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Formic Acid Reduction. XXVIII.[1] Kinetic Studies on the Formic Acid Reduction of 1,1′-Benzylidenedipiperidine

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The formic acid reduction of 1,1′-benzylidenedipiperidine (**1**) was kinetically investigated by the carbon dioxide trapping method. Rate data gave the rate equation, $v = k_{obs}[\mathbf{1}][HCOOH]$. The initial mono- and diprotonation of **1** occur in equilibrium, and monoprotonated form is proposed to be an intermediate for the reduction to 1-benzylpiperidine. The isotope effect value (2.69) and the negative ρ substituent effect (similar to that of the formic acid reduction of N-benzylideneaniline) suggest that the reduction of **1** involves the same intermediate step of decarboxylation of the formic acid ester of the α-amino alcohol.

Keywords——formic acid reduction; 1,1′-benzylidenedipiperidine; kinetic studies; isotope effect; Hammett's substituent effect; hydride transfer

As part of a program of studies on the formic acid reduction mechanism, kinetic studies on the reduction of N-benzylideneaniline[3] and 5-benzylidene-1,3-dimethylbarbituric acid[4] were previously described, showing that the process effected by the formate anion involves hydride transfer with decarboxylation. Furthermore, two decades ago, the formic acid reduction of triphenylcarbinol[5] was interpreted in terms of a hydride transfer mechanism. However, a later paper[6] reported a radical mechanism for the formic acid reduction of 1,1′-benzylidenedipiperidine (**1**), which involves decarboxylation of the formic acid ester of the α-amino alcohol through a radical chain path. This proposal was based, in the main, on the decrease and increase of the rate upon addition of hydroquinone and diphenylamine, respectively, although the effects are not entirely clear because of uncertainty regarding the initial rate change. The function of formic acid in the majority of its reduction reactions may be essentially the same, and should be the same in the reactions of both **1** and N-benzylideneaniline. The above-mentioned two papers[3,6] dealing with the reduction mechanisms described the same intermediate, the formic acid ester of the α-amino alcohol, but proposed different mechanisms, one ionic and one radical.

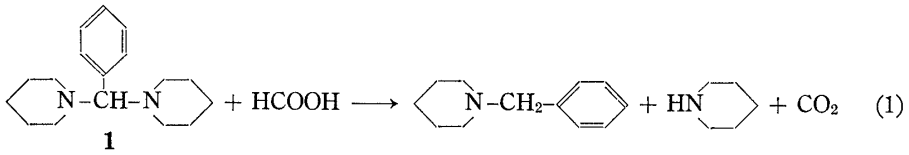
In order to clarify the situation, we conducted a kinetic study on the formic acid reduction of **1**. The effects of concentration of formic acid and triethylamine, the isotope effect and the substituent effect obtained in the present studies clearly favor a hydride transfer mechanism.

Results and Discussion

The formic acid reduction of **1** to 1-benzylpiperidine was kinetically investigated by means of soda-asbestos trapping of carbon dioxide evolved in the reaction. Based on the results of preliminary experiments, all rate measurements were carried out at a temperature of 0° in ethylene glycol monoethyl ether acetate (EGMEA) as a solvent. According to the stoichio-

1) Part XXVII: K. Nanjo and M. Sekiya, *Chem. Pharm. Bull.*, **27**, 198 (1979).
2) Location: *2-2-1 Oshika, Shizuoka-shi 422, Japan.*
3) M. Sekiya, K. Mori, K. Ito, and K. Suzuki, *Tetrahedron*, **29**, 57 (1973).
4) K. Suzuki, H. Fukawa, T. Okugawa, and M. Sekiya, *Chem. Pharm. Bull.*, **24**, 607 (1976).
5) R. Stewart, *Can. J. Chem.*, **35**, 766 (1957); R. Grinter and S.F. Marson, *Trans. Farad. Soc.*, **60**, 889 (1964).
6) A. Lukasiewicz, *Tetrahedron*, **19**, 1789 (1963).

metry of the reduction of **1** with formic acid given by Eq. 1, an experiment under the above conditions gave 1-benzylpiperidine in 86% yield.



1 (1)

Putting a as the initial concentration of formic acid, b the initial concentration of **1** and x the total amount of carbon dioxide evolved at time t, a second-order rate expression for the reduction can be written in the form of Eq. 2, or Eq. 3 as an integrated form.

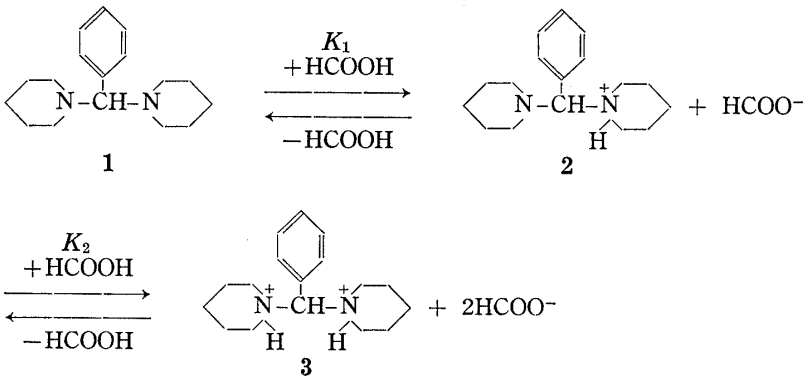
$$dx/dt = k_{obs}(a-x)(b-x) \quad (2)$$

$$1/(a-b)\cdot 1n[b(a-x)/a(b-x)] = k_{obs}t \text{ or } y = k_{obs}t \quad (3)$$

In runs with various initial concentrations of **1** and formic acid, plots of y against t gave a straight line by the least-squares method with a correlation coefficient of over 0.99, giving the second-order rate constants k_{obs}, shown in Table I. It is noticeable that at higher concentrations of formic acid (over 4 molar equivalents against **1**), the values of k_{obs} calculated from Eq. 3 abruptly decrease. This implies that rate constant k_{obs} is related to the acidity of the reaction medium.

A similar observation was also made in experiments on the effect of addition of triethylamine on the rate. Rate measurements were carried out with addition of increasing amounts of triethylamine to a mixture of **1** and formic acid in 1 : 5 molar ratio. As shown in Fig. 1, an increasing rate was observed in the earlier stages of addition of triethylamine, and an abrupt decrease was observed on further addition.

Since the substrate **1** is dibasic, protonation of **1** by formic acid is in the following equilibrium.



1 **2** **3**

The observation that an increasing concentration of formic acid in the reaction medium lowers the rate is considered to be due to a shift of the equilibrium to the right, increasing the concentration of **3**. The diprotonated **3** and a formate anion may form a structure possessing a bridged hydrogen bonding, which allows a favorable and nonstrained configuration as shown in Fig. 2. This structure of **3** may be stable enough to be inert to the subsequent reduction step. Therefore, it is likely that the monoprotonated **2** in the above equilibrium is an intermediate in the path of the transformation into 1-benzylpiperidine, whereas the diprotonated **3** is not. As already mentioned, the observed rate obeys the second-order equation, $v=k_{obs}$ [**1**][HCOOH]. However, we were not able to express the rate as a function of [**2**], because many difficulties were encountered in determination of the equilibrium constants, K_1 and K_2, owing to the subsequent reduction.

Table I. Effect of Initial Concentrations of **1** and Formic Acid

[**1**]	[HCOOH]	[**1**]/[HCOOH]	$k_{obs} \times 10^4$ ($sec^{-1} \cdot M^{-1}$)
0.0667	0.200	1 : 3	6.865
0.100	0.200	1 : 2	7.006
0.100	0.250	1 : 2.5	7.025
0.100	0.300	1 : 3	7.118
0.100	0.400	1 : 4	6.936
0.100	0.500	1 : 5	3.277
0.100	0.600	1 : 6	1.470
0.100	0.700	1 : 7	0.713
0.100	0.800	1 : 8	0.318
0.100	1.00	1 : 10	0.110

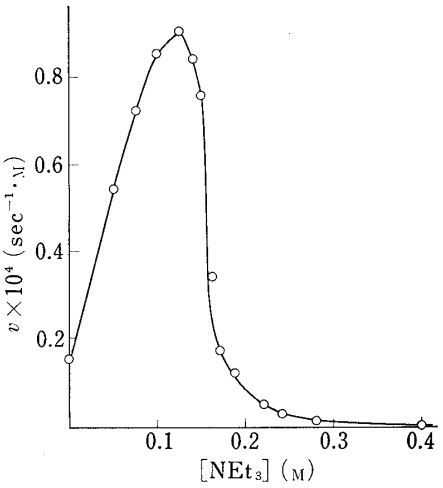


Fig. 1. Effect of NEt_3 at 0° in EGMEA
[**1**]=0.100 M; [HCOOH]=0.500 M.

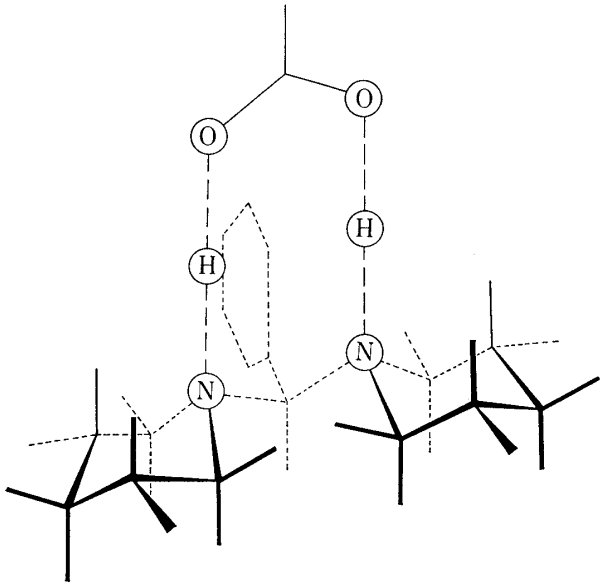


Fig. 2. Structure of **3**

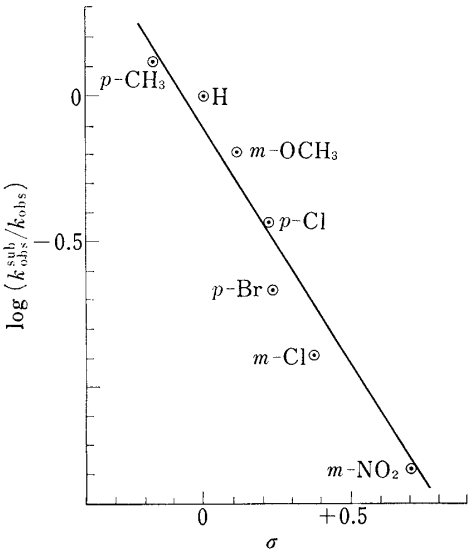


Fig. 3. Hammett Plot for the Formic Acid Reduction of **1** at 0° in EGMEA

In mechanistic treatments of formic acid reductions reported in previous papers,[3-5] considerable isotope effects (1.79—2.79) have been observed and regarded as reliable evidence for the process of hydride transfer from the formate anion. The isotope effect in the formic acid reduction of **1** was examined using deuterated formic-*d* acid (DCOOH) with [**1**]=0.100 M and [DCOOH]=0.300 M. Division of the k_{obs} value (7.118×10^{-4} $sec^{-1} \cdot M^{-1}$) by the obtained k_{obs}^{D} value (2.646×10^{-4} $sec^{-1} \cdot M^{-1}$) gave an isotope effect value of 2.69. This value of isotope effect correspods well to the value previously reported[7] for simple hydride transfer from C to C (1.8—2.6) in contrast to the wide range of values (0.84—11.7) for proton transfer.

Substituent effects in the benzene ring of **1** were then studied. Rate measurements were examined with several *p*- and *m*-substituted 1,1′-benzylidenedipiperidines (0.100 M) using [HCOOH]=0.300 M. Fig. 3 shows plots of $\log(k_{obs}^{sub}/k_{obs})$ *vs.* Hammett's σ-values for the substituents. A negative ρ-value, −1.73, was obtained by the least-squares method.

7) K.B. Wiberg, *J. Am. Chem. Soc.*, **76**, 5371 (1954); P.D. Bartlet and J.D. McCollum, *J. Am. Chem. Soc.*, **78**, 1441 (1956); K.B. Wiberg, *Chem. Rev.*, **55**, 723 (1955); R.P. Bell, "The Proton in Chemistry," Cornell Univ. Press, Ithaca, N.Y. 1959, p. 201.

As described above, the intermediate undergoing formic acid reduction is presumed to be the monoprotonated **2**. Two plausible paths from **2** can be written, *i.e.*, Path A and Path B in Chart 1. From the observed isotope effect, the rate-determining step is inferred to be a transfer of formyl hydrogen to the methine carbon as hydride in either path. In Path A, the hydride transfer step is an internal S_N2-like substitution of the formic acid ester of the α-amino alchol (**4**) which may be formed from the iminium formate derived from **2** by removal of piperidine, whereas Path B involves an S_N2 substitution at the methine carbon attacked by the hydride. It is not clear whether the negative ρ Hammett value is related to the equilibrium constants K_1 and K_2 of the initial protonation steps or the rate-determining hydride transfer step. The increase of the k_{obs} value by an electron-donating substituent can be interpreted in terms of an increase of the equilibrium constant K_1 or the release of the ester bond of **4** in Path A or of the C–N bond of **5** in Path B, which may overcome a hindrance to hydride transfer by increasing the electron density at the methine carbon. The step of decarboxylation of **4**, indicated in Path A, has previously been proposed as an intermediate step in the formic acid reduction of N-benzylideneaniline.[3]

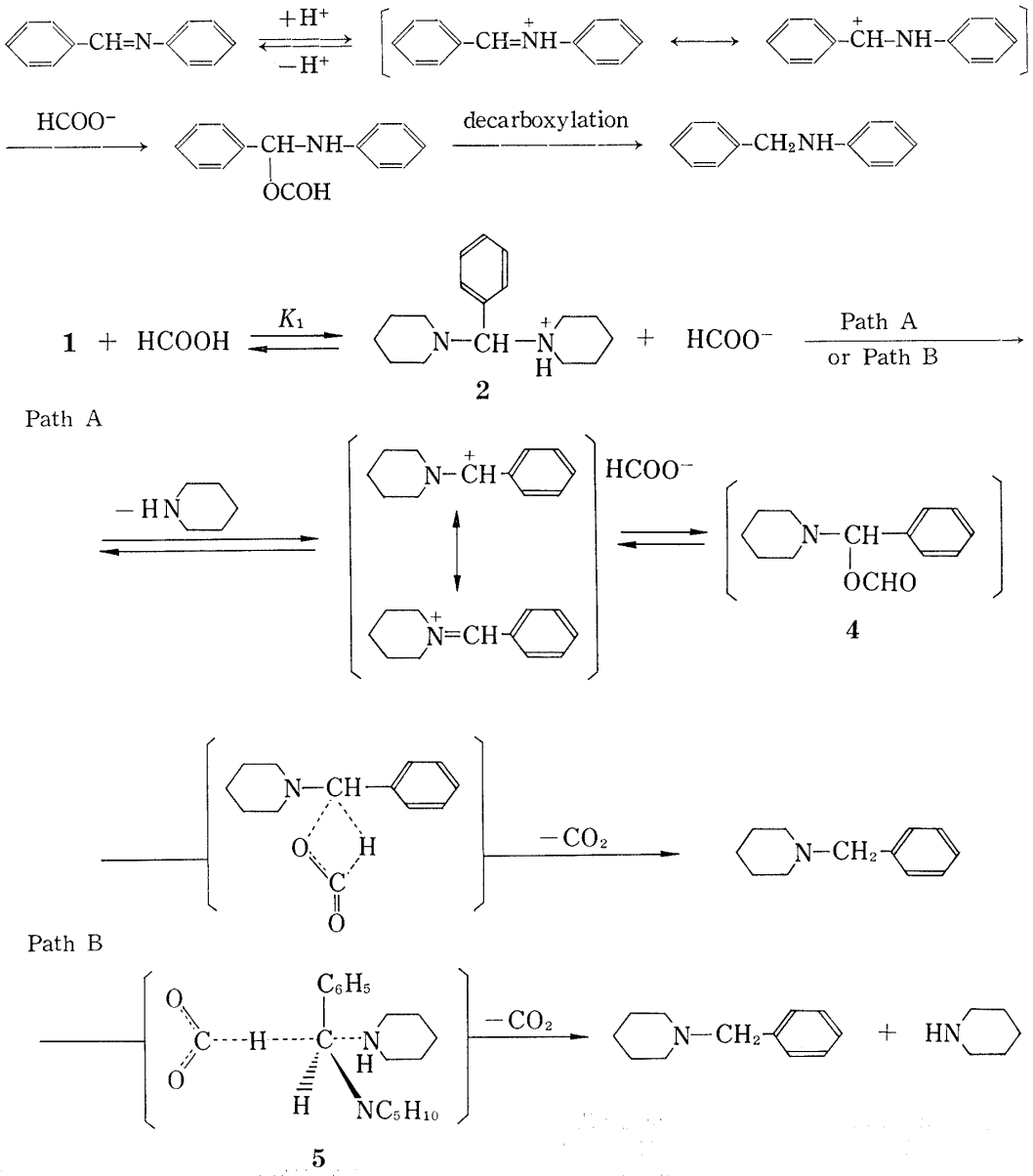


Chart 1

The isotope effect value and the negative ρ substituent effect, similar to that in the formic acid reduction of N-benzylideneaniline, suggest that the reduction of **1** involves the same intermediate step of decarboxylation of the formic acid ester of the α-amino alcohol. The small influence of substituent on the isotope effect in the reduction of N-benzylideneaniline indicated in the previous paper[3] provides further additional support for hydride transfer as a rate-determining step. Taking these considerations into account, Path A involving hydride transfer in the decarboxylation of the formic acid ester **4** may be most plausible; the radical decarboxylation of **4** previously proposed by Lukasiewicz[6] does not seem acceptable.

Experimental[8]

Materials——The following seven 1,1′-benzylidenedipiperidines were prepared from the corresponding benzaldehydes and piperidine according to the previously reported method[9] using B_2O_3 as a dehydrating agent. **1**, mp 80° (lit.[9] mp 81—81.5°). 1,1′-(*m*-Nitrobenzylidene)dipiperidine, light yellow prisms (from iso-Pr_2O), mp 97—98° (lit.[10] mp 93—95°). 1,1′-(*m*-Chlorobenzylidene)dipiperidine, colorless viscous liquid, bp 134—136°/0.06 Torr. *Anal.* Calcd for $C_{17}H_{25}ClN_2$: C, 69.73; H, 8.61; N, 9.56. Found: C, 69.57; H, 8.63; N, 9.34. 1,1′-(*p*-Chlorobenzylidene)dipiperidine, colorless prisms (from Et_2O), mp 59—60°. *Anal.* Calcd for $C_{17}H_{25}ClN_2$: C, 69.73; H, 8.61; N, 9.56. Found: C, 69.51; H, 8.57; N, 9.56. 1,1′-(*p*-Bromobenzylidene)-dipiperidine, colorless needles (from iso-Pr_2O), mp 74—75° (lit.[11] mp 58°). *Anal.* Calcd for $C_{17}H_{25}BrN_2$: C, 60.53; H, 7.47; N, 8.30. Found: C, 60.33; H, 7.46; N, 8.09. 1,1′-(*p*-Tolylidene)dipiperidine, colorless needles (from Et_2O), mp 72—73°. *Anal.* Calcd for $C_{18}H_{28}N_2$: C, 79.36; H, 10.36; N, 10.28. Found: C, 79.55; H, 10.25; N, 10.08. 1,1′-(*m*-Methoxybenzylidene)dipiperidine, colorless viscous liquid, bp 146—147°/0.05 Torr. *Anal.* Calcd for $C_{18}H_{28}N_2O$: C, 74.93; H, 9.80; N, 9.71. Found: C, 75.20; H, 9.97; N, 9.79.

Formic acid (99%) and triethylamine used were of extra pure grade, purchased from Wako Pure Chemical Industry, Ltd. EGMEA was dried over $MgSO_4$ and rectified repeatedly to give a liquid of bp 155—156°.

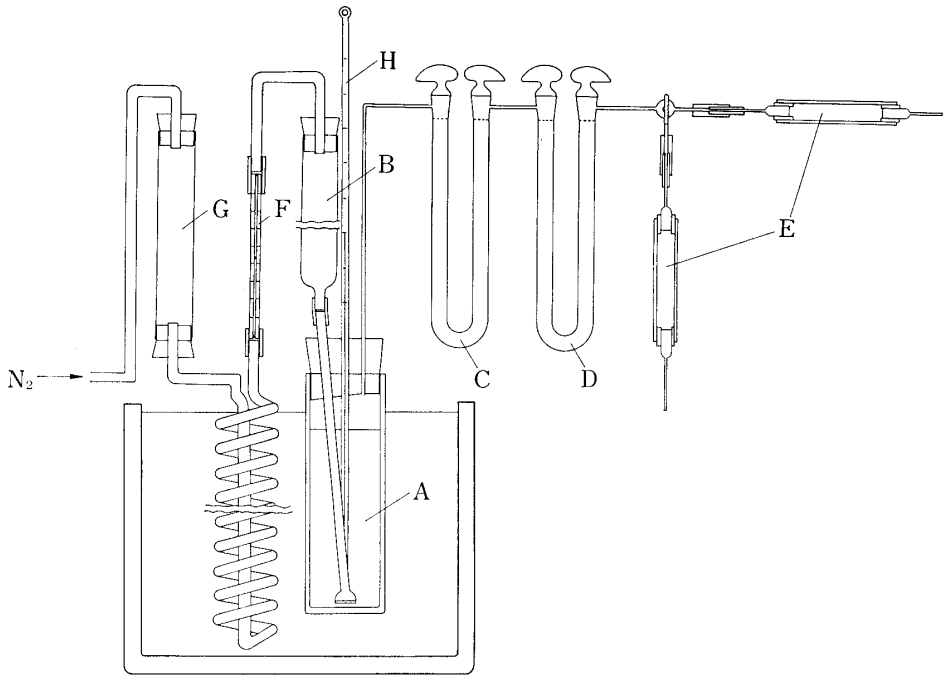


Fig. 4. Apparatus for Kinetic Measurement

A, reaction vessel; B, glass tube for introduction of the formic acid solution; C, H_2SO_4-silica gel packed tube; D, P_2O_5 and $Mg(O_4Cl)_2$ packed tube; E, soda asbestos packed tube; F, flow meter; G, $CaCl_2$ drying tube; H, thermometer.

8) All melting and boiling points are uncorrected.
9) M. Sekiya and H. Sakai, *Chem. Pharm. Bull.*, **17**, 32 (1969).
10) W. Dilthev and B. Stallmann, *Ber.*, **62B**, 1603 (1929).
11) A.S. Safaef, I.T. Turdimnkhamedova, and A.G. Makhsumov, *Uzb. Khim. Zh.*, 13, 42 (1969) [*C.A.*, **71**, 91405*r* (1969)].

Other solvents, anisole (bp 155.5°), toluene (bp 110.6°), chlorobenzene (bp 131—132°), diethyl carbitol (bp 187°) and methyl cellosolve (bp 126—127°), were dried and rectified to give the boiling points shown in parentheses.

Kinetic Measurements——For the determination of rate constants, several solvents were tested (conditions: [**1**]=0.100 M, [HCOOH]=0.400 M; temperature, 0°). EGMEA was selected as a suitable solvent for kinetic measurements. Diethyl carbitol: $k_{obs}=0.0895\times10^{-4}$ sec$^{-1}\cdot$M^{-1}; methyl cellosolve: $k_{obs}=0.221\times10^{-4}$ sec$^{-1}\cdot$M^{-1}; chlorobenzene: $k_{obs}=6.714\times10^{-4}$ sec$^{-1}\cdot$M^{-1}; EGMEA: $k_{obs}=6.936\times10^{-4}$ sec$^{-1}\cdot$M^{-1}; toluene: $k_{obs}=7.678\times10^{-4}$ sec$^{-1}\cdot$M^{-1}; anisole: $k_{obs}=10.33\times10^{-4}$ sec$^{-1}\cdot$M^{-1}.

Rate measurements of the formic acid reduction of **1** were made by the CO_2 trapping method using the apparatus shown in Fig. 4. Reaction vessel A is a cylindrical glass tube (5×12 cm) equipped with a gas inlet tube (internal diameter, 5 mm), which has a fused porous bottom of sintered ground glass, and a gas outlet tube (internal diameter, 1 mm). A glass tube B (2×15 cm) was connected to the top of the gas inlet tube with Teflon tubing. An appropriate amount of **1** and, if necessary, triethylamine were weighed precisely in a 50 ml volumetric flask, dissolved in an appropriate solvent and then diluted to 50 ml at 0°. After transferring the solution into the reaction vessel A in an ice-bath, a constant stream of N_2 (90 ml/min), which was free from CO_2, dried and precooled to 0°, was bubbled through the solution. To start a run, 10 ml of a solution of the requisite concentration of formic acid precooled to 0° was introduced through tube B into the reaction vessel A under the pressure of the stream of N_2. The stream of N_2 containing CO_2 from the reaction vessel was passed through a tube C packed with H_2SO_4–silica gel and a tube D packed with granular P_2O_5 and anhydrous $Mg(O_4Cl)_2$ to remove traces of water and amine, and then CO_2 was absorbed by soda-asbestos packed in a tube E and analyzed by weighing to a precision of 1 μg. The amount of evolved CO_2 was determined at appropriate intervals of time.

Rate measurements with deuterated formic-*d* acid and with 1,1′-benzylidenedipiperidines possessing a substituent on the benzene ring were also made in the manner described above.

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