary N−H bond in **1a** is substantially more acidic than the primary N−H bond attaching directly to a carbonyl group in acetamide (pK_as 19.8 vs 25.5[12a]) and is comparable in acidity with the secondary N−H bond in aromatic carbazole (pK_a = 19.9[12a]). This implies that the Hantzsch dihydropyridine anion possibly adopts a planar or a near-planar homoaromatic structure[19] which allows the negative charge on nitrogen to be effectively delocalized into the two ethoxycarbonyl groups at the 3- and 5-positions. The acidifying effect of the 4-phenyl group is unexpectedly small (ΔpK = 0.7), compared to that on other N−H acids (ΔpK ranging from 4 to 12[12a]), due to a twist of the phenyl ring away from the central plane and the inefficiency of the saturated 4-carbon in transmitting the resonance effect. The acidity changes introduced by the *para* substituents, although not large, follow a pattern expected from their electronic properties. The structural effect on the heterolytic N−H bond energies ΔG_{het}(NH) can be similarly viewed according to eq 6. The nitranion stabilities are therewith exhibited by the pK_a and ΔG_{het} values as both quantities are quantitative measures of anion stability.

The homolytic N−H bond energies (BDE) in Table 2 are, on the other hand, found to be much greater (by 59−68 kcal/mol) than the corresponding ΔG_{het}(NH)'s of the same bonds, indicating that the nitrogen radicals are far less stable than their nitranion counterparts because of a lack of the solvation stabilization. Inspection of the effects of *para* substituents on the BDEs of the 4-aryl-substituted family demonstrates that the dihydropyridinyl radical is stabilized by remote electron-releasing substituents (EDG), but is *destabilized* by remote electron-pulling substituents (EWG). This is a phenomenon which substantially differs from the reported behaviors for most carbon radicals in the literature (where both the EDGs and EWGs were found to be radical-stabilizing),[20] but is similar to the observations on various kinds of heteroatom-centered radicals so far investigated.[21] The findings in the present work further reinforce the hypothesis[13c,22] that radicals centered on an atom of high electronegativity will show "O (opposite)-type" substituent behavior (i.e., the so-called "Class O" radical[23]).

The experimental fact that the BDEs of all the 4-substituted Hantzsch esters (**1b**−**g**) are greater than that of their parent molecule (**1a**) by at least 3.2 kcal/mol is, at first sight, very puzzling, because all the previous BDE measurements indicated that both the alkyl and phenyl groups were radical-stabilizing.[20] This may be understood, however, by considering that the bulky *i*-Pr or Ar group in the present case may destroy the coplanary feature of the dihydropyridine ring, or force the 3- and 5-carbonyl groups to twist with respect to the central

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(14) (a) Bordwell, F. G.; Cheng, J.-P.; Bausch, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 2867. (b) Bordwell, F. G.; Bausch, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 2473.

(15) Well-behaved irreversible peak potentials (E^p) were recorded. Similar phenomena were commonly observed in the literature (e.g., refs 8, 9, 11, 13, and 14) where the uncertainties caused by electrode irreversibility were believed to <2 kcal for absolute values and much smaller for relative values.

(16) (a) Parker, V. D. *J. Am. Chem. Soc.* **1992**, *114*, 7458. (b) Wayner, D. D. M.; McPhee, D. J.; Griller, D. *J. Am. Chem. Soc.* **1988**, *110*, 132.

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(20) (a) McMillen, D. F.; Golden, D. M. *Annu. Rev. Phys. Chem.* **1982**, *33*, 493. (b) Dust, J. M.; Arnold, D. R. *J. Am. Chem. Soc.* **1983**, *105*, 1221 and references therein.

(21) (a) Bordwell, F. G.; Cheng, J.-P. *J. Am. Chem. Soc.* **1991**, *113*, 1736 and references therein. (b) Cheng, J.-P.; Lu, Y.; Liu, B.; Zhao, Y.; Wang, D.; Sun. Y.; Mi, J. *Sci. China Ser. B: Chem.* **1998**, *41*, 215 and references therein.

(22) Cheng, J.-P.; Zhao, Y. *Tetrahedron* **1993**, *49*, 5287.

(23) Walter, R. I. *J. Am. Chem. Soc.* **1966**, *88*, 1923.

plane. It is known that both these structural perturnations substantially reduce the effect of delocalization of substituents on stabilizing the radical. The X-ray single-crystal refraction data of a similar Hantzsch ester[24] do in fact prove that this is indeed the case.

Effect of One-Electron Removal on the N−H Bond Energies. One of the key issues in the NAD(P)H-related mechanistic debates is that whether the hydride is directly transferred from this redox coenzyme to the substrate, or is stepwisely transferred by an electron-transfer-initiated multistep mechanism. While evidence in support of the direct mechanism continues to come out,[25] arguments in favor of the electron-transfer mechanism are also increasingly accumulated.[26] It is well recognized that in the latter cases, an NAD(P)H radical cation intermediate should be formed upon the electron loss, and a proton transfer from the incipient cation is believed to follow up in the next step. To estimate the driving force of this deprotonation, the heterolytic N−H cleavage energies $\Delta G_{het}(NH^{+\bullet})$ were evaluated by an appropriate thermodynamic cycle[14] (eq 8) (Table 2). A simple comparison of these data with the bond energies of the neutral parents reveals that the N−H bonds, upon one electron transfer, are weakened by 23.3−26.9 kcal/mol and 84.7−91.7 kcal/mol, respectively, relative to the corresponding pK_as and BDEs. The very low energy required for this type of bond scission (0.8−2.9 kcal/mol) suggests that proton transfer from the radical cation intermediate should be extremely fast and possibly be diffusion-controlled in solution.

Further inspection of the $\Delta G_{het}(NH^{+\bullet})$ data indicates that both *i*-Pr and Ph groups are bond-weakening compared to their parent (**1a**$^{+\bullet}$). Although this is in an obvious contrast to the bond-strengthening effect of the same substituent on the BDE of **1a** (vide supra), it could be understood if one thinks that the strong need for resonance stabilization of the positive charge in both **1b**$^{+\bullet}$ and **1c**$^{+\bullet}$ will tend to force the radical cation to adopt a more planar structure than that in their parent (**1b** or **1c**), therefore allowing the cation-stabilizing effect of the phenyl or *i*-Pr group to be more effectively executed. It is interesting to note that the phenyl effect is unexpectedly smaller than that of the *i*-Pr. This is probably because the steric congestion within **1c**$^{+\bullet}$ has largely attenuated the effect of phenyl by twisting its plane away from the coplanar system. On the other hand, the effect of *para* groups in phenyl on $\Delta G_{het}(NH^{+\bullet})$ showed a regular pattern as what would be judged from their electronic properties, because no further steric complication is introduced by these remote substituents.

Effect of One-Electron Addition on the N−H Bond Energies. Comparisons of the two different patterns of the N−H cleavage energies of radical anions [i.e., $\Delta G_{homo}(NH^{-\bullet})$ and $\Delta G_{het}(NH^{-\bullet})$] with BDEs of their parent model molecules indicate that the homolytic process (eq 5) can be activated thermodynamically by 53.9 ± 1.8 kcal/mol whereas the heterolytic process (eq 4) by 42.1 + 1.4 kcal/mol upon addition of an electron to the neutral molecule. Obviously, the bond-activating effect of one-electron reduction is also very large, but is not as strong as that of one-electron oxidation on the BDEs of the same N−H bonds. This fact points out that removal of an electron is much more efficient than capture of an electron for bond activation.

One may note from the $(R-H)^{-\bullet}$ bond energy data in Table 2 that the $(R-H)^{-\bullet}$ homolysis (eq 5) requires less energy than heterolysis (eq 4) and, in contrast to the cleavage of the corresponding radical cation $(R-H)^{+\bullet}$, both these processes would not be spontaneously occurring. This is because the radicals and anions in eqs 4 and 5 are of much higher energy than their parent and thus cannot be easily generated. The larger energy for heterolysis may be attributed mainly to the much higher instability of the hydride in solution relative to that of the hydrogen radical.[11a]

In the 4-aryl-substituted Hantzsch ester family, the effect of *para* substituents on the $\Delta G_{het}(RH^{-\bullet})$ and $\Delta G_{homo}(RH^{-\bullet})$s was observed to follow a similar trend as seen on the BDEs of their parent molecules, as is evident from the linear correspondences of these two quantities with the corresponding BDEs (regression coefficients are 0.998 and 0.992, respectively). This suggests that the nitrogen radical anions, like their parent nitrogen radical, can also be classified as the so-called “Class O” radical.

Summary and Conclusion

Although only part of the energetic information derived in this work for the NAD(P)H analogues are related directly to their bio-transformations, the first collection of these fundamental N−H bond data in Table 2 does provide insights for the driving forces of the corresponding processes and can serve as a sound base for a more comprehensive disclosure of the dependence of their chemical and biological features on the bonding properties. From the information disclosed at present, it can at least be concluded that (i) in the presence of a suitable base in solution, the heterolytic N−H bond dissociation is much more favored (by 59.2−67.8 kcal/mol) over the homolytic bond dissociation; (ii) both electron removal from and electron addition to the parent model molecule can greatly activate the N−H bond cleavage, with the former effect being considerably stronger; (iii) the $(N-H)^{-\bullet}$ homolysis is energetically favored over the corresponding heterolysis (by 7−15 kcal); and (iv) from the observed energetic ordering of $\Delta G_{het}(NH^{+\bullet}) < \Delta G_{het}(NH) < \Delta G_{homo}(NH^{-\bullet}) < \Delta G_{het}(NH^{-\bullet}) <$ BDE, it is conceived that electron transfer followed by deprotonation (i.e., the e-H$^+$-e type multistep mechanism) would be an energetically favorable path for oxidation of Hantzsch esters.

Experimental Section

Materials. 4-Substituted 1,4-dihydropyridine derivatives were prepared by condensation of ammonia, ethyl acetylacetate, and the corresponding aldehyde according to the literature procedure.[27] The compounds synthesized were characterized by verifying their melting points, ^1H NMR spectra, and/or elemental analysis. Purification of DMSO solvent and preparation of dimsyl base ($CH_3SOCH_2^-K^+$) were carried out according to the standard method in the literature.[12b] The commercial tetrabutylammonium hexaflourophosphate (Bu_4NPF_6, Aldrich) was recrystallized

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[24] Zhao, B. Ph.D. Dissertation, Nankai University, Tianjin, 1999.

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Table 3. Equilibrium Acidities (pK_a) of Compounds 1a−g in DMSO at 25 °C[a]

compd, G =	pK_a	HIn [b]	pK_{HIn}	pK_a assigned
H (**1a**)	19.8 ± 0.08	I	20.66	19.8
i-Pr (**1b**)	20.3 ± 0.09	I	20.66	20.3
C_6H_5 (**1c**)	19.1 ± 0.07	I	20.66	19.1
4-MeOC_6H_4 (**1d**)	19.2 ± 0.09	I	20.66	19.2
4-MeC_6H_4 (**1e**)	19.2 ± 0.07	I	20.66	19.2
4-ClC_6H_4 (**1f**)	18.7 ± 0.08	II	18.90	18.7
4-CNC_6H_4 (**1g**)	18.3 ± 0.10	II	18.90	18.3

[a] Equilibrium acidities measured in the present work. Runs: ≥2. [b] Abbreviation of indicator, I: 2-naphthylacetonitrile, II: 4-chloro-2-nitroaniline.

from CH_2Cl_2 and was vacuum-dried at 110 °C overnight before preparation of supporting electrolyte solution.

pK_a Measurement. The pK_a values of compounds **1a**−**g** were measured in DMSO at 25 °C by the “Overlapping Indicator Method”[12] on a Beckman DU-8B UV−vis spectrophotometer. The results are summarized in Table 3.

Electrochemical Measurement. Redox potentials were obtained in 0.1 M *n*-Bu_4NPF_6-DMSO by CV at 25 °C on a BAS-100B electrochemical analyzer following the procedure as described earlier.[22] The sweep rate was 100 mV/s. All sample solutions were prepared in DMSO and were 1.5 mM in concentration. The ferrocenium/ferrocene redox couple (F_c^+/F_c) was taken as an internal standard. Reproducibility is usually ≤5 mV for ionic species and ≤10 mV for neutral species.

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