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Electron Transfer. 108. Reductions of Pyridinecarboxylic Acids with Vitamin B_{12s} (Cob(I)alamin)[1]

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Vitamin B_{12s} (cob(I)alamin) is oxidized to its Co(II) analogue by pyridinemonocarboxylic and -dicarboxylic acids in buffered aqueous media. With B_{12s} in excess, the 3- and 4-substituted acids and the 2,4- and 3,5-diacids consume 6 units of Co(I). With the oxidants in excess, conversions are mainly to dihydro derivatives which, in the case of the 3-carboxylic acid, appear to be predominantly 1,6-dihydro species. Further partial conversion to tetrahydro compounds is reflected in biphasic kinetic profiles from which rate constants for both reaction steps have been estimated. For all four oxidants, the specific rate for reduction of the dihydro compound exceeds that for its aromatic parent. Reactions are accelerated by H^+. A common $[H^+]$ dependency, pertaining to glycine buffers, reflects partition of the heterocyclic oxidant into mono- and diprotonated forms and, in addition, a contribution from an extraprotonated path. For the monoacids, the latter contribution is small and may be attributed to protonation of B_{12s} ($pK_A \sim 0.0$), but for the 2,4-diacid, this component is large and reflects participation of the triprotonated substrate (H_3A^+, $pK = 0.8 \pm 0.2$) as well. In strongly acidic media, specific rates for reductions of the 2,4-diacid, the 4-acid, and the 3-acid approach the ratio $10^4:10^2:1$. This reactivity pattern corresponds to that previously observed for reductions of these acids by the 1e reductant, Eu^{2+}, at pH 0 and supports the suggestion that the rates of these net 2e reductions are determined mainly by the initial transfer of a single electron.

The reductions of diverse unsaturated organic species by vitamin B_{12s} (cob(I)alamin, the cobalt(I) form of B_{12})[2] appear to be initiated by 2e transactions, being similar in character to additions of metal hydrides. The resulting kinetic pictures are generally straightforward.[2b,c] More complex rate profiles have been observed[3] for the reductions of pyridinecarboxamides (including the physiologically important[4] 3-$CONH_2$ derivative, niacinamide), and comparative reactivity patterns suggest that such reactions, although net 2e changes, proceed in 1e steps with rates determined by the initial transfer.

The present study pursues this question as it applies to reductions of pyridinecarboxylic acids. Inclusion of two isomeric diacids substantially broadens the range of observed reactivities.

Experimental Section

Materials. Pyridinecarboxylic acids (Aldrich products) and hydroxocobalamin hydrochloride (Sigma) were used as received or after recrystallization from water (which operation did not affect the results). Sodium perchlorate, used as a supporting electrolyte in kinetic experiments, was prepared in solution by treatment of $NaHCO_3$ with $HClO_4$; solutions were adjusted to pH 5.4–6.1 and were purged with purified N_2 for at least 3 h. Cob(I)alamin was generated from the cobalt(III) complex, hydroxocobalamin hydrochloride, in stoppered spectrophotometric cells by reduction with amalgamated zinc in aqueous acid.[5,6]

Stoichiometric Studies. Stoichiometries of all reactions, each with B_{12s} in excess, were determined in buffered media by generating Co(I) in acid solution, buffering the solution, adding a deficiency of the carboxylic acid in water, waiting about 20 min, and then measuring the increase in absorbance (due to formation of cob(I)alamin) at 500 nm. The resulting changes were compared to those observed when B_{12s} reacted with excess oxidant. Corrections were made for the slight change in absorbance when B_{12s} was kept in the same buffer in the absence of pyridine species. Results appear in Table I.

Examination of the Reduction Products from Nicotinic Acid. Reaction mixtures (1.0 mL) contained 0.0067 mmol of B_{12s} and 0.0201 mmol of 3-pyridinecarboxylic acid (nicotinic acid) and were 0.050 M in $HClO_4$.

Table I. Stoichiometries of the Reactions of Vitamin B_{12s} (Cob(I)alamin) with Pyridinecarboxylic Acids[a]

acid (PyR)	10^4mmol of PyR	10^4mmol of B_{12s}	$10^4\Delta$mmol of B_{12s}	$\Delta[B_{12s}]/\Delta[PyR]$
3-COOH	0.33	4.0	1.96	5.9
	0.50	4.0	2.92	5.8
	0.67	4.0	3.85	5.8
4-COOH	0.33	4.0	2.04	6.2
	0.55	8.0	2.86	5.7
	0.67	4.0	3.96	5.9
3,5-$(COOH)_2$	1.33	8.0	7.8	5.9
	1.33	16.0	8.1	6.1
	1.00	16.0	5.8	5.8
2,4-$(COOH)_2$[b]	1.33	8.0	7.9	5.9
	0.67	8.0	4.0	5.9
	1.00	8.0	6.1	6.1

[a] Reactions were carried out in solutions buffered with 0.050 M each of glycine and its hydrochloride (unless otherwise indicated) and were monitored at 500 nm. [b] Faster reactions were carried out in HOAc–OAc^- buffers.

After 30-min reaction time, the products were absorbed onto a column of Bio-Gel P-2 (200–400 mesh; exclusion limit 1800 Da). Slow elution with water gave an initial red-brown fraction (22 mL) with a spectrum characteristic of a mixture of the Co(II) and Co(III) forms of B_{12}. A second fraction (10 mL) exhibited no peaks in the region 200–550 nm. A third colorless fraction (35 mL) featured peaks at 350 and 261 nm. Subsequent fractions showed no significant absorbances.

Kinetic Measurements and Estimation of Specific Rates. Rates were estimated on the basis of absorbance decreases at 387 nm, as monitored on either a Beckman Model 5260 or a Cary 14 recording spectrophotometer. Cob(I)alamin (B_{12a}) was generated in solution from B_{12a} in the optical cell.[6] Known quantities of glycine buffers were added to B_{12a} before reduction to Co(I). Total ionic strength was held at 0.5 M by addition of $NaClO_4$. Kinetic runs were carried out with the oxidant (the pyridinecarboxylic acid) in 10–50-fold excess.

Reactions did not exhibit exponential decay curves. Observed half-lives generally increased during the course of each reaction, but the increase was much less pronounced than that corresponding to a second-order profile. This effect did not reflect autoinhibition, for addition of a fresh sample of B_{12a} to the reaction mixture resulted in an initial rate very close to that observed for the original sample. All reactions yielded B_{12r} (cob(II)alamin), identified from its spectrum.[7] Isosbestic points at 543, 416, and 343 nm were observed.

Nearly all kinetic curves could be fitted to a sequence in which partial reduction of the pyridine acid to a dihydro product is followed, to a lesser extent, by conversion to a tetrahydro species (see Discussion). Such fits were accomplished initially by using the program INTEGRAL to generate

(1) Joint sponsorship of this work by the National Science Foundation (Grant 8619472) and by the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.
(2) (a) Schrauzer, G. N.; Holland, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4060. (b) Pillai, G. C.; Reed, J. W.; Gould, E. S. *Inorg. Chem.* **1986**, *25*, 4734. (c) Pillai, G. C.; Gould, E. S. *Inorg. Chem.* **1986**, *25*, 4740.
(3) Ghosh, S. K.; Balasubramanian, P. N.; Pillai, G. C.; Gould, E. S. *Inorg. Chem.* **1991**, *30*, 487.
(4) See, for example: York, J. L. In *Textbook of Biochemistry*; Devlin, T. M., Ed.; Wiley: New York, 1982; p 156.
(5) Loar, M. K.; Sens, M. A.; Loar, G. W.; Gould, E. S. *Inorg. Chem.* **1978**, *17*, 330.
(6) Balasubramanian, P. N.; Gould, E. S. *Inorg. Chem.* **1983**, *22*, 2635.
(7) Bonnet, R. *Chem. Rev.* **1963**, *63*, 573.

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Table II. Acidity Constants for Pyridinedicarboxylic Acids[a]

acid	λ, nm	$10^{-3}\epsilon_{HA}$, M^{-1} cm^{-1}	$10^{-3}\epsilon_{H_2A}$, M^{-1} cm^{-1}	$10^{-3}\epsilon_{H_3A}$, M^{-1} cm^{-1}	pK_{H_2A}[b]	pK_{H_3A}
2,4-$(COOH)_2$	278	3.87 ± 0.60	5.06 ± 0.28	5.92 ± 0.04	2.12	0.80 ± 0.24
3,5-$(COOH)_2$	265	3.47 ± 0.05	3.78 ± 0.05	4.28 ± 0.01	2.10	1.13 ± 0.09

[a] Measurements were made at 25 °C; μ = 1.00 ($NaClO_4$). Parameters were obtained from nonliinear least-squares refinement of spectral data in terms of eq 1 in the text. ϵ values refer to the protonation levels of the dicarboxylic acids. [b] Values from ref 12.

curves which were compared to the observed traces.[8,9] Specific rates giving approximate agreement between observed and calculated absorbances were refined further by using an iterative least-squares procedure.[10,11] Parameters resulting from these refinements reproduced the observed profiles closely.

Estimation of the Acidity Constants of the Monopositive Forms of the Dicarboxylic Acids. Acidity constants for the uninegative (HA^-) and the zwitterionic (H_2A) forms of the dicarboxylic acids have been tabulated,[12] but those for the more strongly acidic cationic forms (H_3A^+) have apparently not been reported. The latter values for the 2,4- and 3,5-diacids were estimated spectrophotometrically by measuring the variation of absorbance with acidity in the range $[H^+]$ = 0.01–1.00 M. Nonlinear least-squares treatment of data utilized eq 1, where ϵ_{HA}, ϵ_{H_2A}, and ϵ_{H_3A}

$$\text{Abs} = \frac{(\epsilon_{HA}K_{H_2A}K_{H_3A} + \epsilon_{H_2A}[H^+]K_{H_3A} + \epsilon_{H_3A}[H^+]^2)[\text{Ox}]_T}{K_{H_2A}K_{H_3A} + K_{H_3A}[H^+] + [H^+]^2} \quad (1)$$

represent the extinction coefficients of the designated forms of the pyridine diacids and $[Ox]_T$ is the total concentration of the oxidant. Refined K_{H_3A} and ϵ values appear in Table II.

Results

Reactions of pyridinecarboxylic acids with excess B_{12s} are seen (Table I) to consume very nearly 6 units of Co(I). The acids are thus converted to hexahydro derivatives:

$$\text{Py(COOH)} + 6\text{Co}^{\text{I}} + 6\text{H}^+ \rightarrow \text{PyH}_6\text{(COOH)} + 6\text{Co}^{\text{II}} \quad (2)$$

These reductions are stoichiometrically equivalent to those of the more reactive pyridinecarboxamides,[3] but it has been noted also that the more slowly reacting amides are reduced, under the same conditions, just to tetrahydro species:[18]

$$\text{Py(CONHR)} + 4\text{Co}^{\text{I}} + 4\text{H}^+ \rightarrow \text{PyH}_4\text{(CONHR)} + 4\text{Co}^{\text{II}} \quad (3)$$

Table III. Kinetic Data for the Reaction of Vitamin B_{12s} (Cob(I)alamin) with 4-Pyridinecarboxylic Acid (Isonicotinic Acid)[a]

10^4[PyCOOH]	[GlyH$^+$]	[Gly]	pH	$10^{-2}k_1$[b]	$10^{-2}k_2$[b]
0.60[c]	0.050	0.050	2.73	4.6 (4.2)	7.0 (7.0)
1.00[c]	0.050	0.050	2.71	4.5 (4.4)	7.5 (7.2)
2.00	0.050	0.050	2.71	4.5 (4.4)	7.2 (7.2)
2.00	0.100	0.100	2.54	5.9 (6.1)	10.2 (10.1)
2.00	0.20	0.200	2.52	6.2 (6.3)	10.7 (10.4)
2.00	0.050	0.30	3.25	1.77 (1.84)	3.1 (3.0)
2.00	0.050	0.20	3.18	2.1 (2.0)	3.4 (3.3)
2.00	0.050	0.100	2.95	2.9 (2.9)	4.4 (4.7)
2.00	0.100	0.050	2.45	6.5 (7.3)	10.7 (12.1)
2.00	0.200	0.050	2.30	11.4 (10.0)	18.9 (16.5)

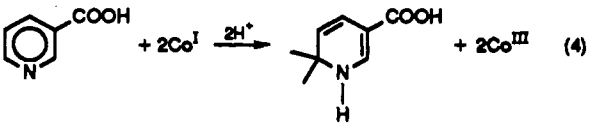
[a] Reactions were run at 25 °C in glycine buffers; μ = 0.50 M ($NaClO_4$); $[B_{12s}] = 4.0 \times 10^{-5}$ M unless otherwise indicated. [b] Bimolecular rate constants (M^{-1} s^{-1}) for successive 2e reductions of isonicotinic acid (reactions 5 and 6 in text), obtained from refinement of kinetic data (refs 8 and 10). Parenthetical values are calculated from eq 8, by using the parameters in Table V. [c] $[B_{12s}] = 2.0 \times 10^{-5}$ M.

Table IV. Kinetic Data for the Reaction of Vitamin B_{12s} (Cob(I)alamin) with 2,4-Pyridinedicarboxylic Acid[a]

10^5[2,4-P]	[Gly]	[GlyH$^+$]	pH	$10^{-2}k_1$[b]	$10^{-2}k_2$[b]
8.0	0.180	0.020	3.56	0.80 (0.82)	1.25 (1.27)
8.0	0.175	0.025	3.45	1.20 (1.23)	1.88 (1.85)
8.0	0.175	0.025	3.43	1.31 (1.31)	1.97 (2.01)
8.0	0.170	0.030	3.35	1.77 (1.76)	2.8 (2.7)
8.0	0.160	0.040	3.22	2.9 (2.7))	4.4 (4.2)
8.0	0.150	0.050	3.05	5.2 (5.3)	7.8 (7.9)
8.0	0.150	0.050	3.04	5.2 (5.5)	7.9 (8.1)
12.0	0.150	0.050	3.04	5.4 (5.5)	8.2 (8.1)
16.0	0.150	0.050	3.04	5.3 (5.5)	8.2 (8.1)
16.0	0.140	0.060	2.98	7.1 (6.9)	10.3 (10.2)
8.0	0.140	0.060	2.95	7.6 (7.7)	11.0 (11.4)
8.0	0.120	0.080	2.80	14.2 (13.8)	20 (20)

[a] Reactions were run at 23 °C in glycine buffers; μ = 0.50 M ($NaClO_4$); λ = 387 nm; $[B_{12s}] = 2.0 \times 10^{-5}$ M throughout. [b] Bimolecular rate constants (M^{-1} s^{-1}) for successive 2e reductions of 2,4-pyridinedicarboxylic acid (reactions 5 and 6 in text), obtained from refinement of kinetic data (refs 8 and 10). Parenthetical values are calculated from eq 8 in the text, by using the parameters in Table V.

This type of reaction may thus be taken to proceed in multiples of 2 oxidation units. Under kinetic conditions (B_{12s} in deficiency) reduction would be expected to yield principally dihydro species. In each case, a mixture of unsaturated products would be anticipated, but the spectrum of the product from nicotinic acid (λ_{max} at 350 and 261 nm) closely resembles that for 1,6-dihydronicotinamide (λ_{max} at 350 and 270 nm)[14] but differs from those of the isomeric dihydro amides, indicating that B_{12s} attacks this acid on the less hindered side of the heterocyclic ring at the 6-carbon (as is the case with the corresponding amide).[3]



(4)

Reductions of the remaining oxidants in this series may be taken to proceed similarly.[15]

(8) Kinetic fits, which utilized a fourth-order Runge–Kutta integration technique,[9] were accomplished by a FORTRAN-77 program on an IBM 3081D computer system. The FORTRAN-IV version of the program, for which we thank Professor Gilbert Gordon (Miami University, Oxford, OH) was modified to incorporate the appropriate differential equations and stoichiometric relationships.

(9) (a) Margenau, H.; Murphy, G. M. *The Mathematics of Physics and Chemistry*; Van Nostrand: New York, 1943; p 469. (b) Wiberg, K. In *Techniques of Chemistry*, 3rd ed.; Lewis, E. S., Ed.; Wiley: New York, 1974; Collect. Vol. VI, Part I, p 764.

(10) This program, which was developed by R. Moore and T. W. Newton of Los Alamos National Laboratory, was obtained from Professor Gilbert Gordon. The FORTRAN-IV version was changed, with the help of Dr. J. W. Reed, to FORTRAN-77 in order to adapt to the IBM 3100 system. The program, which minimizes the function $(\text{Abs}_{\text{calcd}} - \text{Abs}_{\text{obsd}})^2$, uses the Gaussian method described by McWilliams and co-workers.[11] Trial values of the rate constants were obtained from the INTEGRAL procedure. Individual experimental points were unweighted.

(11) McWilliams, P.; Hall, W. S.; Wegner, H. E. *Rev. Sci. Instrum.* **1965**, *33*, 76.

(12) Smith, R. M.; Martell, A. E. *Critical Stability Constants*; Plenum: New York, 1974, 1982; Vol. 1, pp 20–22, 374, 407; Vol. 5, p 131.

(13) Moreover, we find that 2,6-pyridinedicarboxylic acid and the *N*-methyl-2-carboxypyridinium cation, both of which are reduced only slowly with B_{12s}, consume very nearly 4 units of Co(I). The kinetic patterns associated with these acids, with B_{12s} in deficiency, are analogous to those for the more reactive oxidants. Since the structures of the reduction products are uncertain in these instances, we have not pursued these reactions.

(14) Lovesey, A. C.; Ross, W. C. *J. Chem. Soc. B* **1969**, 192.

(15) Reductions of substituted pyridines to dihydro species have been reviewed: (a) Stout, D. M.; Myers, A. I. *Chem. Rev.* **1982**, *82*, 223. (b) Lyle, R. E. In *Pyridine and Its Derivatives*; Abramovich, R. A., Ed.; The Chemistry of Heterocyclic Compounds, Supplement Part One; Wiley-Interscience: New York, 1974; Vol. 14, p 143.

(16) Ryan, D. A.; Espenson, J. H.; Meyerstein, D.; Mulac, W. A. *Inorg. Chem.* **1978**, *17*, 3725.

(17) See, for example: Green, R. W.; Tong, K. H. *J. Am. Chem. Soc.* **1956**, *78*, 4896. Note that further deprotonation of the monoprotonated forms (pK_{HA} 4.6–4.8)[12] plays no part within the pH ranges considered.

(18) Conversions of substituted pyridines to 1,4-dihydro derivatives have been found to increase pK_A values by 1.4–2.0 units. See, for example: Kosower, E. M.; Sorenson, T. S. *J. Org. Chem.* **1962**, *27*, 3764.

Table V. Kinetic Parameters Pertaining to the Reactions of Vitamin B_{12s} (Cob(I)alamin) with Pyridinecarboxylic Acids[a]

acid		pK_{H_2A}	pK_{H_3A}	k_{HA}, M^{-1} s^{-1}	k_{H_2A}, M^{-1} s^{-1}	k', M^{-2} s^{-1}
3-COOH	k_1	2.09			8.6 ± 0.2	106 ± 30
	k_2	3.5[b]			4.3 ± 0.8	(1.71 ± 0.06) × 10^4
4-COOH	k_1	1.81		83 ± 26	(2.9 ± 0.6) × 10^3	(1.9 ± 1.5) × 10^5
	k_2	3.4[d]			130 ± 20	(3.0 ± 0.1) × 10^5
2,4-$(COOH)_2$[c]	k_1	2.12	0.80		(12.5 ± 0.7) × 10^2	(4.2 ± 0.1) × 10^6
	k_2	2.3[e]			(13.8 ± 0.9) × 10^2	(4.6 ± 1.8) × 10^6
3,5-$(COOH)_2$	k_1	2.10	1.13		16.7 ± 2.9	(8.4 ± 1.3) × 10^3
	k_2	2.8[e]			44 ± 6	(2.5 ± 0.3) × 10^4

[a] Reactions were carried out at 25 °C; μ = 0.5 M ($NaClO_4$). Values of k_1 and k_2 (specific rates for the first and second stages of reduction) were obtained from least-squares refinements in which observed absorbances were compared with those obtained by integration of differential equations based on sequence 5–7 in the text. Parameters are those in eq 8. Acidity constants (pK values) were taken from ref 12. [b] pK value taken to be that for β-alanine. [c] Experiments at 23 °C. [d] pK value taken to be that for $^+H_3N(CH_2)_3COOH$. [e] Values giving optimal agreement with observed acidity patterns for k_2.

All two-component kinetic traces (obtained with the oxidant in excess) are analyzed according to sequence 5–7. Step 7 is rapid

$$Py + Co^I \xrightarrow[k_1]{H^+} PyH_2 + Co^{III} \quad (5)$$

$$PyH_2 + Co^I \xrightarrow[k_2]{H^+} PyH_4 + Co^{III} \quad (6)$$

$$Co^I + Co^{III} \rightarrow 2Co^{II} \quad \text{(rapid)} \quad (7)$$

enough ($k > 10^7$ M^{-1} s^{-1})[16] so that it may be combined with (5) and (6). Expression of this sequence as appropriate differential equations, application of numerical integration procedures,[8] and least-squares refinements[10] of the values of k_1 and k_2 were carried out as described for the B_{12s}–pyridine amide systems.[3]

Refined values of k_1 and k_2 for the reactions of B_{12s} with isonicotinic acid (4-PyCOOH) and 2,4-pyridinedicarboxylic acid are assembled in Tables III and IV. In our hands, useful data for the rapidly reacting 2,4-diacid could not be obtained below pH 2.8, whereas the remaining three acids were examined between pH 2.1 and 3.3. Within these ranges, these oxidants are partitioned mainly between their diprotonated forms (PyH^+–COOH, pK_{H_2A} 1.8–2.3)[12] and their monoprotonated (PyH^+–COO^-)[17] conjugate bases. If only these were to contribute to the overall reaction, one would expect to see indications of kinetic saturation with respect to $[H^+]$ at the lower pH's (where H_2A forms predominate). Instead, specific rates exhibit marked acidity dependencies at the highest acidities taken, pointing to contributions from an additional path featuring the two redox partners plus an extra proton.

Operation of three paths at the indicated protonation levels leads to relationship 8, where k_{HA} and k_{H_2A} designate specific rates

$$(k_1)_{obsd} = \frac{k_{HA}K_{H_2A} + k_{H_2A}[H^+] + k'[H^+]^2}{K_{H_2A} + [H^+]} \quad (8)$$

associated with the predominant forms of the pyridine acids and k' pertains to the "extraprotonated" contribution. Refinements of k_1 data for all four oxidants are in terms of (8). An analogous treatment is applicable to k_2 data, but K_{H_2A} values (not yet reported) for the nonaromatic dihydro compounds would be expected to be significantly less than those for their aromatic precursors.[18]

Discussion

Kinetic parameters for reductions of the pyridine acids studied are listed in Table V. Each acid undergoes a two-stage reduction analogous to that indicated for the 4-COOH and 2,4-$(COOH)_2$ oxidants. Although intrusion of the second stage results in substantial departures from exponential profiles, integrations, using the listed rate constants,[8,9] show that the resulting tetrahydro derivative or derivatives comprise only a minor portion of the reduced product. In all cases, specific rates for the second stage (k_2 values) exceed those for the first (k_1), reminding us that it is more difficult to reduce an aromatic ring than its diene-like product. This selectivity mirrors the relative values for the "extraprotonated" term, k', which is generally the major kinetic contributor. For the 2,4-diacid, the difference in k' for the two stages is marginal, and the greater values of k_2 reflect the greater degree of conversion of the more basic dihydro derivative to the more reactive protonated form in a given solution.

Since the unipositive (PyH^+–COOH) forms of the monoacids may be considered their highest acidity level in our media,[19] the k' term here must be attributed to "extraprotonation" of B_{12s}. Lexa and Saveant[20] have presented evidence for such a protonation (possibly at the Co^I center) near pH 1, whereas Pillai[2c] has assigned a pK_A of 0.0 to this equilibrium.

For the very high k' term pertaining to the 2,4-diacid, an additional contribution comes into play, that involving the triprotonated ($PyH^+(COOH)_2$) species. Although the degree of conversion to this strongly acidic cation (pK_A ~0.8) is slight in the solutions examined, the bimolecular rate constant associated with this path, calculated as $k'K_{H_3A}$, approaches 10^6 M^{-1} s^{-1}, consigning to it much of the kinetic burden.

As was observed for the analogous pyridinecarboxamides,[3] the 4-substituted compound is reduced 10^2–10^3 times as rapidly as its 3-isomer under similar conditions, a ratio remarkably near that reported earlier for reductions of these heterocycles with 1e metal-center reductants.[21] The 2,4-diacid is seen to be a still more effective oxidant. If its reactivity is compared with that of the 4-COOH derivative in 1 M H^+ (a medium often chosen for reactions of metal-center reductants), we may estimate an additional 20–100-fold acceleration, an enhancement similar to that observed for the corresponding reductions by the 1e center, Eu^{2+}.[22] Thus the reactivity patterns governing reduction of our pyridine acids closely resemble those for bona fide 1e reductions. This parallelism, already noted for reductions of the analogous pyridine amides,[3] adds support to the proposal that the rates of these net 2e reductions are determined principally by the transfer of a single electron, i.e., that two distinct 1e transactions are required, with the second of these, a Co(I)-radical reaction, proceeding much more rapidly than the first.

The contrast between the present conversions and the B_{12s} reductions of α,β-unsaturated dicarboxylic acids and their esters, for which there is strong evidence for direct formation of a carbanion-like intermediate,[2b,c] may reflect the greater polarity of the site under attack (which lies adjacent to an electron-attracting nitrogen) in the pyridinium-derived substrates. If so, we should expect the reactions of B_{12s} with nitro and nitroso compounds to conform to a radical-like pattern as well, whereas those with fluorinated olefins and with metal–alkylidene complexes would be more likely to exhibit the characteristics of nucleophilic additions. Whether there are families of oxidants which, depending upon reaction conditions, can be induced to react with B_{12s} either homolytically or heterolytically remains an open question.

Acknowledgment. We are grateful to Ms. Arla McPherson for technical assistance.

(19) Further protonation of the carboxyl group, for which there is evidence in very strongly acidic media (see, for example: Arnett, E. M. *Prog. Phys. Org. Chem.* **1963**, *1*, 223 (Table XIa), plays no part in the systems at hand.
(20) Lexa, D.; Saveant, J.-M. *J. Am. Chem. Soc.* **1976**, *98*, 2652.
(21) See, for example: Loar, M. K.; Fanchiang, Y.-T.; Gould, E. S. *Inorg. Chem.* **1978**, *17*, 3689.
(22) Fanchiang, Y.-T.; Heh, J. C.-K.; Gould, E. S. *Inorg. Chem.* **1978**, *17*, 1142. The indicated range in selectivity reflects the large uncertainty in the k' parameter for the 4-COOH heterocycle (Table V).