On the Mechanism of Decomposition of Geminal Diamines

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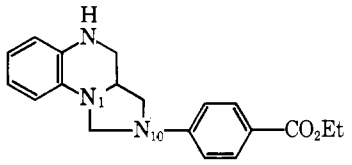
Abstract: The kinetically preferred mode of decomposition of a series of geminal diamines **3a–g**, generated by the in situ reduction of the corresponding amidines, has been determined through the reductive trapping of the iminium cations formed. Each of the geminal diamines has been shown to break down with preferential expulsion of the less basic amine leaving group. This preference is shown to be independent of pH in the range 2–11 and regardless of whether the reaction involves the formation of an aromatic or aliphatic iminium cation. The effects of para substituents on the partitioning of the geminal diamine were analyzed in terms of "effective charges" on the two nitrogens in the ground and transition states. The derived transition state features a symmetrical charge distribution in which the developing positive charge on the nitrogen of the incipient iminium cation is balanced by the depletion of positive charge on the nitrogen of the departing amine.

Introduction

The decomposition of geminal diamine intermediates (Scheme I) is a process both of biological significance[1,2] and of importance in a number of synthetic transformations.[3,4] The process has been demonstrated to be readily reversible in both aqueous[5-7] and nonaqueous[8] media, and it is established that under conditions of thermodynamic control the reaction will proceed with preferential elimination of the less basic amine and formation of the more stable iminium cation. However, the course of the reaction under conditions of kinetic control has, until now, not been unambiguously determined.

A previous study[9] attempted to determine the kinetic product of the ring opening of the imidazoline ring of **1**, a



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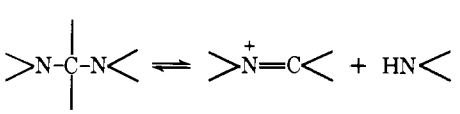
model compound for 5,10-methylenetetrahydrofolic acid, through the reduction of the iminium cations formed with sodium cyanoborohydride. The reaction affords a single product derived from the more stable (N-1) iminium cation. That this also should be the product of kinetic control would be supported by a recent study[10] of acid catalysis in the hydrolysis of symmetrically substituted imidazolidines. However, a kinetic analysis[9] indicated the rate of the trapping reaction to be dependent on borohydride concentration and, therefore, the possibility of an equilibration of the N-1 and N-10 iminium cations prior to their reduction could not be eliminated. Moreover, recently Hogg et al.[7] have suggested that the geminal diamine intermediates involved in transimination reactions involving aromatic Schiff bases breakdown with expulsion of the more basic amine.

The present study was designed to resolve these ambiguities by unequivocally establishing the kinetic course of the breakdown of geminal diamines of the form **3**. It was reasoned that for systems where the product iminium cation and amine may diffuse apart (the reverse reaction not being favored by the reformation of a cyclic structure[9,10]), conditions of high dilution and efficient trapping could be chosen such that the kinetic products of the reaction would be observed.

Scheme I



Results

The procedures used were similar to those employed in the previous study.[9] However, due to their inherent instability the geminal diamines **3** were generated as indicated in Scheme II by the in situ reduction of the corresponding amidines **2**. The amidines were prepared in high yield through the reaction of the appropriate *N*-methylformanilide and aniline with phosphorus pentachloride in chloroform according to the standard procedure.[11,12a] Initial attempts to carry out the reduction of the amidines **2** with sodium cyanoborohydride[9] led to only a poor yield of product. Subsequent experiments showed the more reactive sodium borohydride to be a more suitable reducing agent within the pH range 3–11. Borane–morpholine was used in experiments conducted at lower pH (<3). Within the limits of experimental error the distribution of products formed by the reduction was determined to be independent of both the nature of the reducing agent and its concentration in the reaction medium.

It is assumed in the subsequent discussion that the reduction of the amidines **2** affords a "free" geminal diamine and that the amine products observed result from the decomposition of this species (**3**). Although the mechanism of reduction of carbon–nitrogen double bonds with sodium cyanoborohydride or borohydride is thought to involve hydride transfer to carbon of the protonated imine,[12b] the mechanism of borane–amine reductions[12c,d] is less certain. Mechanisms involving hydride transfer (analogous to that observed with sodium cyanoborohydride[12b]) and involving addition of borane across the imine double bond have been proposed,[12c] and both pathways are known to be operative in the reduction of carbonyl compounds.[12e] However, by analogy with the latter study[12c] and given the acidic reaction media a hydride transfer mechanism appears most likely under the conditions used in the present study. It is also known that borohydride may interact with amines to form a borane–amine complex,[12f] although there is no evidence for such occurring in a dilute aqueous medium. Indeed, there are data to indicate that any complex between

Scheme II

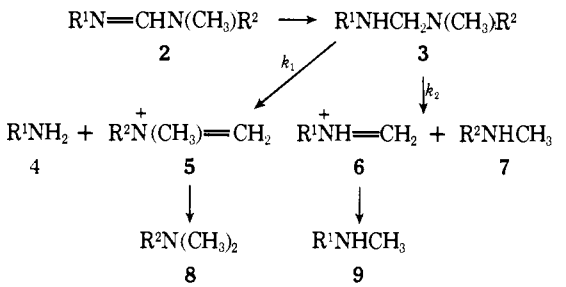


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Table I. Relative Yield of Amines Formed on Reduction of the Amidines **2** with Sodium Borohydride in Dioxane-Water (50% v/v) at pH 5.6 (Acetate Buffer)[a]

system	R^1	R^2	**4**[b]	**8**	**9**	**7**[b]	**12**
a[c]	c-C_6H_{11}	C_6H_5	2	2	48	48	0
b[c]	p-$CH_3C_6H_4$	C_6H_5	10	8	36	42	3
c[d]	p-FC_6H_4	C_6H_5	23	21	27	29	0
d[c]	p-ClC_6H_4	C_6H_5	39	29	11	21	0
e[c]	p-$(CO_2Me)C_6H_4$	C_6H_5	50	41	<0.5	9	0
e[e]	p-$(CO_2Me)C_6H_4$	C_6H_5	50	38	<0.5	12	0
f[e,f]	C_6H_5	$MeO(CH_2)_2$		<0.5		50	0
g[c]	C_6H_5	p-$(CO_2Et)C_6H_4$	5	<0.5	45	50	1
g[e]	C_6H_5	p-$(CO_2Et)C_6H_4$	3	<0.5	47	50	<0.5

[a] See footnote *a*, Table II. [b] The yield of amines **4** and/or **7** have been reduced according to the amount of the formanilides **10** and/or **11** observed. The following yields of formanilides were determined (percent total reaction product): **10a**, 0; **11a**, 0; **10b**, 2; **11b**, 1; **10c**, 2; **11c**, 1; **10d**, <0.5; **11d**, >2 (this product could not be accurately determined; see the Experimental Section); **10e**, 0; **11e**, ~10; **10e**, 0; **11e**, <1; **10f**, ~5; **11f**, −; **10g**, 12; **11g**, 0; **10g**, 2; **11g**, 0. [c] Initial amidine concentration 1.8×10^{-4} M; initial borohydride concentration 3.6×10^{-3} M. [d] Initial amidine concentration 0.9×10^{-4} M; initial borohydride concentration 3.6×10^{-3} M. [e] Initial amidine concentration 1.8×10^{-4} M; initial borohydride concentration 1×10^{-2} M; pH 6-8. [f] The products **4f** and **9f** could not be resolved from dioxane under the conditions of analysis.

Table II. pH Dependence of the Product Distribution from the Reduction of the Amidines **2** with Sodium Borohydride in Dioxane-Water (50% v/v)[a]

system	pH (buffer)	**4**[b]	**8**	**9**	**7**[b]	**12**
b[c]	3.7 (chloroacetate)	11	12	37	38	1
b[c]	8.7 (triethanolamine)	13	10	35	40	2
b[c]	10.9 (borate)	11	11	38	39	<1
d[c]	3.7 (chloroacetate)	40	34	10	15	0
d[c]	8.7 (triethanolamine)	45	40	5	11	0
d[c]	10.9 (borate)	41	32	10	18	0
e[d]	1.8 (trichloroacetate)	50	~47	<0.5	~3	0
e[c]	3.7 (chloroacetate)	50	46	<0.5	4	0
e[c]	8.7 (triethanolamine)	50	39	<0.5	11	0
e[c]	10.9 (borate)	50	20	<0.5	30	0
e[e]	8-10 (phosphate)	50	29	<0.5	21	0

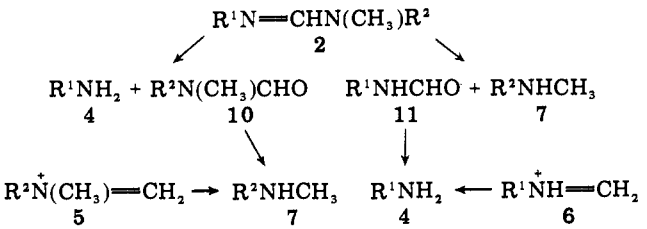
[a] The total conversion to products ranged from 10 to 50%; the appropriate amount of amidine was observed in the product mixture. In the case of reductions conducted at pH 3.7 the yield was limited by the instability of the borohydride, and at pH 10.9 by the low reactivity of the amidine toward reduction. At pH 5.6-8.7 the reaction was stopped after ca. 40% conversion in order to minimize the extent of the hydrolysis side reactions. [b] The yield of amines **4** and/or **7** has been reduced according to the amount of the formanilides **10** and/or **11** observed. The following yields of formanilide were observed (percent total reaction product). At pH 1.8: **10e**, 0; **11e**, ~4. At pH 3.7: **10b**, 3; **11b**, 1; **10d** <1; **11d**, >2 (this product could not be accurately determined; see the Experimental Section); **10e**, 0; **11e**, ~16. No formanilides **10** or **11** were observed in the product of reductions conducted at pH > 5.6. [c] See footnote *c* in Table I. [d] Borane-morpholine (1×10^{-2} M) was used as the reducing agent; initial amidine concentration 1.8×10^{-4} M. [e] See footnote *e* in Table I.

an aromatic amine and borane should be very labile under these conditions.[12d]

Under ideal conditions, with only the reactions depicted in Scheme II contributing to the formation of products, one should observe a 1:1 ratio of the compounds **4** and **8**, and **7** and **9**. That this optimal situation is not observed in each case (see Tables I and II) is due to the fact that both the amidines **2** and the iminium cations **5** and **6** are subject to hydrolysis under the reaction conditions (Scheme III).

It is clear from the data given in Tables I and II that the degree to which these side reactions may compete with reduction is a function of the particular amidine (previous studies[13] have established that those amidines with electron-withdrawing substituents are particularly susceptible to hydrolysis) and iminium cation involved, the pH at which the reaction was conducted, and the buffer used to maintain a

Scheme III

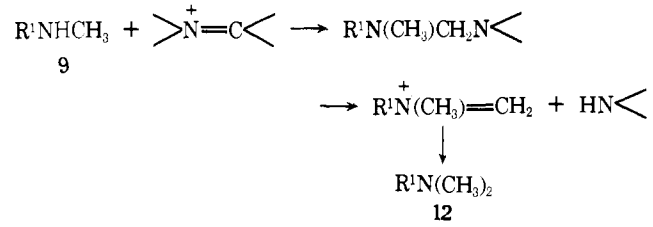


constant pH. Control experiments were conducted in which the amidines **2** were subjected to the identical conditions of pH and buffer used in the reductions. However, these experiments showed little or no hydrolysis of the amidines **2a–c** and, in the case of the amidines **2d–g**, a significantly lesser extent of hydrolysis than that observed in the reduction media.[14] The amidine hydrolysis is thus clearly catalyzed by borohydride, borates, or the products of amidine reduction.

A correction for the amount of aniline released by amidine hydrolysis based on a determination of the amount of formanilide **10** and/or **11** formed has been applied to the data given in Tables I and II (refer to footnote *b* of tables). The extent to which this correction represents the true amount of amidine hydrolysis is, however, dependent on the lability of the formanilide. Separate experiments showed the tertiary formanilides **10a–g** to be stable to hydrolysis at pH 5.6. However, under the same conditions the representative secondary formanilides **11d,e,g** were labile, undergoing 30–60% conversion into the corresponding anilines **4**.[15] Thus, the extent to which the remaining discrepancy in the data is due to incomplete trapping of the iminium cations, owing to their prior hydrolysis, could not be readily determined.

However, in the majority of experiments the total extent of both amidine and iminium cation hydrolysis is small (as may be gauged by comparing the total yield of trapped product (**8** + **9**) with that of the expelled anilines (**4** + **7**); under ideal

Scheme IV



conditions this ratio should assume a value of unity). The exceptions to this are the experiments involving the reduction of the amidines **2e,g,** particularly under conditions of high pH. In order to be able to assess the distribution of products formed in the absence of the side reactions several experiments were conducted using a higher concentration of borohydride so as to enhance the rate of trapping of both the iminium cations and the amidine (these conditions, however, did not allow the pH to be maintained at a constant value). The results of these experiments are given in Tables I and II.

The experiments involving the reduction of the amidines **2a–c** provide relatively consistent product data and demonstrate that those iminium cations without electron-withdrawing substituents may be trapped efficiently. The ratio of *N*-methylaniline to *N,N*-dimethylaniline (**7:8**) thus provides a value of the rate constant ratio k_2/k_1 for the systems a–e which is not a function of the varying hydrolytic stability of the different iminium cations. However, these values should be considered only a maximum for k_2/k_1 since the amount of **7** determined may contain a contribution due to amidine hydrolysis not compensated for in the data because of the hydrolysis of the secondary formanilide **11.** The ratio of the alternate pair of anilines **9:4** will be a minimum value for k_2/k_1. This ratio will be low both due to the lability of the formanilide **11** and the possibility of conversion of the iminium cation precursor into **4.** Similarly the ratio of the anilines **9:4** and **7:8** can be considered upper and lower limits, respectively, of k_2/k_1 for the "reversed" system g.

The reduction of two amidines **2b** and **2g** afforded a small amount (≤3%) of the dimethylaniline **12.** This product undoubtedly arises by way of the geminal diamine formed from the reaction of aniline **9** with iminium cation as shown in Scheme IV. The yield of the dimethylaniline was found to show the dependence on both borohydride and amidine concentration expected on the basis of this scheme (Scheme IV). Indeed, conditions of high borohydride or low amidine concentration could be chosen so as to completely eliminate the formation of the dimethylaniline **12g.** However, the former condition was incompatible with the need to maintain a constant pH throughout the reaction, while under conditions of very high dilution ($<10^{-4}$ M in amidine) the analytical procedure is not sufficiently sensitive to allow an accurate evaluation of the product distribution.

The occurrence of this methylation reaction clearly indicates that the breakdown of the geminal diamine may, to a small extent, be reversible under the reaction conditions. In order to more accurately assess the importance of the reverse reaction in determining the product distribution, a series of experiments was conducted in which the reduction of one amidine **2e** was carried out in the presence of various concentrations of *p*-toluidine. Under conditions where the added *p*-toluidine was in greater than fivefold excess with respect to the aniline formed in the reaction the yield of *N*-methyl-*p*-toluidine observed amounted to less than 5% of the total iminium cation derived product[16] (see Table III). A lower yield of *N*-methyl-*p*-toluidine was observed when the reaction was conducted under conditions of lower pH, a result presumably reflecting that the *p*-toluidine is largely protonated under these conditions and, hence, is a poor nucleophile. A similar explanation would account for the fact that no methylation of the *N*-methylcyclohexylamine **9a** formed in the reduction of **2a** is observed. It would also seem reasonable that anilines less nucleophilic than *p*-toluidine would be less able to compete with borohydride for the iminium cation. Thus, the absence of dimethylation in the reduction of the amidines **2c–e** can be readily rationalized.

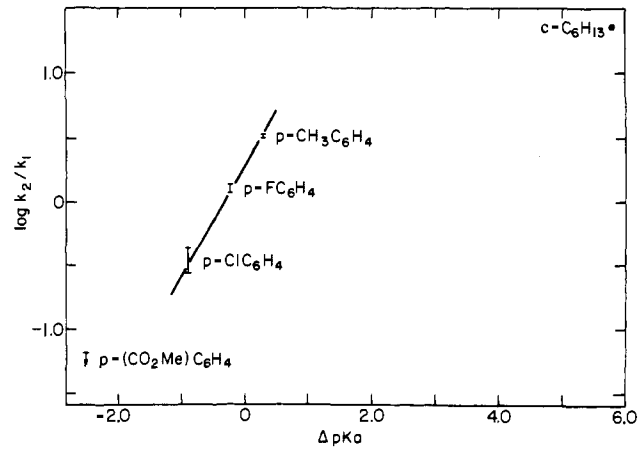


Figure 1. Plot of log k_2/k_1 vs. ΔpK_a [$pK_{a(R^1NH)} - pK_{a(R^2NHCH_3)}$]. The values of log k_2/k_1 were calculated from the data obtained from runs conducted at low pH (≤5.6).

Table III. Effect of Added *p*-Toluidine on the Reduction of Amidine **2e**[a]

pH (buffer, 0.1 M)	[toluidine]$_F$/[**7**][b]	[*N*-methyltoluidine]$_F$/[**8**][b]
3.7 (chloroacetate)	7.2	0.02
5.6 (acetate)	5.1	0.05
	2.1	0.01
	0.8	<0.005
8.7 (triethanolamine)	4.3	0.02

[a] Initial amidine concentration 1.8×10^{-4} M; initial borohydride concentration 3.6×10^{-3} M; initial toluidine concentration 1.8×10^{-4}, 1.8×10^{-4}, 0.9×10^{-4}, 0.5×10^{-4}, and 1.8×10^{-4} M, respectively. [b] Final concentration of *p*-toluidine (*N*-methyl-*p*-toluidine) relative to that of *N*-methylaniline **7** (*N,N*-dimethylaniline **8**).

Discussion

It is clear that each of the geminal diamines **3a–g** breaks down with preferential elimination of the less basic amine. This selectivity is observed regardless of whether the reaction involves the formation of an aromatic or aliphatic iminium cation and, moreover, is seen to be independent of pH within the range 2–11.

Figure 1 shows that, within the limits of experimental error, the log of the rate constant ratio k_2/k_1 for the four fully aromatic systems b–e has a linear dependence on ΔpK_a—the difference between the pK_a values of the varying aniline leaving group R^1NH_2 and the common group *N*-methylaniline (R^2NHCH_3). The upper and lower bounds of log k_2/k_1 were determined from the product ratios **7:8** and **9:4,** respectively (see Results). The progressive divergence of these bounds with decreasing ΔpK_a reflects the increasing importance of the amidine and iminium cation hydrolysis reactions rather than any error associated with the product ratio determination.

The effects of the para substituents on the partitioning of the geminal diamine can be analyzed in terms of the "effective charges" on the reacting groups in the ground and transition states.[17] The change in effective charge is defined by the slope, β, of a structure–reactivity correlation. Typically the log of a rate or equilibrium constant is plotted against the pK_a of a

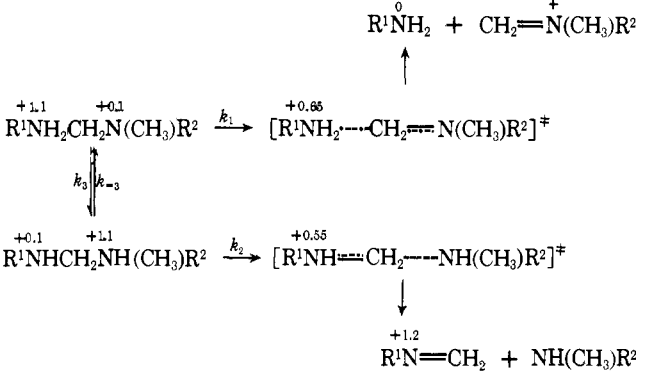
reacting group and the value of β obtained is referenced to that for a standard ionization reaction (for example, the protonation equilibrium of an amine for which β is defined to be equal to +1.0). Consequently, the value of β measures the sensitivity of the reaction to substituent effects relative to that of protonation equilibria. Since the changes in charge on a given group in going from reactant to transition to products are equal to the change for the overall equilibrium (i.e., $\beta_{eq} = \beta_f - \beta_r$, where β_{eq} relates to the effect of substituents on the equilibrium constant and β_f and β_r on the forward and reverse rate constants), it is useful to have the charge distribution in the reactant and product ground state as a starting point for applying β_f and/or β_r.

The large positive slope of Figure 1 ($\beta \simeq 0.9$) results in part from the fact that this structure-reactivity correlation measures the sensitivity of both k_2 and k_1 to changes in aniline pK_a. Viewing the methyl group simply as an analytical marker for product determination—a contention supported by the facts that $k_1 \simeq k_2$ at $\Delta pK_a = 0$ and that the location of the methyl group ("reversed" in system g) does not alter the selectivity of the reaction—the transition state for the symmetrical reaction via either of the k_1 or k_2 pathways must be of a similar nature and involve the same distribution of effective charge. Thus, for the simplest situation in which the depletion of effective charge on the nitrogen of the departing aniline is matched by an equal buildup of charge on that of incipient iminium cation, one can tentatively assign the change in effective charge at the two nitrogens to be −0.45 and +0.45, respectively. Transition states of a less symmetric nature, either more reactant or product-like in effective charge distribution, may be envisioned in which a charge balance is maintained by a charge buildup on the central carbon.

An approximation of the formal charge distribution in the ground-state geminal diamine is derived from the condensation of formaldehyde with symmetrically para-substituted *N,N'*-diphenylethylenediamines to yield the respective imidazolidines.[18] A value of $\beta_{eq} \simeq 0.1$ has been found for the equilibrium formation of the monocationic imidazolidines from the monoprotonated diamines in 50% v/v dioxane-water, whereas $\beta_{eq} \simeq 0.2$ has been determined for the respective equilibrium with the free base species. An approximate effective charge of 0.1 is thus assigned to the nitrogen of the incipient iminium cation function and 1.1 to the nitrogen of the designated leaving group.[19] The description of the reaction in terms of the variable aniline moiety which thus emerges is depicted in Scheme V with the transition state being intermediate in character involving no great imbalance of effective charge distribution.

Scheme V assumes that proton transfer between the two monoprotonated geminal diamines is at equilibrium. This assumption is supported by (a) the absence of a marked change in trapped product distribution with differing buffers or pH (Tables I and II); (b) the interception of the iminium cation derived from **1** by borohydride is first order in reducing agent;[9] and (c) catalysis of the transimination reaction of *N*-*p*-methoxybenzylidenepyrrolidinium cation and hydroxylamine by buffer acids and bases and by hydronium ion of the corresponding proton-transfer step is dependent on the pK_a of the buffer species with the uncatalyzed attack or expulsion of amine becoming rate determining at pH < 2 or buffer concentrations >0.1 M.[7] The apparent negative deviation of the data point for the aliphatic-aromatic geminal diamine **3a**, however, may arise from the proton-transfer step becoming partially rate limiting. Since the initial composition of the monocationic geminal diamines would reflect the tautomeric equilibrium of the precursor amidines, the concentration of $R^1N^+H_2CH_2N(CH_3)R^2$ would dominate owing to the large basicity difference between the two nitrogens. Breakdown via k_1 competitive with k_3 would decrease the k_2/k_1 ratio. Regardless of the pathway for k_3, that is, via a proton switch or

Scheme V



two stepwise proton transfers, the rate of that step should be less for a strongly basic aliphatic amine nitrogen vs. an aniline nitrogen ($\Delta pK_a \simeq 4.6$) for a given pH and buffer. A similar rationale would apply if protonation of the less basic nitrogen was concerted with iminium cation and amine formation.[10] Alternatively, the interaction of the aniline and aliphatic nitrogen with the developing iminium cations may differ and not be manifest relative to their respective conjugate acids, so that pK_a is an inadequate reactivity parameter.

The present results provide clear support for the postulate[9] that the ring opening of the imidazoline ring of 5,10-methylenetetrahydrofolic acid and its analogues affords the more stable iminium cation under conditions of both kinetic and thermodynamic control.

The preferred mode of decomposition of the geminal diamines **3** contrasts with that of systems substituted with nitrogen or oxygen on the central carbon.[9,20] The orthoamides are known to break down with expulsion of the more basic amine. The difference in behavior may be attributed to (a) the fact that there are two electron-donating groups to provide the driving force for the expulsion of amine and (b) the formation of a more stable amidinium ion as the product of the reaction. It will be noted that an aryl substituent may be able to perform these same functions, albeit less efficiently. For this reason it is not possible to predict the kinetic course of the breakdown of the intermediates generated in transimination reactions involving aromatic Schiff bases on the basis of the present data, and additional studies are required to clarify this point.

Experimental Section

Nuclear magnetic resonance spectra were recorded with a Varian Associates A-60 spectrometer and chemical shifts are reported in parts per million from tetramethylsilane as internal standard. Gas-liquid chromatography (GLC) was conducted using a Finnigan 9500 instrument. The following columns were used: (a) 5 ft × 2 mm 3% Silar 5C on Gas Chrom Q, 100–120 mesh; (b) 5 ft × 2 mm 10% Silar 10C on Gas Chrom Q, 100–120 mesh; (c) 5 ft × 2 mm 28% Pennwalt 228 on Gas Chrom R, 100–120 mesh; (d) 5 ft × 2 mm 3% SP2100 on Supelcoport, 100–120 mesh.

GLC-mass spectra were recorded using a Finnigan 3200 instrument employing the same columns as used for product analysis. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were carried out by MHW Laboratories, Phoenix, Ariz. pH measurements were carried out using a Radiometer Model 22M instrument equipped with scale expander and were adjusted for the dioxane-water medium using the correction factors suggested by Irving and Mahnot.[21] Dioxane purified by the method of Fieser[22] and doubly distilled deionized water were used in the trapping experiments. The sodium borohydride was recrystallized from diglyme[23] and was shown to be of >99% purity.

Materials. The aniline and formanilide derivatives required both for the preparation of the amidines **2** and for product identification were either commercial materials or were synthesized using literature procedures.[4,12a,23-26] The physical properties of these materials were in agreement with the published values.

The amidines **2** were in each case prepared as their hydrochloride salts using the procedure of Benkovic et al.[12a] The crude products were

recrystallized from the solvent indicated and their purity was established by NMR and, where necessary, by GLC-mass spectrometry. The amidine hydrochlorides were hygroscopic and subject to hydrolysis on standing. They were, however, stable indefinitely when stored under vacuum in a desiccator.

***N*-Cyclohexyl-*N'*-methyl-*N'*-phenylformamidine (2a):** mp (CH_2Cl_2-benzene) 158-160 °C; NMR ($CDCl_3$) δ 1.2-2.2 (s, 10 H, CH_2), 3.4-3.7 (m, 1 H, CH), 3.95 (s, 3 H, CH_3), 7.1-7.7 (m, 5 H, aromatic CH), 7.95 (br s, 1 H, CH). Anal. Calcd for $C_{14}H_{21}ClN_2$: C, 66.5; H, 8.4; N, 11.1 Found: C, 66.5; H, 8.5; N, 11.1.

***N*-(*p*-Toluyl)-*N'*-methyl-*N'*-phenylformamidine (2b):** mp (CH_2Cl_2-benzene) 88-90 °C; NMR ($CDCl_3$) δ 2.35 (s, 3 H, CH_3), 4.15 (s, 3 H, CH_3), 7.1-7.9 (m, 9 H, aromatic CH), 8.1 (br s, 1 H, CH); mass spectrum *m/e* 224 ($M^{+\cdot}$).

***N*-(*p*-Fluorophenyl)-*N'*-methyl-*N'*-phenylformamidine (2c):** mp (acetonitrile-ether) 133-135 °C; NMR ($CDCl_3$) δ 3.95 (s, 3 H, CH_3), 6.7-7.7 (m, 9 H, aromatic CH), 8.0 (br s, 1 H, CH). Anal. Calcd for $C_{14}H_{14}ClFN_2$: C, 63.3; H, 5.3; N, 10.6. Found: C, 63.5; H, 5.3; N, 10.6.

***N*-(*p*-Chlorophenyl)-*N'*-methyl-*N'*-phenylformamidine (2d):** mp ($CHCl_3$-ethyl acetate) 160-162 °C; NMR ($CDCl_3$) δ 3.95 (s, 3 H, CH_3), 7.0-7.9 (m, 9 H, aromatic CH), 8.0 (br s, 1 H, CH); mass spectrum *m/e* 244, 246 ($M^{+\cdot}$). Anal. Calcd for $C_{14}H_{14}Cl_2N_2$: C, 59.8; H, 5.0; N, 10.0. Found: C, 60.2; H, 5.1; N, 10.0.

***N*-(*p*-Carboxymethylphenyl)-*N'*-methyl-*N'*-phenylformamidine (2e):** mp ($CHCl_3$-ethyl acetate) 142-144 °C; NMR ($CDCl_3$) δ 4.15 (s, 3 H, CH_3), 4.3 (s, 3 H, CH_3), 7.5-8.2 (m, 9 H, aromatic CH), 8.45 (br s, 1 H, CH); mass spectrum *m/e* 268 ($M^{+\cdot}$). Anal. Calcd for $C_{16}H_{17}ClN_2O_2$: C, 63.0; H, 5.6; N, 9.2. Found: C, 62.8; H, 5.8; N, 9.1.

***N*-(*p*-Carboxyethylphenyl)-*N*-methyl-*N'*-(2-methoxyethyl)formamidine (2f).** This compound was available from previous studies.[12a]

***N*-(*p*-Carboxyethylphenyl)-*N*-methyl-*N'*-phenylformamidine (2g):** mp ($CHCl_3$-ethyl acetate) 159-161 °C; NMR ($CDCl_3$) δ 1.55 (t, J = 7 Hz, 3 H, CH_3), 4.15 (s, 3 H, CH_3), 4.6 (q, J = 7 Hz, 2 H, CH_2), 7.4-8.4 (m, 9 H, aromatic CH), 8.5 (br s, 1 H, CH); mass spectrum *m/e* 282 ($M^{+\cdot}$). Anal. Calcd for $C_{17}H_{19}ClN_2O_2$: C, 64.2; H, 6.0; N, 8.4; O, 10.2. Found: C, 64.1; H, 6.0; N, 8.8; O, 10.0.

Reductions. The typical procedure is as follows (the precise conditions of pH, buffer, concentration, etc., used in each experiment are indicated in the appropriate footnote to Tables I-III). To 5 mL of buffer [0.1 M in 50% (v/v) dioxane-water; μ = 0.1, KCl] under nitrogen were added successively 500 μL of 0.002 M amidine and 500 μL of 0.04 M sodium borohydride each in 50% (v/v) dioxane-water. After 30 min-1 h a 1-mL aliquot was withdrawn, made alkaline by the addition of potassium hydroxide, saturated with sodium chloride, and extracted with methylene chloride. The extract was then analyzed immediately by GLC. Where necessary GLC-mass spectrometry was used to confirm the identity and homogeneity of the products. Control experiments demonstrated the extraction efficiency to be better than 97% and showed the amidines to be inert to hydrolysis during the isolation procedure. Measurement of the pH of the reaction mixture immediately prior to workup showed the pH to be unchanged (±0.1 units) from the initial value.

Integration of the GLC traces was carried out using a computer-assisted procedure[27] which afforded the relative peak areas reproducibly to within ±1%. A similar error was associated with response ratio determinations. However, a greater error was involved in the determination of products amounting to <3% of the total reaction product and of the secondary formanilides **11d,e.** The latter compounds could not be completely resolved from the respective amidines under the conditions of analysis. The error associated with the data reported in Tables I-III is certainly less than ±3% but is probably less than ±2% for the majority of experiments.

Column c (100 °C; He, 20 mL/min) was used for the determination of the cyclohexylamines **4a** and **9a.** Column b (temperature program 100-240 °C; He, 20 mL/min) was used for aniline analysis. Columns a and d were used to obtain an estimate of the amount of the formanilide **11e.**

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References and Notes

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(14) In accord with previous studies[9,18] hydrolysis of the amidines **2** was found to involve preferential expulsion of the more basic amine.
(15) The unsubstituted formanilide **11g** underwent ca. 30% conversion into aniline **4g** within the time scale used for the reductions. The *p*-chloro- and *p*-carboxymethylformamidines **11d,e** each underwent 40-60% hydrolysis. The apparent insensitivity of the rate of hydrolysis to the nature of the substituent (*p*-H, *p*-Cl, or *p*-CO_2Me) is consistent with the study of M. L. Bender and R. J. Thomas [*J. Am. Chem. Soc.*, **83**, 4183 (1961)] who found a very low reaction constant ρ (0.1) to be associated with the process.
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