Decarboxylation of 5-Substituted 2-Pyridinecarboxylic Acids[1]

RUSSELL J. MOSER AND ELLIS V. BROWN*[2]

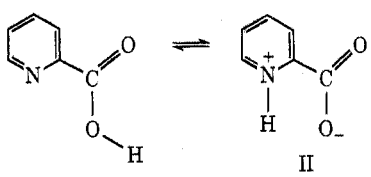
Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

Received February 19, 1971

The rates of decarboxylation of 5-nitro-2-pyridinecarboxylic, 2,5-pyridinedicarboxylic, 5-iodo-2-pyridinecarboxylic, and 5-methoxy-2-pyridinecarboxylic acids in 3-nitrotoluene have been measured. The $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ were then calculated. An examination of the linear free-energy plot of relative rates *vs.* the σ_p constants suggests that electron withdrawal from the 5 position results in lower $\Delta G^{\ddagger}$ values. The observation that 2-pyridinecarboxylic acid does not fall on the same straight line as these acids, suggests that I can either lead to the cyclic transition state (IV) or to the zwitterion intermediate (II) which then decarboxylates. The pathway that a particularly substituted 2-pyridinecarboxylic acid follows depends upon the electron density on the ring nitrogen. A mechanism is given which is consistent with the available data. An assumption of this interpretation is that some monomer exists in solution at high temperature.

The decarboxylation of 2-pyridinecarboxylic acid in various solvents,[3-5] of methyl-substituted 2-pyridinecarboxylic acids,[6] and of 6-substituted 2-pyridinecarboxylic acids[7] has been studied in two different laboratories. Earlier investigators[3-6] found no correlation between the rates of decarboxylation and structure of the transition state. They did try to deduce the structure of the intermediate leading to the transition state. Different methods should be used to study the distribution of reactants other than those used to deduce the structure of the transition state. Thus, we have not postulated that either I or II is the principal reactant, but assumed that both are present and a rapid equilibrium exists between them (Scheme I). We

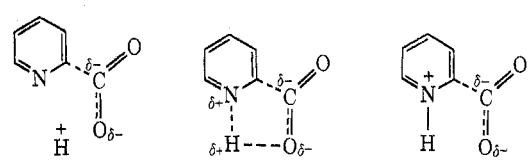
SCHEME I



I II

have also assumed that some monomer is present in solution at the temperatures used in this study. The assumption that some monomer is present at these temperatures,[8] in this solvent,[9] and at the concentrations[10] used in this study is a reasonable one based on evidence with other acids.

Irrespective of which reactant leads to which transition state, there are three reasonable transition states III, IV, and V which could yield apparent first-order kinetics. The electrical effects in these three transition states are different. If transition states III or V lead predominantly to decarboxylation, electron-withdrawing substituents would stabilize the transition



III IV V

state and lead to larger rate constants. If transition state IV leads to products, there are opposing effects. At one position, electron withdrawal would increase the rate constants and, at the other position, decrease the rate constants. Two events are occurring in transition state IV: (a) N–H bond formation and (b) C–C bond cleavage. With these two events, there are three pathways for the reaction to take place: (a) C–C bond cleavage is leading N–H bond formation, resulting in a developing negative charge on C-2 in the transition state, (b) C–C bond cleavage is lagging behind N–H bond formation resulting in a developing positive charge on the ring nitrogen in the transition state, or (c) C–C bond cleavage has progressed at an even rate with N–H bond formation, resulting in no overall charge being developed on the ring in the transition state.

If the electron density on the ring nitrogen is changed (without changing anything else) by substituents, a rate change should be seen if N–H bond formation is leading C–C bond cleavage in the transition state. The electron density on the ring nitrogen is influenced by inductive effects[7,11,12] (*i.e.*, σ_m or σ'). If the electron density on the 2 carbon is changed (without changing anything else) by substituents, the rate constants should change if C–C bond cleavage leads N–H bond formation in the transition state. It has been shown that substituents para to the 2 position do affect the electron density at the 2 position. This relationship correlates well with σ_p.[13] Thus it should be possible to tell whether N–H bond formation or C–C bond cleavage is the major reaction in the transition state by observing if a linear relationship exists with σ_m, σ', or σ_p *vs.* log k/k_0. If pathway a exists, this method will not eliminate any of the possible transition states without reasonable assumptions, and, if pathway c exists, then the method will not work. It has been shown that transition state IV (pathway b) is used by the 6-substituted 2-pyridinecarboxylic acids by the ob-

(1) Presented in part at the Combined 22nd Southeastern and 26th Southwestern Regional Meetings of the American Chemical Society, New Orleans, La., Dec 1970.

(2) To whom inquiries should be made.

(3) L. W. Clark, *J. Phys. Chem.*, **66**, 125 (1962).

(4) L. W. Clark, *ibid.*, **69**, 2277 (1965).

(5) N. H. Cantwell and E. V. Brown, *J. Amer. Chem. Soc.*, **74**, 5967 (1952).

(6) N. H. Cantwell and E. V. Brown, *ibid.*, **75**, 4466 (1953).

(7) R. J. Moser and E. V. Brown, *J. Org. Chem.*, **36**, 454 (1971).

(8) See, for example, H. E. Hallam in "Infrared Spectroscopy and Molecular Structure," M. Davies, Ed., Elsevier, New York, N. Y., 1963, Chapter XII.

(9) See, for example, B. Harrow, and A. Mazer, "Textbook of Biochemistry," 9th ed, W. B. Saunders Co., Philadelphia, Pa., 1968, p 63.

(10) C. M. Huggins, G. C. Pimentel, and J. N. Shoolery, *J. Phys. Chem.*, **60**, 1311 (1956).

(11) H. H. Jaffé and G. O. Doak, *J. Amer. Chem. Soc.*, **77**, 4444 (1955).

(12) M. Charton, *ibid.*, **86**, 2033 (1964).

(13) Y. Otsuji, Y. Koda, M. Kubo, M. Furukawa, and E. Imoto, *Nippon Kagaku Zasshi*, **80**, 1293 (1959); *Chem. Abstr.*, **55**, 6476c (1960).

servation that electron-withdrawing substituents at the 6 position increase $\Delta G^{\pm}$ values.[7] In this case there was a linear relationship between σ' *vs.* ln k_1/k_0 (see Figure 1).

Results and Discussion

The 5-substituted 2-pyridinecarboxylic acids, 5-nitro-2-pyridinecarboxylic, 2,5-pyridinedicarboxylic, 5-iodo-2-pyridinecarboxylic, and 5-methoxy-2-pyridinecarboxylic acids were synthesized and their rates of decarboxylation in 3-nitrotoluene were determined. The rate constants are in Table I, and the activation parameters are in Table II. The coefficient of variation for the data has been calculated in each case. This value is used as a measure of the relative variability of the data. In all cases it is <5%. To get an assurance that the carboxyl group at the 5 position in 2,5-pyridinedicarboxylic acid was not removed under the conditions employed, the rate of decarboxylation of 3-pyridinecarboxylic, 2-chloro-5-pyridinecarboxylic, and 2-nitro-5-pyridinecarboxylic acids at temperatures up to 200° were studied. No carbon dioxide was evolved. This has been noted previously.[14]

TABLE I

APPARENT FIRST-ORDER RATE CONSTANTS FOR THE DECARBOXYLATION OF 5-SUBSTITUTED 2-PYRIDINECARBOXYLIC ACIDS IN 3-NITROTOLUENE

Acid (registry no.)	Temp, °C	Rate constant[a] × 10^a sec^{-1}	Coefficient variation[b]
5-Nitro-2-pyridine-carboxylic acid (30651-24-2)	156.6	1.34	0.94
	159.8	1.78	0.90
	166.2	3.39	0.50
	170.5	4.63	1.57
	174.5	6.65	0.57
	180.0	10.65[c]	
2,5-Pyridinedicarboxylic acid (100-26-5)	166.0	2.03	1.01
	170.4	3.30	1.38
	175.2	3.86	2.44
	180.0	5.91[c]	
	180.5	6.50	1.84
	184.4	7.78	2.73
5-Iodo-2-pyridine-carboxylic acid (32046-43-8)	170.0	0.97	0.63
	175.8	1.83	0.46
	180.0	2.60[c]	
	180.1	2.63	0.54
	185.7	4.33	0.89
	190.0	6.39	1.29
2-Pyridinecarboxylic acid[d] (98-98-6)	158.5	0.57	3.51
	163.6	1.22	4.31
	169.8	1.92	1.21
	175.5	2.96	1.73
	179.5	4.49	1.14
5-Methoxy-2-pyridine-carboxylic acid (29082-92-6)	180.0	0.36[c]	
	189.6	0.95	0.39
	194.9	1.58	0.24
	200.2	2.89	1.05
	204.2	3.95	0.76
	210.0	6.78	1.43

[a] The initial concentration is $\sim 10^{-2}$ *M* in acid. [b] The coefficient of variation is calculated as follows: [(standard deviation) ÷ (average value of ln $a/a - x$)] × 100. [c] Calculated from rate constants at other temperatures. [d] See ref 7.

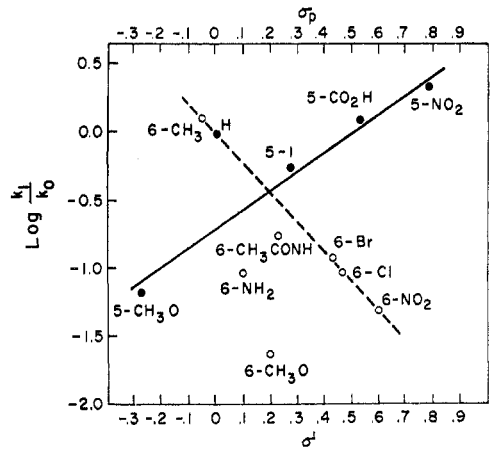


Figure 1.—A plot of σ *vs* log k_1/k_0. The 6 substituents (from ref 7) are plotted σ' *vs.* log k_1/k_0 at 200° and the 5 substituents are plotted σ_p *vs.* log k_1/k_0 at 180°.

Table II shows that, as the electron-withdrawing ability of substituents increase, the activation energies ($\Delta G^{\pm}$) decrease. 2-Pyridinecarboxylic acid does not fit into this generalization, and it will be discussed later. A correlation of rates of decarboxylation *vs.* σ_m or σ' was not found. Figure 1 shows that a linear relationship exists between the σ_p values of the 5-nitro, 5-carboxyl, 5-iodo, and 5-methoxyl groups and their relative rate constants. The slope of this line is +1.4. A positive value of this magnitude indicates that a negative charge is being developed in the transition state. This does not eliminate any of the proposed transition states, since a negative charge can be developed in any of them. Transition state III can be eliminated because it is difficult to envision a decarboxylation mechanism under the present conditions that does not involve acid–base interaction as in transition state IV and V. Because different trends were observed in the Hammett $\sigma\rho$ plots the transition state for the 5-substituted 2-pyridinecarboxylic acids must be different from the transition state for the 6-substituted 2-pyridinecarboxylic acids (see Figure 1). The first approach to present a unifying picture of decarboxylation of 5- and 6-substituted acids is to assume that, if IV is the transition state for both the 5- and 6-substituted 2-pyridinecarboxylic acids, then pathway a and not b exists in this case. This results in a developing negative charge at C-2 in the transition state. This idea is dismissed because it is difficult to explain why N–H bond formation should lead C–C bond cleavage in the 6-substituted 2-pyridinecarboxylic acids and not in the 5-substituted 2-pyridinecarboxylic acids. The electron density on the ring nitrogen is less affected by a 5 substituent than a 6 substituent. This type of argument eliminates transition state IV.

A more satisfying mechanism is presented in Scheme II. Assume that the two steps in transition state IV, bond making and bond breaking, are affected by substituents. N–H bond formation is difficult in the 6-substituted 2-pyridinecarboxylic acids, because electron withdrawal by the inductive effect from the nitrogen would be strong. These acids decarboxylate by transition state IV in the top mechanism (*i.e.*, N–H bond formation is the determining factor). N–H bond formation is easier in the 5-substituted 2-pyridinecarboxylic acids, because of the meta position and greater

(14) A. Kaneda and T. Hara, *Sci. Eng. Rev. Doshisha Univ.*, **7**, 172 (1967).

TABLE II

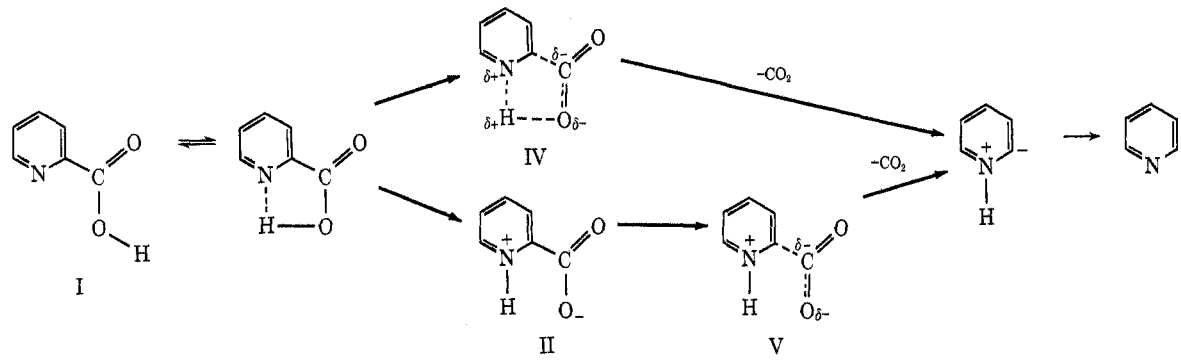
APPARENT FIRST-ORDER ACTIVATION PARAMETERS FOR THE DECARBOXYLATION OF 5-SUBSTITUTED 2-PYRIDINECARBOXYLIC ACIDS IN 3-NITROTOLUENE

Acid	$\Delta G^{\ddagger}_{180}$, kcal/mol	E_{act}, kcal/mol	$\Delta H^{\ddagger}_{180}$, kcal/mol	$\Delta S^{\ddagger}_{180}$, cal/deg mol	Coefficient variation[a]
5-Nitro-2-pyridinecarboxylic acid	33.06	34.19	33.25	+0.40	0.34
2,5-Pyridinedicarboxylic acid	33.86	28.66	27.72	−12.97	1.03
5-Iodo-2-pyridinecarboxylic acid	34.21	38.13	37.19	+6.28	0.39
2-Pyridinecarboxylic acid[b]	33.71	36.54	35.60	+3.99	1.14
5-Methoxy-2-pyridinecarboxylic acid	35.87	42.98	42.04	+13.04	0.41

[a] This is the value for the least-square fit in the calculation of E_{act}. It is calculated as follows: [(standard deviation) ÷ (average value of ln k)] × 100. [b] See ref 7.

SCHEME II

SUGGESTED MECHANISMS FOR DECARBOXYLATION OF 2-PYRIDINECARBOXYLIC ACID



distance of the substituent from the ring nitrogen. These acids decarboxylate by transition state V in the bottom mechanism (*i.e.*, C–C bond cleavage is the determining factor).

One of the results of a Hammett $\sigma\rho$ plot is that all of the compounds which fall on the plotted line decarboxylate by the same mechanism if the $\Delta S^{\ddagger}$ is relatively constant or increases[15] with increasing $\Delta H^{\ddagger}$. We propose that 5-nitro-, 5-carboxy-, 5-iodo-, and 5-methoxy-2-pyridinecarboxylic acids all have transition state V for decarboxylation, and it is shown in the bottom mechanism of Scheme II.

2-Pyridinecarboxylic acid does not fall on the line in Figure 1 for the 5-substituted 2-pyridinecarboxylic acids. This points out the fact that two different mechanisms do operate in the decarboxylation of the 5- and 6-substituted 2-pyridinecarboxylic acids. This acid does fall on the Hammett plot for the 6-substituted 2-pyridinecarboxylic acids. Thus, 2-pyridinecarboxylic acid has a transition state in which N–H bond formation leads C–C bond cleavage. This acid decarboxylates by the top mechanism in Scheme II. Why 2-pyridinecarboxylic acid should decarboxylate like the 6-substituted acids and not the 5-substituted acids is open to speculation.

(15) H. H. Jaffé and H. L. Jones, *Advan. Heterocycl. Chem.*, **3**, 209 (1964).

Experimental Section

The apparatus and procedure used to collect the kinetic data has been described previously.[7] All of the acids had satisfactory C, H, and N analyses which are reported only for new compounds. Melting points were determined with a Fisher-Johns block and are uncorrected.

Preparation of 5-Nitro-2-pyridinecarboxylic Acid.—6-Chloro-5-nitro-2-methylpyridine was prepared as described.[16] This compound was then reduced to 5-nitro-2-methylpyridine[17] and oxidized to the corresponding acid.[17] It had mp 209° (lit.[18] mp 210°).

Preparation of 2,5-Pyridinedicarboxylic Acid.—This compound was purchased from Aldrich Chemical Co., Inc. It had mp 257° (lit.[18] mp 256–285°).

Preparation of 5-Iodo-2-pyridinecarboxylic Acid.—The method of Plazek and Rodewald was used to prepare 5-iodo-2-methylpyridine.[19] This compound was then oxidized to 5-iodo-2-pyridinecarboxylic acid.[20] It had mp 202° (lit.[18] mp 204°).

Preparation of 5-Methoxy-2-pyridinecarboxylic Acid.—This compound was prepared by M. B. Shambhu. 5-Methoxy-2-methylpyridine was prepared[21] then oxidized to the acid.[17]

Anal. Calcd for $C_7H_7O_3N$: C, 54.8; H, 4.6; N, 9.2. Found: C, 54.5; H, 4.9; N, 9.1.

(16) H. E. Baumgarten and H. C. Su, *J. Amer. Chem. Soc.*, **74**, 3828 (1952).

(17) E. V. Brown, *ibid.*, **76**, 1367 (1954).

(18) E. P. Oliveto, *Heterocycl. Compounds*, **14** (3), Chapter 10 (1962).

(19) E. Plazek and Z. Rodewald, *Rocz. Chem.*, **21**, 150 (1947); *Chem. Abstr.* **42**, 5456*b* (1948).

(20) G. Gerrari and E. Marcon, *Educ. Sci.*, **14**, 594 (1959); *Chem. Abstr.*, **54**, 6709*a* (1960).

(21) L. Marion and W. F. Cockburn, *J. Amer. Chem. Soc.*, **71**, 3403 (1949).