Marcus Theory of a Parallel Effect on α for Hydride Transfer Reaction between NAD+ Analogues

In-Sook Han Lee,*,† Eun Hee Jeoung,† and Maurice M. Kreevoy*,‡

Contribution from the Department of Science Education, Kangweon National University, Chuncheon 200−701, Korea, and Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455-0431

Received October 29, 1996[⊗]

Abstract: Rate and equilibrium constants for hydride transfer from a series of 1,3-dimethyl-2-substituted phenyl-benzimidazolines to a pyridinium ion, a quinolinium ion, and a phenanthridinium ion have been evaluated. Each oxidizing agent gives a linear Brønsted plot with slope, α. The α values vary systematically with the spontaneity of the reactions. They are in reasonable agreement with the predictions of modified Marcus theory. Their trend is very accurately predicted, showing a parallel (Leffler−Hammond) effect. These results make a multistep mechanism, involving high energy intermediates, very unlikely.

Introduction

Marcus theory of the relation between rate and equilibrium constants has been applied successfully and widely to proton transfer,[1] hydride transfer,[2] and group transfer[3] as well as electron transfer reactions.[4] Application of a modification of Marcus theory to the hydride transfer reaction shown in eq 1 leads to an interpretation of the Brønsted α, defined as [d(ln k)/d(ln K)] in terms of a parallel (Leffler−Hammond) effect and a perpendicular (Thornton) effect.[5]

$$A_i^+ + A_jH \rightarrow A_j^+ + A_iH \tag{1}$$

The Marcus formalism can be summarized in eqs 2 and 3. It can be expected to work best if A_i and A_j are structurally related. Equations 4 and 5 give the standard thermodynamic expression for K and quasithermodynamic expression for k, respectively.

$$\Delta G^* = W^r + (1 + \Delta G°/\lambda)^2 \cdot \lambda/4 \tag{2}$$

$$\lambda = (\lambda_i + \lambda_j)/2 \tag{3}$$

$$K = \exp(-\Delta G°/RT) \tag{4}$$

$$k = k_BT/h \exp(-\Delta G^*/RT) \tag{5}$$

ΔG^* is the free energy of activation of the reaction, and $\Delta G°$ is the standard free energy of the reaction.

$$A_i^{*+} + A_iH \rightarrow A_i^*H + A_i^+ \tag{6}$$

$$A_j^{*+} + A_jH \rightarrow A_j^*H + A_j^+ \tag{7}$$

As shown in eq 2, ΔG^* is taken as the sum of two parts. The first, W^r, is that part of ΔG^* which is independent of $\Delta G°$.[5b] The second is a function of $\Delta G°$ and estimated as shown. If $\Delta G° = 0$ the second term in eq 2 reduces to $\lambda/4$, which is called the intrinsic barrier. λ is given by eq 3, in which λ_i and λ_j are the λ values for the symmetrical reactions shown in eqs 6 and 7. Since, if W^r can be estimated, λ_i and λ_j can be obtained from the rate constants for the symmetrical reactions shown in eqs 6 and 7, an estimate of W^r makes it possible to evaluate all the parameters of the theory. In the present work we have consistently assumed W^r to be -2 kcal mol^{-1}, as before,[2] because of the likelihood that the reactants form a weak charge transfer complex before the covalency changes are initiated.

In early applications of Marcus theory $\lambda/4$ was regarded as a constant, characteristic of a particular class of reactions, but in modified Marcus theory it is recognized that λ_i (and/or λ_j) may vary systematically with $\Delta G°°$, the standard free energy of reaction of A_i^+ with a standard hydride donor.[5,6] Any hydride donor could have been chosen as the reference. For historic reasons, and reasons of convenience, 10-methylacridan has been used.[2] If λ_i (and/or λ_j) is assumed to be a linear function of $\Delta G°°$ eqs 8−10 follow.[5] These equations relate the Brønsted α to the Marcus parameters and define a new tightness parameter, τ.

$$\alpha = \chi \pm 1/2(\tau - 1) \mp 1/2(\Delta G°/\lambda)^2 \cdot (\tau - 1) \tag{8}$$

$$\chi = (1 + \Delta G°/\lambda)/2 \tag{9}$$

$$\tau - 1 = d\lambda_i/d(\Delta G°°) \tag{10}$$

χ, which is defined in eq 9, is a measure of the parallel effect on the transition state and gives the Leffler−Hammond contribution to α. It becomes progressively smaller than unity as

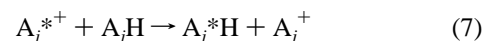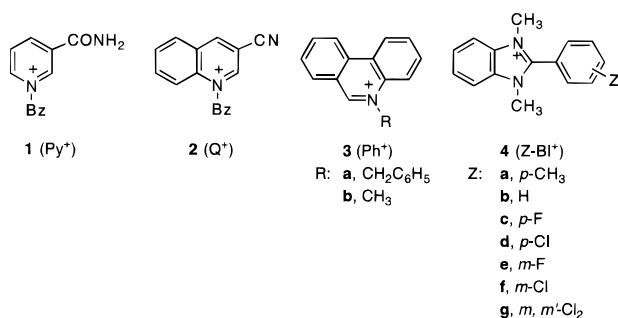† Kangweon National University.
‡ University of Minnesota.
⊗ Abstract published in *Advance ACS Abstracts,* February 15, 1997.
(1) (a) Hassid, A. I.; Kreevoy, M. M.; Liang, T.-M. *Symp. Faraday Soc.* **1985**, *10*, 69−77. (b) Kreevoy, M. M.; Konasewich, D. E. *Adv. Chem. Phys.* **1971**, *21*, 243−252. (c) Kreevoy, M. M.; Oh, S. *J. Am. Chem. Soc.* **1973**, *95*, 4805−4810. (d) Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475−503.
(2) Kreevoy, M. M.; Ostovic D.; Lee, I.-S. H.; Binder, D. A.; King, G. W. *J. Am. Chem. Soc.* **1988**, *110*, 524−530.
(3) (a) Albery, W. J. *Annu. Rev. Phys. Chem.* **1980**, *31*, 227−263. (b) Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891−899. (c) Hine, J. *J. Am. Chem. Soc.* **1971**, *93*, 3701−3708. (d) Albery, W. J.; Kreevoy, M. M. *Adv. Phys. Org. Chem.* **1978**, *16*, 87−153. (e) Lewis, E. S.; Hu, D. D. *J. Am. Chem. Soc.* **1984**, *106*, 3292−3296. (f) Guthrie, J. P. *Can. J. Chem.* **1996**, *74*, 1283−1296. (g) Reference 3f provides a large number of additional relevant references.
(4) (a) Marcus, R. A. *J. Chem. Phys*. **1957**, *26*, 867−871. (b) Marcus, R. A. *J. Chem. Phys*. **1957**, *26*, 872−877. (c) Marcus, R. A. *Annu. Rev. Phys. Chem*. **1964**, *15*, 155−196.

(5) (a) Kreevoy, M. M.; Lee, I.-S. H. *J. Am. Chem. Soc.* **1984**, *106*, 2550−2553. (b) Kim, Y.; Truhlar, D. G.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 7837−7846. (c) Lewis, E. S.; Hu, D. D. *J. Am. Chem. Soc.* **1984**, *106*, 3292−3296.
(6) In the present work, we assumed W^r to be constant and to have -2 kcal mol^{-1} according to ref 2.

the reaction becomes more spontaneous because the transition state structures become more similar to the reactants and less similar to the products. The perpendicular effect on the transition state is represented by $(\tau - 1)$ and gives the Thornton contribution to α. τ can be measured experimentally as shown in eq 10. The upper signs in eq 8 are to be used when the structural variation is in the hydride acceptor, A_i^+, and the lower signs are used when the variation is in the hydride donor, A_jH.[7] In each case the other reactant is not varied. The third term on the right hand side of eq 8 is the cross term. As shown in eq 8, the Brønsted α is mainly determined by the parallel effect (χ) and the perpendicular effect $(\tau - 1)$ since the cross term is negligible in most cases.

1 (Py⁺)　　**2 (Q⁺)**　　**3 (Ph⁺)**　　**4 (Z-BI⁺)**

R: **a**, CH₂C₆H₅　　Z: **a**, *p*-CH₃
　　b, CH₃　　　　　**b**, H
　　　　　　　　　　　c, *p*-F
　　　　　　　　　　　d, *p*-Cl
　　　　　　　　　　　e, *m*-F
　　　　　　　　　　　f, *m*-Cl
　　　　　　　　　　　g, *m, m′*-Cl₂

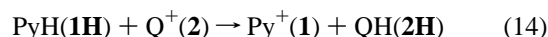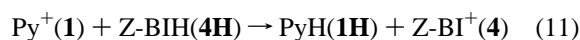In the present paper, we report the rate constants, k, for the reactions of the type shown in eq 1. The NAD⁺ analogues, 1-benzyl-3-carbamoylpyridinium ion, **1**; 1-benzyl-3-cyanoquinolinium ion, **2**; and 5-benzylphenanthridinium ion, **3a**, were used as the oxidizing agents, A_i^+. 1,3-Dimethyl-2-substituted phenylbenzimidazolines (*p*-CH₃, H, *p*-F, *p*-Cl, *m*-F, *m*-Cl, *m,m′*-Cl₂) **4H**, which are regarded as analogues of NADH, were used as reducing agents, A_jH. (NAD⁺ is the enzyme cofactor, **N**icotinamide **A**denine **D**inucleotide, and NADH is its dihydroderivative.)

We chose the 2-phenylbenzimidazoline derivatives as reducing agents, because these substances have been reported to have high standard reduction potentials (i.e., $E°_{4b} = -1.780$ V)[8] which should make it possible to measure quite a wide range of the reaction rates. We found the reduction potential of **4b** to be much less negative than reported, but the variants of **4** served our purpose, and, with one exception, we were able to measure all of the intended rate constants.

We have also measured the rate constants for reduction of substituted 2-phenylbenzimidazolium ions, **4**, by 1-benzyl-3-carbamoyl-1,4-dihydropyridine, **1H**. This allowed the evaluation of the equilibrium constants and standard free energies for the reactions shown in eq 11. In this paper, when a parameter refers specifically to reactions involving one of our three oxidizing agents, it will be identified by an appropriate subscript. Thus the equilibrium constants for the reactions shown in eq 11 are designated K_{Py}.

Equation 12 can be generated from eq 11 by adding eq 14 to it. So the standard free energies of the reactions shown in eq 12, $\Delta G°_Q$, can be obtained from the corresponding $\Delta G°_{Py}$ by adding $\Delta G°_{14}$, where the latter is the standard free energy of the reaction shown in eq 14. The $\Delta G°_{Ph}$ can be obtained analogously. Since $\Delta G°_Q$ and $\Delta G°_{Ph}$ are related to $\Delta G°_{Py}$ by additive, substituent-independent quantities, Brønsted plots could be made using the rate constants for the reduction of **2** and **3** and the K_{Py} values. The slopes of these plots have their usual significance. It will be shown that they are in satisfactory

agreement with the values given by eq 8.

$$Py^+(\mathbf{1}) + Z\text{-BIH}(\mathbf{4H}) \rightarrow PyH(\mathbf{1H}) + Z\text{-BI}^+(\mathbf{4}) \quad (11)$$

$$Q^+(\mathbf{2}) + Z\text{-BIH}(\mathbf{4H}) \rightarrow QH(\mathbf{2H}) + Z\text{-BI}^+(\mathbf{4}) \quad (12)$$

$$Ph^+(\mathbf{3}) + Z\text{-BIH}(\mathbf{4H}) \rightarrow PhH(\mathbf{3H}) + Z\text{-BI}^+(\mathbf{4}) \quad (13)$$

$$PyH(\mathbf{1H}) + Q^+(\mathbf{2}) \rightarrow Py^+(\mathbf{1}) + QH(\mathbf{2H}) \quad (14)$$

When the structural variation for the hydride transfer reaction is in the hydride donor as shown in eqs 11−13, the perpendicular effect on α is the same for all three systems, and the magnitude of the variation of α depends entirely on the χ. Ratios of α values are given by equations like 15.

$$\alpha_{Q^+}/\alpha_{Py^+} = d(\ln k_{Q^+})/d(\ln k_{Py^+}) \quad (15)$$

These ratios demonstrate the Leffler−Hammond or parallel effect. They are much less dependent on the accuracy of the K values than the individual α values. These ratios will be shown to be in excellent agreement with those given by eq 8.

The rate constants were all measured spectrophotometrically at 25 °C in a solvent consisting of four parts of 2-propanol to one part of water by volume. This solvent system was chosen, because it dissolves all the participants in the reaction, and the 2-propanol in the mixed solvent is known as an efficient trapper of free radicals.[9] 1,3-Dimethyl-2-phenylbenzimidazoline has been reported to undergo the free-radical chain reaction with α-haloketones,[10] but in our solvent system free-radical chain reactions should be minimized. And also, it is a great advantage for the present work to utilize the considerable infrastructure of data already available in this solvent.[2]

To tie these results more firmly to the main body of reaction rate correlations, acid dissociation constants, K_a, have been measured in our solvent system for substituted benzoic acids with the same substituents as those used in the variants of **4**. The K_a values are shown to be related to the hydride transfer rate and equilibrium constants in the expected ways, that is, the effect of the substituent on K_a will appear to be opposite to that on k and K.

Experimental Section

Materials. Compounds **1**, **2**, and **3** are well-known substances which were prepared by benzylation of the corresponding bases and identified by their physical and spectroscopic properties.[5,11] Compounds **4a−g** were prepared by the method of Craig and co-workers with small modifications.[12] The typical procedure was as follows:

4b (X = I): A mixture of benzoic acid (3.07 g), *o*-phenylenediamine (2.71 g), and polyphosphoric acid (10.48 g) was heated with stirring at 175−180 °C for 1.5 h and then cooled to room temperature. About 100 mL of 6% NH₄OH was added to neutralize unreacted acid. The solid was filtered off, thoroughly rinsed with the NH₄OH solution, and then dried to give 2-phenylbenzimidazole. The yield was generally over 90%, mp 290 °C. The product was identified by ¹H-NMR. Without further purification, 3 g of this product was treated with 8 g of methyl iodide in 15 mL of methanol containing 0.64 g of NaOH. The reaction mixture was heated at 110 °C overnight in a pressure tube. The longer the reaction period, the higher was the yield of the salt, especially for the substances having the electron-withdrawing substituents. The crude product was decolorized by the activated carbon in hot aqueous ethanol (EtOH:H₂O, 5:1 v/v). After removal of the

(7) Kreevoy, M. M.; Lee, I.-S. H. *Z. Naturforsch.* **1989**, *44a*, 418−426.

(8) Timofeeva, Z. N.; El'tsov, A. V. *Zh. Obshch. Khim.* **1967**, *37*, 2599−2602.

(9) Fieser, L. F.; Williamson, K. L. Organic Experiments, 3rd ed.; D. C. Heath; Lexington, MA, 1975; pp 242−243.

(10) Tanner, D. D.; Chen, J. J. *J. Org. Chem.* **1989**, *54*, 3842−3846.

(11) Ostovic, D.; Roberts, R. M. G.; Kreevoy, M. M. *J. Am. Chem. Soc.* **1983**, *105*, 7629−7631.

(12) Craig, J. C.; Ekwuribe, N. N.; Fu, C. C.; Walker, K. A. M. *Synthesis* **1981**, 303−305.

solvent, the product was recrystallized from absolute ethanol. The yield was over 80%.

4b (X = ClO₄): The iodide counterion was exchanged by perchlorate. **4b** (1 g) was dissolved in 50 mL of hot water and treated with 10 mL of hot aqueous solution containing excess NaClO₄ (3.5 g). The exchange reaction took place instantaneously, and the perchlorate precipitated when the solution was cooled. It was recrystallized from EtOH:H₂O (10:1 v/v) to give a 90% yield (0.85 g). The perchlorate product was identified by a negative silver nitrate test and an IR spectrum showing the presence of perchlorate. It should be noted that for the reverse reaction of **4** (X = I) with **1H** the formation of a charge transfer complex between I⁻ and the product, **1**, which also results in an absorbance band at 360 nm, interferes with the monitoring of the decay of **1H** at 360 nm. Therefore, the counterion was exchanged from iodide to perchlorate to prevent the formation of the complex.

4bH: To a solution of 3 g of **4b** in 80 mL of methanol was slowly added 1.19 g of NaBH₄. The reaction took place instantaneously to give a cloudy, white suspension. The reaction mixture was stirred vigorously for 1 h under N₂. After removal of the solvent under reduced pressure, the white solid was recrystallized from EtOH:H₂O (2:1 v/v) to give a colorless crystalline product. The yield was over 90% (1.86 g).

The yields, melting points, spectroscopic properties, and elemental analyses of the materials used were as follows.

4a: 75%; mp 217−218 °C (lit.[8] 207.5 °C); IR (KBr) 3066 (w), 1613 (m), 1520 (s), 1472 (m), 1090 (vs, $\nu_{Cl=O}$), 837 (m), 768 (s) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 2.49 (s, 3 H, CH₃), 3.88 (s, 6 H, NCH₃), 7.59 (d, 2 H, 3′-H), 7.74 (d, 2 H, 2′-H), 7.76 (dd, 2 H, 5-H), 8.11 (dd, 2 H, 4-H); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 282 (4.22), 244 (4.20).

Anal. Calcd for C₁₆H₁₇ClN₂O₄ (336.77): C, 57.06; H, 5.09; N, 8.32; Cl, 10.53. Found: C, 56.82; H, 4.96; N, 8.22; Cl, 10.48.

4b: 90%; mp 222−3 °C (lit.[8] 212−4 °C); IR (KBr) 3006 (w), 1608 (m), 1477 (m), 1090 (vs, $\nu_{Cl=O}$), 767 (m), 717 (m), 716 (m), 629 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 3.92 (s, 6 H, NCH₃), 7.88−7.94 (m, 5 H, phenyl), 7.76 (m, 2 H, 5-H), 8.13 (m, 2 H, 4-H); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 282 (4.15).

Anal. Calcd for C₁₅H₁₅ClN₂O₄ (322.73): C, 55.82; H, 4.68; N, 8.68; Cl 10.99. Found: C, 55.80; H, 4.77; N, 8.63; Cl, 11.12.

4c: 90%; mp 232−3 °C; IR (KBr) 3077 (w), 1607 (m), 1472 (s), 237 (m), 1092 (vs, $\nu_{Cl=O}$), 858 (m), 761 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 3.89 (s, 6 H, NCH₃), 7.66 (m, 2 H, 3′-H), 7.76 (dd, 2 H, 5-H), 7.99 (m, 2 H, 2′-H), 8.14 (dd, 2 H, 4-H); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 282 (4.26), 238 (4.27).

Anal. Calcd for C₁₅H₁₄ClFN₂O₄ (340.74): C, 52.87; H, 4.14; N, 8.22; Cl, 10.41; F, 5.58. Found: C, 52.66; H, 4.30; N, 8.21; C, 10.61; F, 5.66.

4d: 95%; mp 289−90 °C (lit.[8] 276 °C); IR (KBr) 3081 (w), 2960 (vw), 1605 (m), 1522 (m), 1476 (m), 1103 (vs, $\nu_{Cl=O}$), 843 (m), 762 (m), 621 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 3.90 (s, 6 H, NCH₃), 7.78 (dd, 4 H, 2′,3′-H), 8.16 (m, 2 H, 4-H); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 282 (4.23), 244 (4.23).

Anal. Calcd for C₁₅H₁₄Cl₂N₂O₄ (357.20): C, 50.44; H, 3.95; N, 7.84; Cl, 19.85. Found: C, 50.23; H, 4.14; N, 7.75; Cl, 19.76.

4e: 80%; mp 274 °C; IR (KBr) 3076 (w), 2964 (vw), 1592 (m), 1528 (s), 1474 (s), 1271 (m), 1077 (vs, $\nu_{Cl=O}$), 895 (s), 806 (m), 756 (s), 623 (s) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 3.94 (s, 6 H, NCH₃), 7.72−7.58 (m, 4 H, aromatic H), 7.76 (m, 2 H, 5-H), 8.15 (dd, 2 H, 4-H); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 282 (4.18), 234 (4.15).

Anal. Calcd for C₁₅H₁₄ClFN₂O₄ (340.74): C, 52.87; H, 4.14; N, 8.22; Cl, 10.41; F, 5.58. Found: C, 52.76; H, 4.39; N, 8.43; Cl, 10.36; F, 5.66.

4f: 80%; mp 235−6 °C (lit.[8] 229 °C); IR (KBr) 3071 (w), 2961 (vw), 1522 (m), 1464 (m), 1408 (w), 1077 (vs, $\nu_{Cl=O}$), 760 (s), 623 (w) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 3.89 (s, 6 H, NCH₃), 7.77 (m, 2 H, 5-H), 7.81−8.00 (m, 3 H, 4′,5′,6′-H), 8.05 (s, 1 H, 2′-H), 8.12 (m, 2 H, 4-H); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 282 (4.17).

Anal. Calcd for C₁₅H₁₄Cl₂N₂O₄ (357.20): C, 50.44; H, 3.95; N, 7.84; Cl, 19.85. Found: C, 50.52; H, 4.12; N, 7.78; Cl, 20.01.

4g: 70%; mp 296−8 °C; IR (KBr) 3071 (w), 1562 (m), 1525 (s), 1479 (m), 1089 (vs, $\nu_{Cl=O}$), 872 (m), 765 (m), 623 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 3.89 (s, 6 H, NCH₃), 7.71 (dd, 2 H, 5-H), 8.15 (dd, 2 H,

4-H), 8.02 (s, 2 H, 2′-H), 8.13 (s, 1 H, 4′-H); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 282 (4.10).

Anal. Calcd for C₁₅H₁₃Cl₃N₂O₄ (391.64): C, 46.00; H, 3.34; N, 7.15; Cl, 27.16. Found: C, 45.83; H, 3.23; N, 6.99; Cl, 27.40.

4aH: 80%, mp 90−1 °C; IR (KBr) 3047 (w), 2949 (w), 2863 (w), 2795 (w), 1604 (m), 1495 (s), 1450 (m), 1368 (s), 1297 (m), 1116 (m), 837 (m), 778 (m), 730 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 2.40 (s, 3 H, CCH₃), 2.51 (s, 6 H, NCH₃), 4.85 (s, 1 H, 2-H), 6.44 (dd, 2 H, 5-H), 6.60 (dd, 2 H, 4-H), 7.23 (d, 2 H, 3′-H), 7.41 (d, 2 H, 2′-H); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 312 (3.82), 260 (3.70)

Anal. Calcd for C₁₆H₁₈N₂ (238.33): C, 80.63; H, 7.61; N, 11.76. Found: C, 80.75; H, 7.40; N, 11.79.

4bH: 80% mp 93−4 °C (lit.[12] 93−4 °C); IR (KBr) 3038 (w), 2953 (w), 2861 (w), 2801 (w), 1601 (m), 1495 (s), 1456 (m), 1368 (s), 1295 (m), 1234 (m), 1157 (m), 1121 (m), 1061 (m), 777 (m), 741 (m), 700 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 2.52 (s, 6 H, NCH₃), 4.88 (s, 1 H, 2-H), 6.46 (m, 2 H, 5-H), 6.64 (m, 2 H, 4-H), 7.44−7.59 (m, 5 H, phenyl); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 312 (3.82), 260 (3.70).

Anal. Calcd for C₁₅H₁₆N₂ (224.31): C, 80.32; H, 7.19; N, 12.49. Found: C, 80.12; H, 6.98; N, 12.29.

4cH: 80%; mp 116−8 °C; IR (KBr) 3061 (w), 2959 (w), 2864 (w), 2803 (w), 1602 (m), 1496 (s), 1450 (m), 1367 (s), 1294 (m), 1215 (m), 1118 (m), 848 (m), 736 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 2.51 (s, 6 H, NCH₃), 4.87 (s, 1 H, 2-H), 6.46 (m, 2 H, 5-H), 6.64 (m, 2 H, 4-H), 7.28 (dd, 2 H, 3′-H), 7.61 (dd, 2 H, 2′-H); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 312 (3.84), 260 (3.74).

Anal. Calcd for C₁₅H₁₅FN₂ (242.30): C, 74.35; H, 6.24; F, 7.84; N, 11.57. Found: C, 74.52; H, 6.34; F, 8.03; N, 11.45.

4dH: 95%; mp 93−4 °C; IR (KBr) 3044 (w), 2952 (w), 2864 (w), 2798 (w), 1598 (m), 1493 (s), 1356 (w), 1296 (m), 1196 (m), 1116 (m), 840 (m), 775 (m), 731 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 2.50 (s, 6 H, NCH₃), 4.90 (s, 1 H, 2-H), 6.47 (m, 2 H, 5-H), 6.63 (m, 2 H, 4-H), 7.52 (d, 2 H, 3′-H), 7.59 (d, 2 H, 2′-H); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 312 (3.82) 260 (3.72).

Anal. Calcd for C₁₅H₁₅ClN₂ (258.75): C, 69.63; H, 5.84; Cl, 13.70; N, 10.83. Found: C, 69.79; H, 5.60; Cl, 13.58; N, 10.83.

4eH: 60%; mp 92−3 °C; IR (KBr) 3039 (w), 2950 (w), 2868 (w), 2803 (w), 1599 (m), 1357 (m), 1297 (m), 1248 (m), 1118 (m), 901 (m), 789 (m), 732 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 2.51 (s, 6 H, NCH₃), 4.93 (s, 1 H, 2-H), 6.47 (m, 2 H, 5-H), 6.64 (m, 2 H, 4-H), 7.28 −7.53 (m, 4 H, aromatic H); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 312 (3.84), 260 (3.79).

Anal. Calcd for C₁₅H₁₅FN₂ (242.30): C, 74.35; H, 6.24; F, 7.84; N, 11.57. Found: C, 74.25; H, 6.36; F, 7.76; N, 11.43.

4fH: 85%; mp 99 °C; IR (KBr) 3065 (w), 2960 (w), 2869 (w), 2805 (w), 1577 (m), 1491 (s), 1442 (m), 1357 (m), 1284 (m), 1192 (m), 1116 (m), 895 (m), 781 (m), 734 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 2.52 (s, 6 H, NCH₃), 4.93 (s, 1 H, 2-H), 6.47 (dd, 2 H, 5-H), 6.64 (dd, 2 H, 4-H), 7.51 (m, 3 H, 4′,5′,6′-H), 7.60 (s, 1 H, 2′-H); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 312 (3.80) 260 (3.70)

Anal. Calcd for C₁₅H₁₅ClN₂ (258.75): C, 69.63; H, 5.84; Cl, 13.70; N, 10.83. Found: C, 69.79; H, 5.74; Cl, 13.91; N, 10.63.

4gH: 80%; mp 105−6 °C; IR (KBr) 3049 (w), 2956 (w), 2872 (w), 2799 (w), 1571 (m), 1497 (s), 1440 (m), 1347 (s), 1291 (m), 1116 (m), 801 (m), 772 (m), 732 (m) cm⁻¹; ¹H-NMR (DMSO-d_6) δ 2.50 (s, 6 H, NCH₃), 4.96 (s, 1 H, 2-H), 6.47 (dd, 2 H, 5-H), 6.62 (dd, 2 H, 4-H), 7.58 (s, 2 H, 2′-H), 7.68 (s, 1 H, 4′-H); UV (2-propanol−H₂O, 4:1 v/v) λ_{max} nm (log ε) 312 (3.86), 260 (3.76).

Anal. Calcd for C₁₅H₁₅Cl₂N₂ (293.20): C, 61.44; H, 4.81; Cl, 24.19; N, 9.56. Found: C, 61.28; H, 5.00; Cl, 24.12; N, 9.62.

Measurements. All kinetic measurements were conducted in a solvent containing four parts of 2-propanol to one part of water by volume at 25 ± 0.1 °C to facilitate comparison with a large body of analogous results which have been reported.[2] 2-Propanol and water were distilled before use. In previous work solvents have been distilled from a small amount of H₂SO₄ in order to remove any basic impurity. This resulted in slightly acidic solutions (pH around 5). However **4H** is subject to acid catalyzed hydrolysis and oxidation. For the slower reactions it is not adequately stable at a pH of 5. Therefore, solvents were distilled without using H₂SO₄. Rates of reactions of **1** and **3** with **4Hb** and of **1H** with **4b** were the same in unbuffered solutions and in

solutions buffered to a pH of 7.5 with a boric acid−borate buffer. Therefore, unbuffered solutions which had measured pH around 6 were used, except the reactions of **2**, which has a pK_{R^+} of 5.11 in the present solvent system.[13] The solution of **2** was made acidic by using 4.58×10^{-4} M of $HClO_4$ in the solvent to give the reaction mixture a pH of 3.4. For this reaction **4Hb** was adequately stable at this pH, as the reactions required only a few minutes.

Values of pH were determined electrometrically with a POPE pH meter (Model 501) and combined electrode. In order to determine the correction to the observed pH for our solvent system the apparent pH values of four standard solutions of $HClO_4$ (10^{-2}−10^{-4} M) were measured. An average correction of −0.17, substracted from the apparent pH values, was required to match the negative logs of the concentrations.

Reactions of **4H** with 5×10^{-4} M **2** had half-lives around 10 s. The reaction rate constants were determined with a stopped-flow apparatus (Hi-Tech Scientific, SFA-12) attached to the spectrophotometer (Milton Roy 3000) by monitoring the growth of the absorption due to the product, **4**, at 280 nm. Reaction of **1** with **4H** was slower, and the stopped-flow apparatus was not needed. These reactions went to completion in the presence of excess of **1** (5×10^{-3} M). The rate constants were measured by monitoring the growth of the absorption of **1H** at 360 nm, where other substances do not interfere.

The reaction of **3a** with **4H** was monitored by observing the decay of the absorption of the reactant, **3a**, in the presense of excess of **4H,** at 380 nm. All kinetic experiments were carried out with at least a 20-fold excess of the spectroscopically inactive constituent. Therefore, k_{obs} was obtained from the first-order rate law in the usual way.[14] The second-order rate constants, k, were given by k_{obs}/C, where C is the concentration of substance in excess.

All kinetic experiments were performed at least four times, in separate experiments. More than 20 experiments were performed for the reactions of **2**, because the stopped-flow apparatus required small volumes, which gave rise to greater-than-usual uncertainties in the concentrations. The average deviations from mean values of k_{obs} were around 3% for compounds **1** and **3a** and 5% for compound **2**.

To get the equilibrium constants for the reactions of **1** with the variants of **4H** rate constants for the reverse reactions were needed. These reactions reached equilibrium with substantial amounts of both reactants still present, so the rate constants were evaluated using eq 16.[15,16]

$$k_{-1} = [x_e/(2a - x_e)]t^{-1} \ln\{[ax_e + x_t(a - x_e)]/a(x_e - x_t)\} \quad (16)$$

The initial concentration of the limiting reactant is a, x_e is the equal concentration of the two products at equilibrium, and x_t is the concentration of the products at time t. These were determined from the stoichiometry of the reaction mixture and its absorbance at 360 nm, which was entirely due to the dihydropyridine, **1H**. The second-order rate constant for the reverse reaction, k_{-2}, is k_{-1}/C, where C is the concentration of the reactant in excess. A value of K ($= k/k_{-2}$) is also required, to calculate x_e, since these reactions are too slow to follow to completion. A trial value of K gave a first estimate of x_e. With this value of x_e, k_{-2} was evaluated. Then K was reevaluated, and a new value of x_e was obtained. The cycle was repeated until consistency was achieved. Usually no more than two iterations were neccessary. It has been estimated that K values determined in this way are uncertain by about 10%[16] and that estimate is probably applicable to the present values, as well.

Under our reaction conditions **1H** was found to undergo a pseudo-first-order oxidation to **1**, with a rate constant of around 2.4×10^{-7} s^{-1}. This very slow reaction (half-life around one month) was not further investigated, and the oxidizing agent is not known. It is fast enough to make a significant contribution to the apparent rate constants for the oxidation of **1H** by the variants of **4** (about 10% for **4a**, declining

(13) Lee, I.-S. H.; Kim, S. H.; Kreevoy, M. M.; Lee, C. K.; Lee, C. H. *J. Phys. Org. Chem.* 1992, 5, 269−274.

(14) Frost, A. A.; Pearson, R. G. Kinetics and Mechanism, 2nd ed.; Wiley: New York, 1961; p 29.

(15) Reference 14, pp 186−187.

(16) Ostovic, D.; Lee, I.-S. H.; Roberts, R. M. G.; Kreevoy, M. M. *J. Org. Chem.* **1985**, *50*, 4206−4211.

Table 1. Rate Constants and Equilibrium Constants for Hydride Transfer Reactions

| reductant 4H | oxidant, k (M^{-1} s^{-1}) | | | K | pK_a |
	1	2	3a		
a	2.96×10^{-3}	2.82×10^2	1.60	6.58×10	7.37
b	1.85×10^{-3}	2.08×10^2	1.13	3.60×10	7.22
c	1.03×10^{-3}	1.13×10^2	5.41×10^{-1}	1.72×10	7.10
d	7.00×10^{-4}	9.75×10	3.85×10^{-1}	4.46	6.97
e	4.72×10^{-4}	7.16×10	3.00×10^{-1}	2.52	6.88
f	3.49×10^{-4}	3.74×10	2.13×10^{-1}	1.65	6.76
g	5.02×10^{-5} ^{a}	7.73	3.15×10^{-2}	1.12×10^{-1}	6.18

^{a} The rate constant for this reaction was too small for accurate measurement. Values of ln k for reactions of **4H** with **1** were a linear function of ln k values for reactions of ln k values for reactions of **4H** with **2**, as would be expected, since both are linear functions of ln K. The linear relation between the two sets of ln k values was extrapolated to give the ln k value for reaction of **4Hg** with **1**. A second value was obtained from the similar relation between the rate constants for reaction of **4H** with **1** and the reaction of **4H** with **3a**. The two, very similar, inferred values of the rate constant for reaction of **4Hg** with **1** were averaged to get the tabulated value.

to about 1% for **4g**). The k_{-1} values were corrected by subtracting 2.4×10^{-7} from them before they were used to calculate k_{-2} values.

The pK_a's of the corresponding benzoic acids were measured by pH titration with a glass electrode and a pH meter (Metrohom 686) with NaOH solution (10^{-3} M) in the same mixed solvent. And the activity coefficient, $\gamma_{\pm}$, for the present solvent system was obtained from the Debye−Huckel formula, eq 17.

$$\log \gamma_{\pm} = \frac{-1.87(I)^{1/2}}{1 + 4.05(I)^{1/2}} \quad (17)$$

The mixed solvent correction was redetermined for this equipment by the method described above. The correction required the substraction of 0.22 from the observed pH.

Results and Discussion

The rate constants for hydride transfer reactions and the pK_a's of the benzoic acids are listed in Table 1. The order of reactivity for the oxidant is **2** > **3a** > **1**. This corresponds to the order of their reduction potentials, $E°_{red}$ (i.e., **1**: −361 mV; **3a**: −222 mV; and **2**: −39 mV).[16] The measured equilibrium constants for the reactions of **1** with **4H** are also given in Table 1.

With 36 as the value of K for the reaction of **4Hb** with **1**, we can calculate the equilibrium constant for the reaction of **4Hb** with 10-methylacridinium ion in the same solvent system by using a ladder procedure, to give 1.23×10^{11}. The equilibrium constant for the reaction of **1H** with 10-methylacridinium ion is 3.41×10^9.[2] This gives a reduction potential of −361 mV for **1**.[16] With the value of K, a reduction potential, $E°_{red}$, of −407 mV can be obtained for **4b** by means of eq 18, where F is the Faraday constant and n is the number of electrons transferred; i.e., two in this case.

$$RT \ln K = nF\Delta E° \quad (18)$$

This value is much less negative than the reported value, −1.78 V.[8]

For all three systems Brønsted plots were made by plotting the values of ln k against the values of ln K for reaction of **1** with the variants of **4H**. This procedure is justified above. All three plots are quite reasonably linear, as shown in Figure 1. Their slopes, the Brønsted α values, are given in Table 2, along with the probable errors of the slopes. Most of the uncertainties in these α values are due to the uncertainties in the K values (about 10%, as noted above). Since the same K values were used for all three Brønsted plots, errors in α values due to errors in K values are completely compensated when ratios of α values
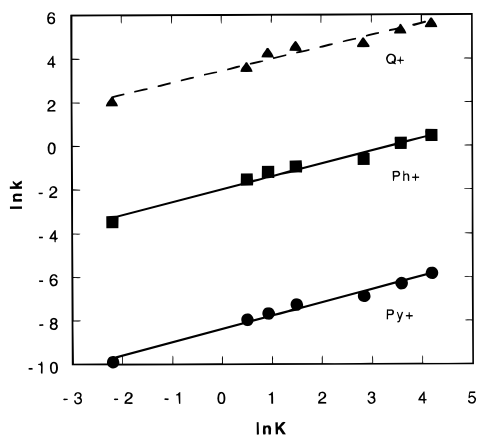
Figure 1. Values of ln k as a function of ln K (Brønsted plots). Points for reactions of **1** with the variants of **4H** are represented by circles. Points for reaction of **2** are represented by triangles. Points for reaction of **3a** are represented by squares. The slopes of these plots are the Brønsted α's. They are shown in Table 2, along with the values given by modified Marcus theory.

Table 2. Equilibrium Constants, Brønsted α's, and Hammett ρ's for Reduction of Cations by Variants of **4H**

	oxidant		
parameter	**1**	**2**	**3a**
K^a	36^b	$2.7 \times 10^{12\ c}$	$1.8 \times 10^{6\ c}$
α(exptl)	0.61 ± 0.03^d	0.54 ± 0.05^d	0.59 ± 0.04^d
χ	0.49	0.41	0.45
λ(kcal mol^{-1})^e	98.9	98.9	99.0
α(calcd)	0.58	0.51	0.55
$\rho(k)$	-1.92 ± 0.12^d	-1.70 ± 0.18^d	-1.85 ± 0.15^d
$\rho(K)$	-3.15 ± 0.13^d		

^{a} Equilibrium constant for reaction of each oxidant with **4Hb**. ^{b} Determined by measuring rate constants for the forward and reverse reactions. ^{c} Determined by the ladder procedure. ^{d} The uncertainty is a probable error. ^{e} Determined from eq 2, for the reaction of each oxidant with **4Hb**.

are taken. Since the α values are not too different, differences in α values are also almost completely unaffected by errors in the K values. As a result, such ratios and differences are much more reliable than would be suggested by the probable errors of the α values themselves.

Marcus theory values for the three Brønsted αs can be calculated using eqs 8 and 9 if values are available for W^r, τ, and λ. As indicated, -2 kcal mol^{-1} has been used for W^r, following earlier practice.[2] The negative value is qualitatively justified by the observation of charge transfer complexes between NAD$^+$ analogues and NADH analogues.[17] In any event, the value of W^r has little effect on the agreement between theory and experiment as long as the value is small compared to ΔG^*, and it is used consistently. A more positive value of W^r is simply compensated by a smaller value of λ. From related hydride transfer reactions a value of 0.81 has been obtained for τ,[2] and it is used in the present work.

With values of W^r and $\Delta G°$ in hand, λ was evaluated for the reactions of **4Hb** with **1**, **2**, and **3a**, using eq 2. The values are given in Table 2. From each of these a value of λ_{4b} was calculated, using eq 3. The three values should be the same. The values of λ_1 and λ_2, needed for the calculation, are given in Table 1 of ref 2. They are 95.1 and 93.5 kcal mol^{-1}, respectively. No value of λ_{3a} is available, but it can be estimated from λ_{3b}, which is given, using eq 13 of ref 2. The value

(17) (a) Florkin, A.; Stotz, E. H. *Comprehensive Biochemistry*; Elsevier; Amsterdam, 1967; Vol. 22, p 109. (b) Hajdu, J.; Sigman, D. S. *J. Am. Chem. Soc.* **1976**, *98*, 6060−6061.
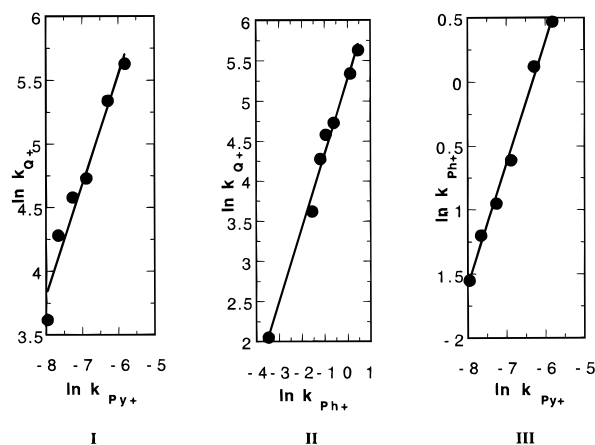
Figure 2. A demonstration of the parallel effect. The slopes are 0.87, 0.92, and 0.96 for I, II, and III, respectively. They are in good agreement with the ratios of calculated α values, as shown in Table 3. These ratios vary from unity because of the gradual shift in transition state structures, which is anticipated by the theory.

Table 3. Demonstrations of the Parallel Effect

oxidant	slope^{a,b}	ratio of ρ's	calcd ratio of α's
Q$^+$−Py$^+$	0.87 ± 0.05	0.89	0.88
Q$^+$−Ph$^+$	0.92 ± 0.02	0.92	0.93
Ph$^+$−Py$^+$	0.96 ± 0.03	0.96	0.95

^{a} The slopes of plots of ln k in one series against ln k for the same imidazoline reacting with a different oxidizing agent. ^{b} The cited uncertainties are the probable errors of the slopes.

obtained is 88.8 kcal mol^{-1}. The three values of λ_{4b} then obtained are 98.9, 98.9, and 99.0 kcal mol^{-1} as shown in Table 2. The three values are identical within the limits of their reliability. In fact, the agreement seems fortuitously good, since the λ values used in the calculation are probably uncertain by about one kcal mol^{-1}.

The perfect agreement among the three λ_{4b} values establishes that the variants of **4/4H** are members of the series of hydride acceptors/donors previously defined and confirms that Marcus theory applies to their hydride transfer reactions. It justifies the use of the λ values to calculate the α values, for comparison with the experimental values.

The calculated and experimental α values are compared in Table 2. They are in very reasonable agreement. The discrepancies do not exceed the probable errors of the experimental values, and the calculated values reproduce the trend in the experimental values almost exactly. This trend is an expression of the Leffler−Hammond or parallel effect.[18] It shows the gradual change in transition state structures as the reactions become more spontaneous.

The parallel effects can also be demonstrated by plotting ln k values for reduction of one oxidant against ln k for reduction of another oxidant by the same set of **4H** variants. This avoids the use of the series of K values. The plots are shown in Figure 2. The slopes of these plots differ from unity because of the parallel effect. They should be given by ratios of calculated α values. The calculation requires one K value for each oxidant. The experimental and calculated slopes are compared in Table 3. The agreement is almost exact.

The Hammett ρ values can also be used to demonstrate the variation of transition state structure, in a similar way. In all three series the ln k values show good linear correlations with

(18) (a) Leffler, J. E. *Science* **1953**, *117*, 340−341. (b) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334−338.
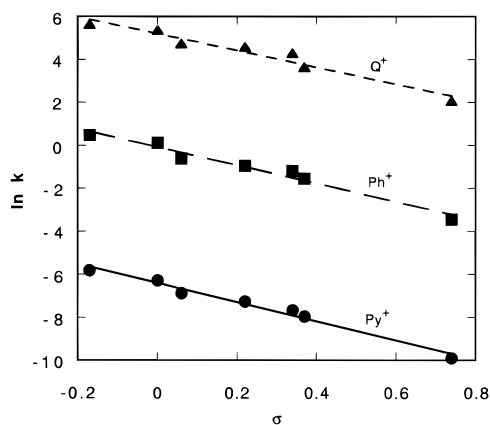
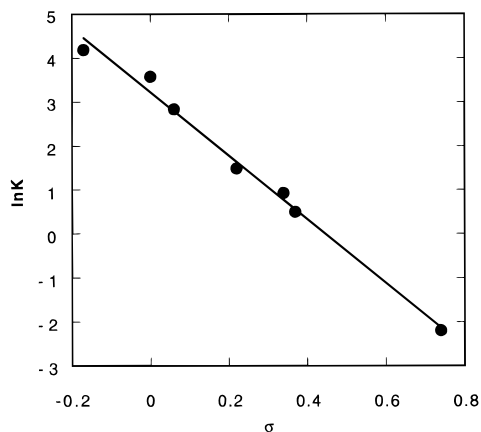**Figure 3.** $\ln k_{Py^+}$, $\ln k_{Q^+}$, and $\ln k_{Ph^+}$ as a funtion of σ.

Figure 4. $\ln K$ as a function of σ.

Hammett parameter, σ,[19] as shown in Figure 3, giving ρ values of -1.92, -1.70, and -1.85 for **1**, **2**, and **3a**, respectively after dividing by 2.3 to put them on the usual scale. These ρ values vary monotonically with typical $\Delta G°$ value of the series. As shown in Table 3 the ratios of ρ are very similar to the slopes of the related $\ln k - \ln k$ plots (Figure 2). (They would be identical if the correlations were perfect.) They are also very similar to the ratios of the calculated α values. Since the calculation anticipates the parallel effect, the agreement illustrates its occurrence.

The $\ln K$ values are also correlated with σ as shown in Figure 4. The ρ value is -3.15 with the correlation coefficient of 0.996. For compound **1**, both $\ln k$ and $\ln K$ are linearly correlated with the $\ln K_a$ values of the corresponding benzoic acids, as shown in Figure 5, giving the slopes of 1.50 and 2.41, with correlation coefficients of 0.998 and 0.987, respectively. Again, the slopes of the correlation lines have been divided by 2.3 to put them on the customary scale.

The magnitude of α, within the Marcus formalism, depends on the location of the structural variation. In the present system the structural variation is in the hydride *donor*. When the structural variation is in the hydride donor, the perpendicular effect $(\tau - 1)$ should be subtracted from χ. Since $(\tau - 1)$ is negative in the present case, this gives a larger value of α than χ by itself. The logic of this is best appreciated by considering the extreme case, where the bonds to the transferring atom or group are both completely broken in the transition state. In that case τ is zero, $(\tau - 1)$ is -1.0, and eq 8 would give an α value close to 1.0 for reactions with equilibrium constants not too far from unity. That value is consistent with the intuition
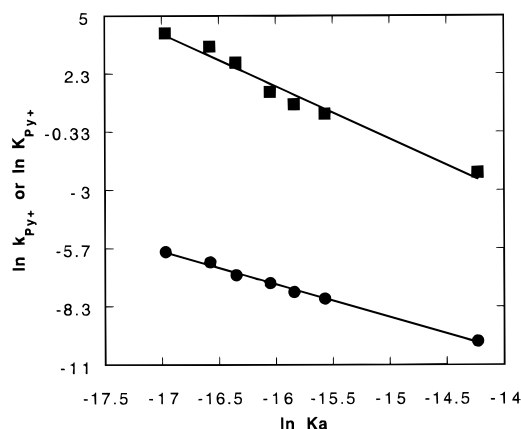
(19) Leffler, J. E.; Grunwald, E. Rates and Equilibria or Organic Reactions; Wiley: New York, 1963; p 173.

Figure 5. The correlation of $\ln k_{Py^+}$ (circles) and $\ln K_{Py^+}$ (squares) with $-\ln K_a$ of the corresponding benzoic acids.

that the rate constant would be about as sensitive to changes in the donor bond strength as the equilibrium constant, since the donor bond is completely broken in the transition state. Similar logic suggests that the rate constant will be nearly insensitive to changes in the *acceptor* bond strength in the case of a no-bond transition state within an equilibrium constant not far from unity. The α value should be close to 0.0 in that case. Equation 8 will provide such a value if the *upper* signs are used when the structural changes are in the *acceptor*.

In the present series of reactions these effects are best illustrated by the reactions of **4H** with **2**. The equilibrium constants are much larger than unity, giving the value of 0.41 for χ, but the calculated value of α is 0.51, due to addition of the tightness factor. The experimental result is in good agreement with the calculation which includes the tightness factor.

The present system demonstrates the parallel effect through the comparison of reactions of quite different reactivity. The equilibrium constants cover a range of over 10^{12}. Parallel effects are seldom reliably observed due to difficulty of experimental measurement of equilibrium constants over a sufficiently wide range. Even in the present case, with such a wide range of equilibrium constants, the sums of the uncertainties in the experimental α's nearly equals the differences between them, which show the effect. It is only the consistency of the experimental results with the theoretical expectations which gives confidence that the parallel effect has really been observed. Marcus formalism provides a useful indication of the range of reactivity needed to demonstrate a parallel effect on the Brønsted α, and a neccessary confirmation that it has been observed.

The ρ value for the pK_a's of benzoic acids in the present solvent system is 1.27 with correlation coefficient of 0.986. The substituent effect is larger in the mixed solvent than in water. This is consistent with prior observations.[20] As expected, the plot of $\ln K$ *vs.* $\ln K_a$ in Figure 5 has a negative slope, because the reacting site at C-2 on the benzimidazole ring of **4H** develops a positive charge in the transition state, while benzoic acid develops a negative charge in the process of dissociation. In our previous study of the reaction of 1-benzyl-3-cyanoquinolinium ions, substituted in the benzyl group, with 10-methylacridan,[5a] the value of the slope of the plot of $\ln K$ vs. $\ln K_a$ for the corresponding benzoic acid was $+1.75$. In that case the positive charge on the quinoline ring diminishes in the course of reaction due to hydride transfer from 10-methylacridan. And the magnitude of the slope in the previous case is smaller than that in the present system (2.41). The reacting site in the

(20) Nummert, V.; Palm, V. *Organic Reactivity* (English Edition) **1980**, *17*, 292–311.

previous system has a methylene group between the phenyl ring and quinoline ring, while the substituted phenyl group is directly connected to the reacting site in the present case.

The foregoing results are consistent with the conclusion that 1,3-dimethyl-2-substituted phenylbenzimidazolines transfer hydride ion to NAD^+ analogues without high energy intermediates, just as previously concluded for similar reactions.[2] If a multistep mechanism (electron transfer followed by proton transfer followed by another electron transfer) were used, the proton transfer step presumably would be rate limiting for the reactions of **4H** with **1**, for which the K values are not far from unity. However the first electron transfer would probably become rate limiting for the reactions of **4H** with **2**, since these reactions have equilibrium constants which are 11 powers of 10 larger. Because of the additional bottleneck the rate constants for the more spontaneous reactions would be smaller than those obtained by Marcus theoretical calculation, since Marcus theory is based on a one step model. The value of λ_{4b} calculated from the rate constant for the reaction of **4H** with **2** would be much smaller than the value calculated from the reaction of **4H** with **1**. In fact, these two values of λ_{4b} are in perfect agreement.

If the rate limiting step did not change, the standard free energy of the first electron transfer would be incorporated in W^r. It would make a large, positive contribution, close to the overall free energy of activation, because the reaction produces a radical and a radical ion from paired-electron reactants. We would expect to require a large, positive value for W^r and small values for λ. This is not observed.

For the reaction of acridan with the acridinium ion in acetonitrile, radical and radical ion intermediates are definitively excluded by comparing the reduction potentials, determined by Saveant and co-workers,[21] with the measured rate of the symmetrical reaction.[2] The present reactions are similar, and we believe that our results exclude high energy intermediates in these cases, also.

JA963768L

(21) Hapiot, P.; Mairoux, J.; Saveant, J.-M. *J. Am. Chem. Soc.* **1990**, *112*, 1337−1343.