source, NIH Division of Research Resources (RR 02231). Support of high-field NMR spectrometer purchases at the University of South Carolina by the NSF (CHE84-11172) and the NIH (1-S10-RR02425) is acknowledged. Work done at Los Alamos National Laboratory was performed under the auspices of the U. S. Department of Energy. We would especially like to thank Dr. "Bud" Whaley for his input on the preparation of this manuscript and Debbie Ehler for obtaining elemental analyses and for her editing skills.

Registry No. **1a**, 136846-24-7; **1b**, 132377-00-5; **1c**, 132376-99-9; **1d**, 75866-71-6; **1e**, 136794-50-8; **1e**, 136846-25-8; **1g**, 132377-01-6; **2a**, 127399-16-0; **2b**, 136794-51-9; **2c**, 136794-52-0; **2d**, 136794-53-1; **2e**, 136794-54-2; **2f**, 136794-55-3; **2g**, 136794-56-4; **3a** (isomer 1), 136794-57-5; **3a** (isomer 2), 136794-64-4; **3b** (isomer 1), 136794-58-6; **3b** (isomer 2), 136794-65-5; **3c** (isomer 1), 136794-59-7; **3c** (isomer 2), 136794-66-6; **3d** (isomer 1), 136794-60-0; **3d** (isomer 2), 136794-67-7; **3e** (isomer 1), 136794-61-1; **3e** (isomer 2), 136794-68-8; **3f** (isomer 1), 136794-62-2; **3f** (isomer 2), 136794-69-9; **3g** (isomer 1), 136794-63-3; **3g** (isomer 2), 136822-50-9; LHMDS, 4039-32-1; Se, 7782-49-2; (*R*,*S*)-2-phenylpropanoyl chloride, 59981-93-0.

Relative Bond Dissociation Energies for Some NADH Model Compounds from Hydride Transfer/Electron Transfer Equilibria in Acetonitrile[1]

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Summary: Electrochemical oxidation potentials of a number of *N*-alkylpyridinyl radicals (measured using photomodulation voltammetry) were combined in a thermochemical cycle with hydride transfer equilibrium data to provide an estimate of the relative C–H bond dissociation enthalpies of the NADH model compounds.

Recently, Bordwell and his co-workers[2] have shown that reliable relative bond dissociation energies (BDE) can be obtained by combining relative pK_a and redox data in a thermochemical cycle (eqs 1–3). This acidity oxidation

$$R^- + R'H \rightarrow RH + R'^- \qquad \Delta G^\circ = 2.303RT\Delta pK_a \qquad (1)$$

$$R^\bullet + R'^- \rightarrow R^- + R'^\bullet \qquad \Delta G^\circ = 23.06\Delta E^\circ \qquad (2)$$

$$R^\bullet + R'H \rightarrow RH + R'^\bullet \qquad \Delta G^\circ \approx \Delta BDE \qquad (3)$$

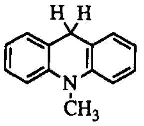
potential approach (ΔAOP) has provided bond energy estimates for a number of R–H bonds that are not amenable to direct measurement. The efficacy of this approach is based essentially on two assumptions. It is assumed that the differences in the irreversible potentials are the same as the differences in the standard potentials, E° (the vast majority of oxidation potentials of the anions are irreversible electron processes). This assumption will be justified provided that the electrode mechanisms for the reactions being compared are the same and the rates of the homogenous follow-up reactions do not vary by more than a factor of ten.[3] It also is assumed that the entropy contributions cancel since the pK_a and E° values are free energies while the BDE's are enthalpies. This assumption has been shown to be justified for most simple hydrocarbons.[4]

The utility of the Bordwell method can be attributed to the large number of pK_a values for weak carbon acids that are available in the literature.[5] However, this approach is not restricted to proton-transfer equilibria. In this work, we have used hydride-transfer equilibrium data that are available for a number of NADH model compounds (**1H**–**3H**, eq 4)[6,7] along with the reduction potentials of the corresponding pyridinium salts (1^+–3^+) in acetonitrile (eq 5) in order to determine the relative C–H BDE's for these species. To our knowledge, this is the first time that this approach has been used. Furthermore, we have addressed the issue of the use of irreversible electrode potentials in the thermochemical cycles. Thus, we have determined the reduction potentials of the pyridinium salts (by cyclic volammetry) and, under the same conditions (i.e., solvent, electrolyte, electrode material) determined the oxidation potential of the corresponding pyridinyl radical (by photomodulation voltammetry[8]). Under these conditions, E° must be bracketed by the two measurements.[9] Both of the electrochemical techniques have been described in detail elsewhere.[8,10]

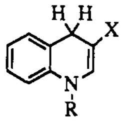
$$R^+ + R'H \rightarrow RH + R'^+ \qquad \Delta G^\circ = 2.303RT\Delta pK_{H^-} \qquad (4)$$

$$R^\bullet + R'^+ \rightarrow R^+ + R'^\bullet \qquad \Delta G^\circ = 23.06\Delta E^\circ \qquad (5)$$

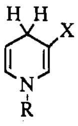
$$R^\bullet + R'H \rightarrow RH + R'^\bullet \qquad \Delta G^\circ \approx \Delta BDE$$



1H



2Ha, R = CH_3; X = CN
2Hb, R = $PhCH_2$; X = CN



3Ha, R = $PhCH_2$; X = CN
3Hb, R = $PhCH_2$; X = C(O)CH_3
3Hc, R = $PhCH_2$; X = C(O)NH_2

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Table I. Thermochemical Data for the NADH Model Compounds

compd	Ep(red)[a] (V vs SCE)	$E_{1/2}$ (ox)[b] (V vs SCE)	E°[c] (V vs SCE)	$\Delta\Delta G^{\circ}(\mathrm{H}^-)$[d] (kcal mol^{-1})	ΔBDE[e] (kcal mol^{-1})
1$^+$	−0.393	−0.45	−0.41	(0)[f]	(0)[f]
2a$^+$	−0.530	−0.56	−0.53	−0.20	2.7 ± 1.2
2b$^+$	−0.482	−0.52	−0.49	1.72	3.5 ± 1.3
3a$^+$	−0.838	−0.84	−0.82	−6.61	3.0 ± 1.1
3b$^+$	−0.973	−0.99	−0.97	−9.80	3.1 ± 1.2
3c$^+$	−1.058	−1.13	−1.08	−11.2	4.3 ± 1.5
4$^+$		0.30[g]			(0)[h,i]
5$^+$		0.20[g]			−5.0 ± 1.5[i]

[a] Measured by cyclic voltammetry in acetonitrile, 0.1 M tetrabutylammonium perchlorate (TBAP) at a gold disk electrode (0.100 V/s scan rate). The peak potentials have been corrected assuming an EC(dimerization) mechanism (−108 mV for $2k_t = 2 \times 10^9$ M^{-1} s^{-1}). [b] Refers to the oxidation of **1**–**5**$^\bullet$ measured by photomodulation voltammetry in acetonitrile/di-*tert*-butyl peroxide (9:1, v/v)/0.1 M TBAP at a gold minigrid electrode. Modulation frequency was 53 Hz with detection of the quadrature component of the signal. Under these conditions where the product (cation) is infinitely long lived and the radical has a lifetime of ca. 1 ms, a +38 mV correction has been applied to $E_{1/2}$ (Nagaoka, T.; Griller, D.; Wayner D. D. M. *J. Phys. Chem.* **1991**, *95*, 6264). [c] $E^{\circ} = 0.5\,[E_p(\mathrm{red}) + 0.03 + E_{1/2}(\mathrm{ox})]$. [d] Equilibrium constant for hydride exchange (eq 4, ref 7). [e] $\Delta\mathrm{BDE} = \Delta\Delta G(\mathrm{H}^-) - 23.06\Delta E^{\circ}$. [f] All values are relative to **1**$^+$/**1H** unless otherwise indicated. [g] Reference 12 a. [h] BDE = 78 ± 1 kcal mol^{-1} (ref 10). [i] BDE value relative to **4H** (ref 12b).

The compounds **1**$^+$–**3**$^+$ were synthesized by alkylation of the appropriate nitrogen heterocycle using either methyl iodide or benzyl bromide.[6] The reduced form of these species were synthesized by dithionite reduction of the pyridinium salt.[6] The cyclic voltammetric data for the reduction of the cations in acetonitrile containing 0.1 M tetrabutylammonium perchlorate (TBAP) are given in Table I. The photomodulation voltammetric data for the oxidation of the radicals, **1**$^\bullet$–**3**$^\bullet$, also are given in Table I. In the latter case, the radicals were generated by the photolysis of di-*tert*-butyl peroxide folllowed by hydrogen atom abstraction from **1H**–**3H** by the *tert*-butoxyl radical (eqs 6 and 7).

$$t\text{-BuO–OBu-}t \xrightarrow{h\nu} 2t\text{-BuO}^\bullet \qquad (6)$$

$$t\text{-BuO}^\bullet + \mathrm{RH} \rightarrow \mathrm{R}^\bullet + t\text{-BuOH} \qquad (7)$$

Hydride-transfer equilibrium data both in 2-propanol/water (4:1)[6] and in acetonitrile[7] are available in the literature. There is little solvent effect on the equilibrium constants,[11] and for consistency, only those data that pertain to acetonitrile have been used in the calculations. The free energy changes associated with the hydride transfer between the NADH model compound (AH) and **1**$^+$ (eq 8) in acetonitrile are given in Table I.

$$\mathrm{AH} + \mathbf{1}^+ \rightleftarrows \mathrm{A}^+ + \mathbf{1H} \qquad (8)$$

The combination of cyclic voltammetry and photomodulation voltammetry to determine the E° value for a given redox couple has the advantage, in this case, of bracketing the value of E° to a small potential range (typically ±20–30 mV, 0.5–0.7 kcal mol^{-1}). Hence, the uncertainties associated with the BDE values are more easily defined than they are when only one irreversible potential for each ion or radical is available.

The ΔBDE values are given in Table I. For comparison, BDE(C–H) values for 9,10-dihydroanthracene (**4H**)[10] and cyclohexadiene (**5H**)[12] (compounds in which the N–R group has been replaced by methylene) also are included. Interestingly, benzannelation tends to decrease the BDE(C–H) by 3–4 kcal mol^{-1} for the dihydropyridines (Table I) while, in the hydrocarbon systems, benzannelation increases the BDE(C–H) by ca. 5 kcal mol^{-1}. A more detailed EPR, kinetic (laser flash photolysis) and thermodynamic (photoacoustic calorimetry), study of these systems as well as systems with other heteroatoms (e.g., O, S) is underway in order to gain some insight into the nature of these substituent effects.

These data also make an important contribution to understanding the energetics for the various mechanisms that have been proposed for reduction reactions of NADH and a number of structurally similar model compounds. Mechanisms that have been demonstrated in simple chemical reductions include a single-step hydride transfer,[6,7,13] a two-step electron/hydrogen atom transfer,[14] and a three-step electron/proton/electron transfer.[15] It is clear from Table I that changes in E° for the oxidation of the NAD$^\bullet$ model are actually energetically greater than changes in the hydride affinity of the NAD$^+$ model (i.e., the large change in E° is partially offset by the change in the BDE). For example, the change in hydride affinity between **1**$^+$ and **3c**$^+$ (a common NADH mimic) is −11 kcal mol^{-1}, while the change in E° is equivalent to −15.5 kcal mol^{-1}. The corresponding change in the BDE is only +4 kcal mol^{-1}. Since the variations in the BDE are relatively small, these results lead to two conclusions: (1) the more effective hydride donors also have a predilection to participate in the electron/hydrogen atom transfer radical chain reactions[14] so care must be taken to avoid adventitious radical initiation with these reagents and (2) the best hydride-transfer reagents can be designed by focusing on those factors that influence the reduction potential of the pyridinium ion.

Registry No. 1H, 4217-54-3; **1**$^+$, 136863-40-6; **1**$^\bullet$, 136863-46-2; **2a**H, 72594-76-4; **2a**$^+$, 136863-41-7; **2a**$^\bullet$, 136863-47-3; **2b**H, 73184-18-6; **2b**$^+$, 136863-42-8; **2b**$^\bullet$, 136863-48-4; **3a**H, 37589-77-8; **3a**$^+$, 136863-43-9; **3a**$^\bullet$, 136863-49-5; **3b**H, 19350-64-2; **3b**$^+$, 136863-44-0; **3b**$^\bullet$, 136863-50-8; **3c**H, 952-92-1; **3c**$^+$, 136863-45-1; **3c**$^\bullet$, 136863-51-9; NADH, 58-68-4.

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