3,4-Dihydroisocarbostyril (X) was prepared by two independent methods, both of which gave identical products which could not, however, be obtained crystalline.[33]

In the first, an ether solution of 5.0 g. (0.03 mole) of *o*-carboxyphenylacetonitrile[34] was esterified with diazomethane. After removal of the solvent, the residue was taken up in ethanolic hydrochloric acid containing platinum oxide and hydrogenated at 50 p.s.i.g. in a Parr apparatus. After H_2 uptake had ceased (2 hr.), the solution was filtered and evaporated to dryness on a rotary evaporator. The residual β-(*o*-carbomethoxyphenyl)ethylamine hydrochloride was recrystallized from ethanol; m.p. 183–184°. One gram of the above salt was shaken with ether and 5% sodium hydroxide solution. The ether layer was washed and dried over sodium sulfate, then evaporated, leaving 0.8 g. of oily 3,4-dihydroisocarbostyril (X) having ν_{max} 1657 cm.$^{-1}$. No other carbonyl bands appeared in the infrared spectrum.

The second method for preparing X involved reaction of ethyl chloroformate (0.18 mole) with β-phenylethylamine (0.36 mole) in ether, from which amine hydrochloride precipitated. After 2 hr., the ether solution was filtered and distilled, yielding ethyl N-(β-phenylethyl)carbamate, b.p. 165–175° (14 mm.), which solidified on standing, m.p. 37–39°. A mixture containing 2.0 g. of the above carbamate and 40 g. of PPA was heated at 150° for 2 hr., then cooled and poured into excess ice–water. Ether extraction, followed by washing with sodium bicarbonate solution, water, and drying over sodium sulfate, yielded, after solvent evaporation, *ca.* 1.0 g. of oily X. The infrared and n.m.r. spectra of this lactam sample were identical with those of the product of the first synthesis.

Reaction of II with Deuterated PPA.—As mentioned in the Discussion, experiments designed to distinguish between nitrene and iminium ion insertion mechanisms had to be carried out in a special way in order to avoid extraneous H/D exchange in the work-ups.

Deuterated polyphosphoric acid (PPA-*d*) was prepared from the reaction of 16.4 g. of phosphorus pentoxide and 3.6 g. of D_2O. The resulting viscous liquid had 82% P_2O_5 content, as does ordinary PPA.

In experiments where a fast work-up was necessary to minimize exchange after the insertion had occurred (Table II, runs 1 and 3) the cooled mixture of II (0.3–0.6 g.) in PPA-*d* was poured directly into a rapidly stirred, two-phase mixture of ether and concentrated aqueous potassium hydroxide, which was cooled to −5° in an ice–salt bath. The ether layer, which contained all of the products, was immediately separated from the basic aqueous solution, filtered through anhydrous sodium sulfate, and treated with 2–3 drops of 70% perchloric acid to precipitate III-perchlorate directly (lactams remained in solution). The salt (70–75% yield) was removed by suction filtration, washed with anhydrous ether, and dried overnight *in vacuo* at 55° before combustion analysis[28] for D content. Qualitative estimates of the extent of deuterium incorporation were possible from the n.m.r. spectra of III-perchlorate samples obtained from the PPA-*d* reactions, by noting the intensity of the 3.47 p.p.m. signal, which would show a relative area corresponding to 4 methylene protons on adjacent carbons if no D were present, and comparing it with the *gem*-dimethyl signal (1.5 p.p.m., relative intensity 6) and/or the aromatic proton signal (relative intensity 2).

As a control, it was necessary to check the change in deuterium content, if any, when III-perchlorate containing a known amount of deuterium at the carbon α to the imine carbon was subjected to the above fast work-up, after being dissolved in PPA-*d*. The control sample was obtained by treating II with PPA-*d*, then diluting with D_2O and using the *slow* work-up procedure to allow maximum exchange before isolation of III-perchlorate (Table II, run 2). Thus a sample containing essentially *two* D atoms was obtained. This material was found to retain *ca.* 55% of its deuterium content when dissolved in PPA-*d* and worked up by the fast procedure just described (Table II, run 3).

Acknowledgment.—This research was partially supported by Grant No. 550-A of the Petroleum Research Fund, American Chemical Society. Grateful acknowledgment is made to the donors of this found for their generous support. We also appreciate a gift of polyphosphoric acid from Victor Chemical Corporation.

(33) C. J. Cavallito and T. H. Haskell, *J. Am. Chem. Soc.*, **66**, 1166 (1944).
(34) C. C. Price and R. G. Rogers, *Org. Syn.*, **22**, 30 (1942).

[CONTRIBUTION NO. 1681 FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES, LOS ANGELES, CALIFORNIA]

Kinetic Studies of the Decarboxylation of Some N-Substituted Pyridinecarboxylic Acids

BY PAUL HAAKE AND JOAQUIN MANTECÓN

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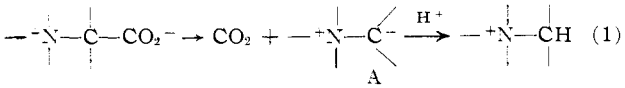
The relative rates of decarboxylation of N-methylpicolinic acid (homarine) (F), picolinic acid N-oxide (G), and picolinic acid (H) are found to be 720:160:1 at 134° in ethylene glycol as solvent. Homarine (F) is found to decarboxylate about 10^3 times faster than the other position isomers, trigonelline (I) and N-methylisonicotinic acid (K). Possible explanations are offered on the basis of the activation parameters. Divalent metal ions, Cu^{+2}, Mg^{+2}, and Mn^{+2}, are found to inhibit the decarboxylation of picolinic acid and picolinic acid N-oxide. The enhanced rate of decarboxylation of homarine is related to a possible role of this betaine in invertebrate biochemistry and physiology.

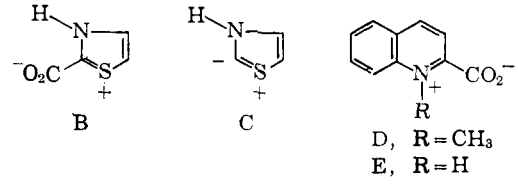
Introduction

The decarboxylation of acids with the carboxylate group α to a quaternary ammonium function (eq. 1) is well known[1] to proceed at an accelerated rate presumably attributed to inductive stabilization of the carbanion in the form of an ylid intermediate (A).



(1)

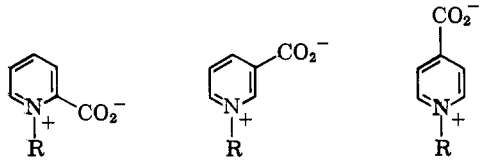
Thiazole-2-carboxylic acid (B) was observed[2] to decarboxylate several powers of 10 faster than the 4- or 5-carboxylic acids, a result which apparently was not used in the search for the active site of thiamine but which clearly reflects the unusual stability of the thiazolium ylid (C).[3,4]



Brown and Hammick[5] measured the rates of de-

(1) B. R. Brown, *Quart. Rev.* (London), **5**, 131 (1951).
(2) H. Schenkel and M. Schenkel-Rudin, *Helv. Chim. Acta*, **31**, 924 (1948).
(3) R. Breslow, *J. Am. Chem. Soc.*, **79**, 1792 (1957).
(4) P. Haake and W. B. Miller, *ibid.*, **85**, 4045 (1963).
(5) B. R. Brown and D. Ll. Hammick, *J. Chem. Soc.*, 659 (1949).

carboxylation of quinaldinic and isoquinaldinic acids, and on the basis of a single, crude experiment estimated that the betaine, N-methylquinaldinic acid (D), decarboxylated 50 times faster than quinaldinic acid (E) in quinoline as solvent. A preparative paper[6] on N-methylpyridinecarboxylic acids states that solutions of N-methylpicolinic acid (homarine) (F) "must not be heated or decomposition takes place" indicating rapid decarboxylation of this N-methylbetaine. Picolinic acid (G), on the other hand, does not decarboxylate readily at temperatures below 150°.[7] These results suggest that methylation produces a large rate enhancement, but there has been no reliable measurement of this effect. Since homarine (F) has been found in invertebrates in large quantities[8,9] and no function has been found for this simple molecule,[9] there is further interest in the decarboxylation of homarine as a possible model for a biochemical role.



F, R = CH_3
G, R = H
H, R = OH

I, R = CH_3
J, R = H

K, R = CH_3
L, R = H

Experimental

Materials.—Homarine hydrochloride[10] was dried under vacuum over H_2SO_4. The purity was determined by titration with standardized base and was found to be 97.5%. In all calculations involving homarine, corrections for the degree of purity were made. The material does not have a melting point and decomposes slowly when heated. The amounts of CO_2 evolved in decarboxylations were in agreement with the neutralization equivalent. Commercially available picolinic acid was recrystallized twice from absolute ethanol and dried over H_2SO_4 under vacuum, m.p. 136-137°. Crystalline picolinic acid N-oxide was obtained from Aldrich Chemical Co.; m.p. 165-166°. Crystalline trigonelline hydrochloride[10] showed a neutralization equivalent 99.5% of theoretical. N-Methylisonicotinic acid (L) was prepared by the method of Kosower and Patton[6] from 4-carboxy-1-methylpyridinium iodide ethyl ester.[11] The n.m.r. of L in D_2O showed the expected methyl singlet and a doublet of doublets at lower field for the ring protons (J = 6 c.p.s.). The ratio of the integrated areas was 3:4 as expected. Nicotinic acid and isonicotinic acid were both U.S.P. grade and were used after drying over H_2SO_4 under vacuum. Eastman Kodak synthetic grade quinoline was distilled before use. Commercially available ethylene glycol (Eastman Kodak, White Label) was used without further purification.

Rate Measurement.—The apparatus employed in the kinetic measurements is a modification of the one employed by Cantwell and Brown[12] for gravimetric estimation of rates of decarboxylation. It consisted of a 100-ml. round-bottom flask equipped with a condenser. A vacuum take-off was placed at the top of the condenser. The inner inlet tube of the vacuum take-off had been pulled to a thin capillary that reached to the bottom of the flask and enabled a current of dry nitrogen to be passed through the solution in order to provide agitation and to ensure efficient removal of CO_2 from the solution. The take-off was connected to a three-way stopcock attached to an absorption train consisting of two sets of U-shaped absorption tubes. The first absorption tube of each set contained anhydrone and the second one Ascarite. The tubes were connected to one another by short lengths of rubber tubing. The average weight of the Ascarite-filled absorption tubes was 60 g. During an experiment they were removed alternatively and weighed on an analytical balance to 0.1 mg.

In each experiment, 1.5 mmoles of the compound being studied was dissolved in 30 ml. of solvent in the reaction flask. The connections were made and the system was swept free of air by a carefully regulated stream of nitrogen (35 cc. $min.^{-1}$). After the reaction flask was lowered into the constant temperature bath, first one absorption tube was exposed and then the other to the exiting gas stream by turning the stopcock in the absorption train providing time for alternate weighing of the absorption tubes. The temperature of the bath was kept constant to ±0.2° and the temperature readings were made with calibrated thermometers with divisions of 0.1°.

Calculations.—The values reported in the results section were calculated graphically from the equation

$$\log \frac{W_\infty}{W_\infty - W_t} = \frac{k}{2.303}t$$

where

W_∞ = calculated weight of CO_2 produced at 100% reaction

W_t = weight of CO_2 evolved at time, t

After the reacting solution reached bath temperture (10–20 min.), good straight lines were obtained to more than 80% reaction in all cases except picolinic acid N-oxide, where anomalous behavior appears after 50% reaction (see Fig. 1). For this compound, the slope obtained for the first half-life after a 20 min. warm-up was used to evaluate the rate constant.

Least-squares treatment of typical data showed high precision of the method for individual runs excepting the N-oxide (Fig. 1); the standard deviation of the slope was always smaller than 2.5%.

A typical rate plot is shown in Fig. 2. The initial curvature of the line corresponds to the heating period during which the solution reaches the temperature of the bath.

Activation parameters were calculated[13] from the Arrhenius energy of activation which was estimated graphically from a plot of log k *vs.* $1/T$.

Results

Decarboxylation of N-Methylbetaines.—Since homarine was available as the hydrochloride, quinoline in excess of the homarine concentration was added to the solvent, ethylene glycol, to ensure that homarine was present as the zwitterion (F); the first pK_a of protonated picolinic acid is 1.03[14] and the pK_a of quinolinium ion is 4.85.[15] The rate of decarboxylation was then found to be slightly dependent on quinoline concentration, so that the observed rate constant could

$$k_{obsd} = k_1 + k_2[\text{quinoline}] \qquad (2)$$

be expressed as in eq. 2. The observed rate constants are shown in Table I; plots of k_{obsd} against concentration of unprotonated quinoline ([quinoline total] − [homarine]) gave straight lines with the results shown in the last two columns of Table I. It was also possible to get straight line plots when k_{obsd} was plotted against volume % of quinoline. Thermodynamic activation parameters for both k_1 and k_2 are given in Table IV.

The decarboxylations of the other N-methylbetaines, trigonelline hydrochloride and N-methylisonicotinic

(6) E. M. Kosower and J. W. Patton, *J. Org. Chem.*, **26**, 1318 (1961).
(7) L. W. Clark, *J. Phys. Chem.*, **66**, 125 (1962).
(8) F. A. Hoppe-Seyler, *Z. physiol. Chem.*, **223**, 105 (1933).
(9) E. L. Gasteiger, P. C. Haake, and J. A. Gergen, *Ann. N. Y. Acad. Sci.*, **90**, 622 (1960).
(10) Purchased from Aldrich Chemical Co.
(11) C. A. Grob and E. Renk, *Helv. Chim. Acta*, **37**, 1677 (1954).
(12) N. H. Cantwell and E. V. Brown, *J. Am. Chem. Soc.*, **74**, 5967 (1952).
(13) K. J. Laidler, "Chemical Kinetics," McGraw–Hill Book Co., Inc., New York, N. Y., 1950, p. 73.
(14) P. O. Lumme, *Suomen Kemi.*, **30B**, 168 (1957).
(15) H. C. Brown, D. H. McDaniel, and O. Höfliger in E. A. Braude and F. C. Nachod, "Determination of Organic Structures by Physical Methods," Vol. 1, Academic Press, Inc., New York, N. Y., 1955, p. 600.

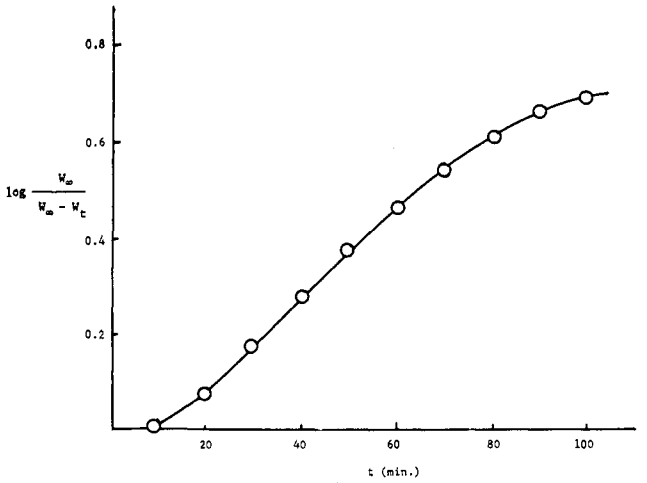


Fig. 1.—Rate plot for picolinic acid N-oxide decarboxylation.

acid, were studied in ethylene glycol containing 5% (v./v.) quinoline to provide a uniform medium for comparison of the rates, although N-methylisonicotinic acid was available in the nonprotonated form. The results of these decarboxylations are shown in Table II and compared with an extrapolated value for homarine at the same temperature.

TABLE I

RATE CONSTANTS FOR THE DECARBOXYLATION OF HOMARINE IN ETHYLENE GLYCOL[a]

Temp., °C.	[Quinoline] % v./v.	[Quinoline] M[b]	10^3k_{obsd}, sec.$^{-1}$	10^3k_{av}, sec.$^{-1}$	10^4k_1, sec.$^{-1}$	10^4k_2, M^{-1} sec.$^{-1}$
134.3	1.3	0.060	1.86			
134.3	1.3	.060	1.85	1.86		
134.3	5.0	.373	2.17			
134.3	5.0	.373	2.13	2.15	17.5	9.40
134.3	10.0	.797	2.56			
134.3	10.0	.797	2.54	2.55		
123.6	1.5	.066	0.523			
123.6	1.5	.066	.514	0.519		
123.6	5.0	.373	.622			
123.6	5.0	.373	.622	0.622	4.72	3.44
123.6	10.0	.797	.765			
123.6	10.0	.797	.778	0.772		
115.1	1.5	.066	.165			
115.1	1.5	.066	.165	0.165		
115.1	5.0	.373	.199	0.199	1.52	1.06
115.1	10.0	.797	.230			
115.1	10.0	.797	.246	0.238		

[a] Homarine concentration 0.050 M. [b] The molarity given is for the concentration of unprotonated quinoline which was obtained by subtracting the concentration of homarine from the total quinoline concentration.

TABLE II

DECARBOXYLATION OF N-METHYLPYRIDINECARBOXYLIC ACIDS IN ETHYLENE GLYCOL[a] AT 196.1°

Carboxyl position	[Quinoline], % v./v.	$k \times 10^3$, sec.$^{-1}$	Rel. k
4 (K)[b]	5	0.742	1
3 (I)[c]	5	2.11	2.8
2 (F)[d]	5	1.2×10^3[e]	1600

[a] Concentration of substrate 0.05 M. [b] N-Methylisonicotinic acid betaine was used. [c] Trigonelline hydrochloride was used. [d] Homarine hydrochloride was used. [e] Value extrapolated from measurements at lower temperatures.

Decarboxylation of Picolinic Acid and Picolinic Acid N-Oxide.—The decarboxylation of picolinic acid showed well behaved rate plots in ethylene glycol as

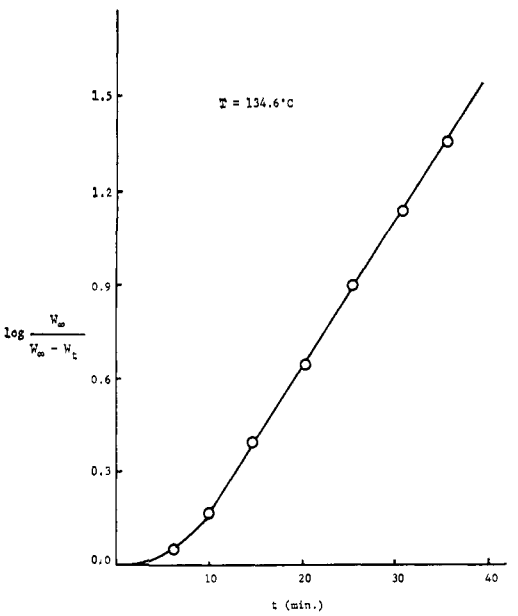


Fig. 2.—Rate plot for homarine.

expected. Addition of quinoline in the case of the N-oxide led to a lowered rate of decarboxylation. The results of these experiments are shown in Table III,

TABLE III

RATE CONSTANTS FOR THE DECARBOXYLATION OF PICOLINIC ACID AND PICOLINIC ACID N-OXIDE[a]

Temp., °C.	Metal ion[c]	$k \times 10^4$, sec.$^{-1}$	$k_{av} \times 10^4$, sec.$^{-1}$
	Picolinic acid (G)		
155.9	...	0.228	
155.9	...	.201	0.214
171.5	...	.921	0.902
171.5	...	.884	
171.5	Cu^{+2}	.0403	
171.5	Mn^{+2}	.292	
171.5	Mg^{+2}	.472	
185.9	...	3.25	
185.9	...	3.20	3.23
134.3	...	...	0.0243[b]
	Picolinic acid N-oxide (H)		
115.1	...	0.405	
115.1	...	0.401	0.403
123.2	...	1.05	
123.2	...	1.08	1.06
134.3	...	3.92	3.95
134.3	...	3.98	
134.3	Cu^{+2}	2.07	
134.3	Mg^{+2}	2.60	
134.3	Mn^{+2}	3.11	
146.3	...	10.6	10.6
146.3	...	9.14[d]	9.14

[a] Solvent = ethylene glycol; [substrate] = 0.05 M. [b] Value extrapolated on basis of measurements at higher temperatures. [c] [Metal ions] = 0.025 M, added as chloride salts. [d] 10% quinoline present.

and the activation parameters calculated graphically from these results are given in Table IV. Divalent copper, manganese, and magnesium ions at a concentration equal to one-half the substrate concentration showed inhibitory effects on the decarboxylation of picolinic acid and picolinic acid N-oxide. As shown in Fig. 1, the rate data for picolinic acid N-oxide were not well behaved beyond 50% reaction and the rate constants were therefore estimated from data

TABLE IV

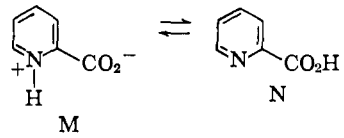
ACTIVATION PARAMETERS FOR THE DECARBOXYLATION OF HOMARINE, PICOLINIC ACID, AND PICOLINIC ACID N-OXIDE[a]

Substrate	Order of the reaction	ΔF^{*},[b] kcal. mole^{-1}	ΔH^{*},[b] kcal. mole^{-1}	ΔS^{*},[b] e.u.
Picolinic acid	First	34.6	34.4	−0.5
Picolinic acid N-oxide	First	30.4	36.8	15.7
Homarine	First	29.2	39.2	24.5
Homarine	Second	29.7	35.3	13.7

[a] Solvent = ethylene glycol; values calculated for 407.5°K. = 134.3°C. [b] The usual errors prevail in, these activation parameters[16]; a reasonable estimate would be ±1 kcal. in ΔF^{*} and ΔH^{*} and ±5 e.u. in ΔS^{*} for the decarboxylation of picolinic acid and the first-order decarboxylation of homarine which are the most important values in this study.

over the first half-life. Inaccuracies in the data for picolinic acid N-oxide will have no effect on the central conclusions in this paper, but there is, of course, considerably more uncertainty in the activation parameters for the N-oxide than for homarine and picolinic acid (see footnote *b*, Table IV).

Ground State of Picolinic Acid in Glycol.—A spectral study[17] indicated that picolinic acid exists as the zwitterion (M) in water and in the uncharged state (N) in ethanol. It is important to the ensuing discussion to know which state predominates in ethylene



M N

glycol. We find that the following extinction coefficients for picolinic acid and models for M and N indicate that in ethylene glycol picolinic acid must be mostly in the zwitterionic form: homarine (F) (a model for M), ϵ_{max} = 5830; methyl picolinate (a model for N), ϵ_{max} = 4000; picolinic acid, ϵ_{max} = 5240. The elevated temperatures used in this study will also have an effect on the above equilibrium.

Discussion

State of Substrates.—In ethylene glycol, homarine must exist as the zwitterion, the N-oxide by hydrogen bonding will have the proton bonded to both the N-oxide and the carboxyl groups, and our spectra indicate that picolinic acid is mostly, but not completely, in the zwitterionic form in the ground state.

Quinoline Effect.—Although the decarboxylation of homarine shows apparent first-order dependence on the concentration of quinoline as had been observed previously[18] for the decarboxylation of malonic acid, the effect of quinoline which we observed could be a simple medium effect. The lower ΔS^{*} and ΔH^{*} for the second-order decarboxylation of homarine compared to the first-order process support the idea that there is a direct interaction in the transition state between quinoline acting as a nucleophile and the carboxyl group.[18] Clark[7] has suggested that many solvent effects in decarboxylations which he has studied can be explained by bimolecular mechanisms involving nucleophilic attack of solvent on the carboxyl group. This conclusion is based largely on analogy with the decarboxylation of malonic acid which he assumes to be decarboxylating in all solvents by such a mechanism because of the earlier work on malonic acid[18] involving only quinoline. Clearly, solvents such as phenetole and dimethoxybenzene are relatively poor nucleophiles, and decarboxylations in such solvents at temperatures around 150° may well be unimolecular[1] with little participation by solvent. The ΔS^{*} values[7] for the decarboxylation of picolinic acid show no order with nucleophilicity of solvent as might be expected if the decarboxylations were partially bimolecular.

Pyridinium-2-carboxylates.—Comparison of the results in Tables I and III give the relative rates shown in Table V; homarine decarboxylates about 10^3 times faster than picolinic acid. Thus there is quantitative support for the previous qualitative observations[5,6] that N-methylbetaines decarboxylate more readily than the acids, but the relative rate of 50^5 observed for N-methylquinaldinic acid and quinaldinic acid may well be in error by an order of magnitude. Table IV shows that ΔH^{*} values are in the reverse order from the relative rates; ΔH^{*} (homarine) is nearly 5 kcal. greater than ΔH^{*} (picolinic acid).

TABLE V

RELATIVE RATES OF DECARBOXYLATION OF PYRIDINIUM-2-CARBOXYLATES

Compound	k (relative, 134°)
Picolinic acid	1
Picolinic acid N-oxide	160
Homarine (first-order rate)	720
(total at 10% quinoline)	1070

The ΔH^{*} values are not unreasonable in view of the electronic effects which might be expected. Any increase in electron density in the ring or any decrease in electron density on the carboxylate group should increase ΔH^{*}; the larger ΔH^{*} for homarine at least partly reflects the electron-donating ability of the N-methyl. Since the N-oxide is hydrogen bonded, there will be decreased electron density on the carboxyl group in this compound.

Since picolinic acid in the ground state is partially in the uncharged form (N; see Results), some solvent organization will occur during the decarboxylation of this compound which could partially explain the $\Delta\Delta S^{*}$ = 24.5 e.u. between homarine and picolinic acid. In addition, Fisher–Taylor–Hirschfelder models confirmed the suspicion that in the ground state of homarine (F) there is strong interaction between the N-methyl and the carboxyl. The model may be built and the carboxyl may be coplanar with the ring, but any attempt to rotate the methyl group causes the carboxyl to turn out of the plane of the ring and ring-carboxyl π-bonding would be lost. Consequently, in the decarboxylation of homarine, unlike picolinic acid, rotational and vibrational (mostly rotational) degrees of freedom would be gained in going from ground state to transition state thereby making contribution toward

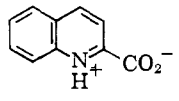
(16) S. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p. 91.

(17) H. P. Stephenson and H. Sponer, *J. Am. Chem. Soc.*, **79**, 2050 (1957). Extinction coefficients (increased in pyridinium ions) were used to decide the state of picolinic acid in ethanol and water. The same critierion is used here, but our models are different from those used by Stephenson and Sponer. We also measured the spectra in ethanol and water, and our results also indicate that picolinic acid is predominantly M in water and N in ethanol.

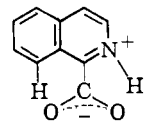
(18) G. Fraenkel, R. L. Bedford, and P. E. Yankwich, *ibid.*, **76**, 15 (1954).

a positive ΔS^* for homarine.[19] The loss of H-bonding in the transition state for decarboxylation of picolinic acid N-oxide would also allow more degrees of freedom than in the ground state.

The large difference in rates[5] (Table VI) of decarboxylation of quinaldinic (O) and isoquinaldinic acids (P) can probably be attributed to a steric effect; the carboxyl in (P) cannot be coplanar with the ring owing to interaction with the *peri* hydrogen; this raises the



O



P

energy of the ground state, less energy is needed to get to the transition state, and ΔH^* is smaller than for O which can have its carboxyl coplanar with the ring. Therefore, the steric effect in homarine appears in $\Delta\Delta S^*$, but the steric effect in isoquinaldinic acid appears in $\Delta\Delta H^*$.

TABLE VI

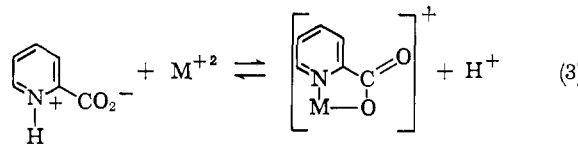
DECARBOXYLATION OF QUINALDINIC ACID AND ISOQUINALDINIC ACID IN ACETOPHENONE[a]

Compound	T, °K.	10^4k, sec.$^{-1}$	ΔH^*, kcal./mole	ΔS^*, e.u.	Rel. rate (100°)
Quinaldinic acid (O)	373.4	0.0048[a]	36.7	10.5	1
Isoquinaldinic acid (P)	373.4	1.73	32.1	9.82	350

[a] Rate constant obtained by extrapolation to 373.4°K.

Position Isomers of Homarine.—Table II shows that the rate of decarboxylation of the N-methyl acids decreases by a factor of 2.8 as the site of the decarboxylation moves from the 3- to the 4-position of the pyridinium ring. This factor, 2.8, is very close to the normal fall off of inductive effects with distance[20]; this shows that the primary electronic effect on decarboxylation is inductive and, in contrast to the pyridylacetic acids,[21] resonance effects through the π-system have little influence on the rates of these decarboxylations. The 2-carboxyl isomer, homarine, decarboxylates at a greatly increased rate (Table II) over that expected from inductive effects alone; this is probably partly attributable to the carboxyl–methyl interaction in the ground state of homarine.

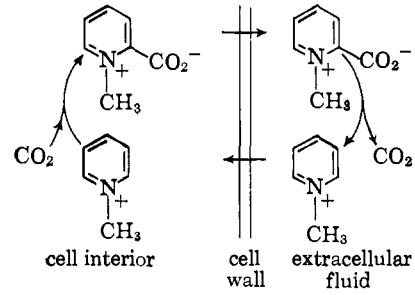
Effect of Metal Ions.—Unlike β-keto acids,[22] divalent metal ions *inhibit* the decarboxylation of picolinic acid and picolinic acid N-oxide. The order of increasing inhibition of the decarboxylation of picolinic acid (Table III) is very likely due to chelate formation (3) which decreases the electronic density on the carboxyl;



(3)

both AM^+ and A_2M chelates are possible. The stability constants of such chelates in water have been evaluated[23]; they increase in the same order, $Mg^{+2} < Mn^{+2} < Cu^{+2}$, as our rate constants and this explanation require. The weaker inhibition of the decarboxylation of picolinic acid N-oxide by the same metal ions is probably caused by one or both of two factors: (a) weaker binding of metal ion to oxygen than to nitrogen,[24] and (b) lesser stability of 6-membered compared to 5-membered chelate rings.[25]

Biological Function of Homarine.—The unusually large quantities of homarine in invertebrates[8,9] suggest that there must be some physiological role for this molecule. The amounts present[9] seem to be far more than would be required for a coenzyme of the DPN type to which there is some structural analogy. An important observation is that there is the most homarine in the largest invertebrates examined and in the tissues that are metabolically most active.[9] A possible hypothesis for the function of homarine is that the poorly developed circulatory systems of invertebrates require that the larger species have a CO_2 sink to store this metabolic product during periods of activity, and that homarine is the result of carboxylation of N-methylpyridinium ion as part of such a CO_2 storage. This hypothesis could also involve homarine in the active transport of ions by passage of the dipolar but neutral homarine out of cells and return of the positive N-methylpyridinium ion into cells (4). Our studies show that homarine is unusual in its rate of decarboxylation compared to similar compounds and to this extent support the above speculation concerning its biological function.



(4)

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