Intramolecular Catalysis in the Basic Methanolysis of *N*-2-Pyridinylbenzamide and Related Compounds

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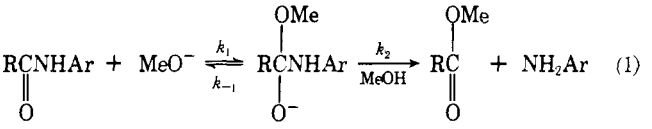
Abstract: Rate data for the basic methanolysis of *N*-2-pyridinylbenzamide and some derivatives substituted in the pyridine ring are reported. The mechanism changes from rate-determining methoxide addition at low base concentration to decomposition of the tetrahedral intermediate at higher base concentration. It is postulated that, in these compounds at low base, a unique rapid breakdown of the intermediate can occur by protonation of the most basic site (the oxygen) and cleavage of this neutral species to neutral products through a six-center transition state. The effect is not observed in 3-pyridinyl, 4-pyridinyl, or 8-quinolinyl systems.

A considerable amount of work has been reported in recent years on details of the mechanisms of the basic hydrolysis and methanolysis of *N*-arylamides.[1] The overall reaction path is apparently determined by a number of finely balanced effects so that mechanism changes can be observed in seemingly similar systems.

In methanolysis (eq 1), decomposition of the tetrahedral



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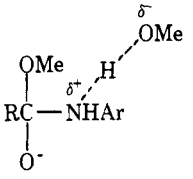
intermediate **1** is usually rate determining and can proceed by protonation of the nitrogen (transition state **2**) or solvent-assisted bond cleavage (transition state **3**).



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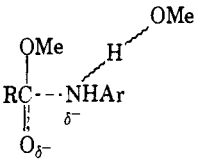

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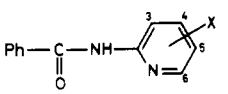
In the particular case of the basic methanolysis of *N*-arylbenzamides,[1c] PhCONHAr, reaction proceeds via **3** irrespective of the aryl substituent. These reactions are followed under pseudo-first-order conditions and the second-order rate constants for the overall conversion of reactants to products, k_e, are obtained from $k_e = k_\psi/\mathrm{MeO^-}$.

During an investigation of this reaction with some heterocyclic amides we observed that, for *N*-2-pyridinylbenzamide (**4a**) and the acetamide analogue, k_e decreased as the base



4a, X = H
b, X = 3-Me
c, X = 6-Me
d, X = 4-Me
e, X = 5-Me
f, X = 4-MeO
g, X = 5-Br

concentration increased. The same phenomenon was not observed for the 3- and 4-pyridinyl isomers. We have therefore carried out a more detailed study of the reaction of **4a** and related compounds and report here the discovery of a novel reaction path available in this series.

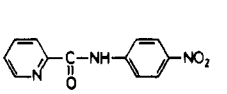
Results

The trend in k_e values for **4a** could be simply explained if ionization of the NH group occurred in basic methanol. There was, however, no spectroscopic evidence of ionization in methanol. In addition, the relative acidities of **4a**, the 4-pyridinyl isomer, and *N*-(4-nitrophenyl)benzamide (which also gives normal kinetic results[1c]) were determined in 50% dimethyl sulfoxide–methanol by a standard spectrophotometric method.[2] Values of K = 9.8 (2-pyridinyl), 83 (4-pyridinyl), and 197 (4-nitrophenyl) were obtained for the equilibrium

$$\mathrm{AnH + MeO^- \rightleftharpoons An^- + MeOH}$$

where AnH represents the amide, and these ruled out ionization as the cause of the base effect in the kinetics of reaction of **4a**.

Pseudo-first-order rate constants were then determined at various base concentrations in methanol for derivatives of **4a** substituted in the pyridine ring, *N*-2-pyridinylacetamide, and model compounds *N*-(4-nitrophenyl)-2-pyridinecarboxamide (**5**), *N*-(5-nitro-8-quinolinyl)benzamide (**6**), and 3-nitro-*N*-(8-quinolinyl)benzamide (**7**).



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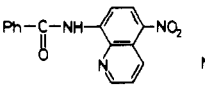

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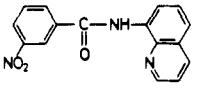

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Variable k_e values were noted for all compounds **4** (a very small effect only for the 5-bromo compound) and *N*-2-pyridinylacetamide, and the pseudo-first-order rate constants for these compounds are listed in Table I. Otherwise, k_e values were constant and are summarized in Table II. The rate-base profiles for compounds **4a–f** are shown in Figure 1.

Discussion

Rate–Base Profiles. A complex pattern is evident in Figure 1 and the relative k_ψ values show no obvious relation to substituent effects.

The curved plots indicate that a change in rate-determining step occurs.[3] The slope of the linear portion of the plot for **4a** gives a second-order rate constant, k', which, when fitted to the Hammett plot for the reaction of *N*-arylbenzamides[1c] under these conditions gives $\sigma_{2\text{-aza}} = 0.91$. The k_e values for the 3- and 4-pyridinyl isomers likewise give $\sigma_{3\text{-aza}} = 0.68$ and $\sigma_{4\text{-aza}} = 1.10$. These effects of the pyridine nitrogen are very similar to those found[4] (1.0, 0.59, and 1.17, respectively) in nucleophilic substitution in halopyridines (a reaction also powerfully enhanced by electron withdrawing substituents). This suggests that all three amides react by the same mechanism. Furthermore, the k' values for **4a,d–g**, Table III, give a linear Hammett plot of slope 3.0 at 100 °C, which is practically identical with ρ for the *N*-arylbenzamides under these conditions.[1c]

Table I. Pseudo-First-Order Rate Constants for the Basic Methanolysis of Substituted *N*-(2-Pyridinyl)benzamides (**4**) and *N*-(2-Pyridinyl)acetamide in Methanol at 100 °C

Substituent	Anal. λ, nm							
H, **4a**	231[a]	10^3 MeO⁻, M	1.18	2.64	5.29	10.5	15.5	31.1
		$10^4 k_\psi$, s^{-1}	1.04	1.57	2.08	2.85	3.50	5.65
3-Me, **4b**	294[a]	10^3 MeO⁻	10.7	21.4	30.2	40.1	60.3	
		$10^4 k_\psi$	3.45	6.83	9.06	10.8	12.2	
4-Me, **4d**	279[b]	10^3 MeO⁻	1.20	5.36	10.7	21.5	32.3	59.8
		$10^4 k_\psi$	0.98	2.22	2.79	3.68	4.46	6.27
5-Me, **4e**	286[b]	10^3 MeO⁻	1.20	5.36	10.7	21.4		
		$10^4 k_\psi$	0.536	0.954	1.20	1.66		
6-Me, **4c**	284[b]	10^3 MeO⁻	1.20	5.40	10.8	21.5	32.9	
		$10^4 k_\psi$	0.883	2.06	2.52	3.16	3.69	
4-MeO, **4f**	258[b]	10^3 MeO⁻	1.02	2.04	5.10	10.0	19.9	29.9
		$10^4 k_\psi$	1.45	2.45	3.83	4.96	6.44	8.15
5-Br, **4g**	292[b]	10^3 MeO⁻	2.04	5.10	10.7	21.5		
		$10^4 k_\psi$	1.58	3.89	7.35	13.9		
H[c]	275[b]	10^3 MeO⁻	2.78	5.56	10.2	20.4	30.0	40.8
		$10^4 k_\psi$	1.48	1.82	2.21	3.01	4.00	4.93

[a] Product formation. [b] Reactant disappearance. [c] *N*-(2-Pyridinyl)acetamide.

Table II. Second-Order Rate Constants[a] for the Basic Methanolysis of Some Model Amides

Compd	MeO⁻ range, M	Anal. λ, nm	$10^3 k_e$, $M^{-1} s^{-1}$
N-3-Pyridinylbenzamide	0.01-0.06	231[b]	2.97
N-4-Pyridinylbenzamide	0.005-0.015	236[b]	49.0
5	0.002-0.01	321[c]	226
6	0.005-0.02	422[b]	31.4
7	0.005-0.02	320[c]	10.6

[a] T = 100 °C except for **6** (28 °C). [b] Product formation. [c] Reactant disappearance.

Table III. Rate Constant Data Obtained from the Linear Portions of the Curves in Figure 1

Compd	Slope = k', $M^{-1} s^{-1}$	10^4 intercept, s^{-1}	Slope/intercept
4a	1.39×10^{-2}	1.35	103
4c	5.63×10^{-3}	1.90	30
4d	7.93×10^{-3}	1.90	47
4e	4.21×10^{-3}	0.75	56
4f	1.65×10^{-2}	3.25	51
4g	6.35×10^{-2}	0.30	2100

Thus, for those compounds which give curved plots, the linear portion corresponds to the "normal" mechanism, i.e., rate-determining solvent-assisted breakdown of intermediate **1** and $k' = k_e = k_1 k_2/(k_{-1} + k_2)$.

The curved portion of the plots therefore represents a change to rate-determining methoxide attack. The increased slope of the plot occurs because $k_1 > k_1 k_2/(k_{-1} + k_2)$. At low base concentration a route for rapid decomposition of **1** becomes available for **4** (with the possible exception of **4g**).

There is the possibility that the 2-aza group allows an intramolecular acyl transfer reaction. However, this would require the ring nitrogen to act as a nucleophile and **4c** would be expected to show a reduced rate due to steric hindrance. This is not observed and the small difference in behavior of the 4-methyl (**4d**) and 6-methyl (**4c**) groups is typically found in side-chain reactions at the 2-position of substituted pyridines.[5]

Intramolecular catalysis has been observed in reactions of 2-pyridinyl[6] and 8-quinolinyl[7] esters. In these reactions, formation of the tetrahedral intermediate is rate determining and the catalytic effect is produced by the basic nitrogen acting on an incoming nucleophile. Catalysis of this form cannot explain the present results, since it would always aid the formation of **1**.

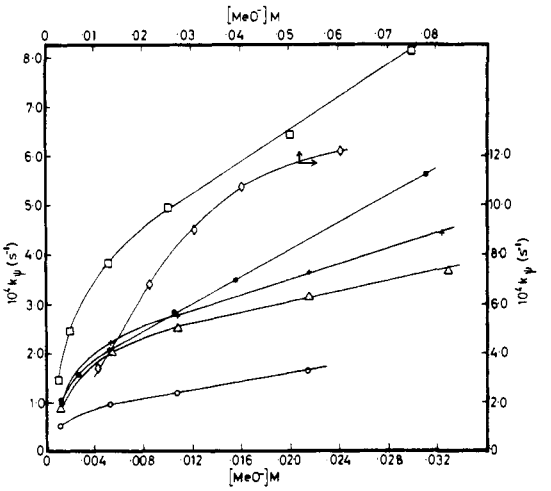


Figure 1. Rate-base profiles for methanolysis of substituted *N*-(2-pyridyl)benzamides at 100 °C: □ 4-MeO (**4f**); ◇ 3-Me (**4b**); ● H (**4a**); + 4-Me (**4d**); △ 6-Me (**4c**); ○ 5-Me (**4e**).

The mechanism change can be accounted for if acid-catalyzed breakdown of **1** is particularly favored for 2-pyridinyl compounds. This suggests the involvement of the ring nitrogen as a basic site and the failure of **4g** to show any significant effect is attributable to the low basicity (pK_a 3-bromopyridine, 2.84; pK_a pyridine, 5.17[8]). In fact, the line of best fit through the points for this compound (not shown in Figure 1) does not go through the origin, but the intercept is small and curvature in the plot is insignificant. The much greater effect observed for the 3-methyl compound (**4b**) than for any other isomer (note the different scale applying to this compound in Figure 1) is discussed below.

The results are encompassed by the following kinetic scheme:

$$\mathrm{AnH} + \mathrm{MeO^-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{1} \overset{k_2,\ k_3[\mathrm{H^+}]}{\longrightarrow} \text{products}$$

$$-\mathrm{dAnH}/dt = (k_2 + k_3[\mathrm{H^+}])\mathbf{1}$$

Solving for **1** and using $K_s = [MeO^-][H^+]$

$$k_\psi = \frac{k_1k_2[MeO^-]}{k_{-1} + k_2 + k_3K_s/[MeO^-]} + \frac{k_1k_3K_s}{k_{-1} + k_2 + k_3K_s/[MeO^-]} \quad (2)$$

The extremes are:
High base $k_{-1} + k_2 > k_3K_s/[MeO^-]$

$$k_\psi = k_1k_2[MeO^-]/(k_{-1} + k_2) + k_1k_3K_s/(k_{-1} + k_2) \quad (3)$$

Low base

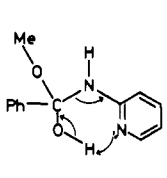
$$k_\psi = k_1k_2[MeO^-]^2/k_3K_s + k_1[MeO^-] \approx k_1[MeO^-]$$

It can be seen that the position of a curve in relation to the vertical axis, as measured by the intercept of the linear part (eq 3), does not relate simply to the basicity of the ring nitrogen. However from eq 3

$$\text{slope/intercept} = k_2/k_3K_s$$

and this (Table III) does give a measure of the relative importance of the two routes for breakdown of the intermediate. These figures give qualitatively the right picture (quantitatively, the result for the 5-bromo compound (**4g**) is not satisfactory because of the lack of clear curvature in the plot at low base). Thus, donor substituents make Ar a poorer leaving group while increasing the basicity of the ring nitrogen, and thereby decrease k_2/k_3 relative to the hydrogen substituent. The electron withdrawing bromo group has the opposite effect.

Origin of the Effect. The acid catalysis clearly requires the ring nitrogen to act as a base, but does not involve simple protonation of the nitrogen. If this were the case the 3- and 4-pyridinyl isomers would show the same effect. The most basic site in **1** is the oxygen and we believe that in these particular compounds alone, protonation of the oxygen of **1** is kinetically significant and a rapid reaction via **8** occurs.



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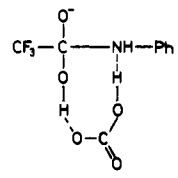

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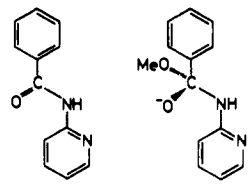
There are a number of energy advantages of such a path. The main one is that, unique to this system, the proton required for the conversion of **1** to products can be incorporated into the most basic site of **1**. An uncharged intermediate can then split into uncharged fragments (the amino pyridine can separate initially as the imino tautomer). A six-membered ring transition state is involved which explains why only the 2-pyridinyl compound shows the effect. The importance of these factors in rate terms is evident from a simple calculation for **4a**. Using $K_s = 10^{-16.7}$ for methanol,[9] $k_3 \approx 10^{15}k_2$.

The nearest analogy for this effect probably comes from a suggestion of Eriksson and Holst.[10] They noted that the hydrolysis of trifluoroacetanilide was strongly catalyzed by bicarbonate ions and suggested that simultaneous acceptance and release of protons, as depicted in **9**, was a possible cause of the rate enhancement. It is clear that the path available in **8** has advantages over that available in **9**.

Effect of the 3-Methyl Substituent. A most interesting finding was that the 3-methyl compound was much more reactive than the other methyl isomers and that the mechanism changeover occurred at a higher base concentration. There is obviously a conformation requirement for formation of **8**. The preferred conformation for the amide **4** is **10**,[11] with the pyridine nitrogen oriented away from the carbonyl oxygen, which



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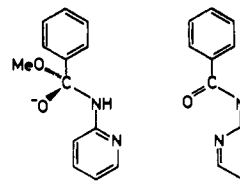

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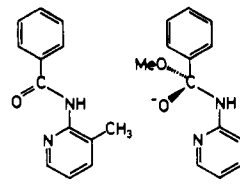

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gives **11** on the addition of methoxide. Rotation of the pyridine ring about the C–NH bond is necessary before the intramolecular breakdown can occur. This is apparently quite readily achieved. However, in **4b**, models show that **12** will be preferred, giving rise to **13**, which is ideal for the required reaction after protonation. This conformational effect so aids the k_3 step for this compound that methoxide attack on the amide remains the rate-determining process to a rather higher base concentration than for any of the other compounds.

Other Compounds. Though esters derived from 8-hydroxyquinoline have been found to show interesting examples of intramolecular catalysis during hydrolysis,[7] the amides **6** and **7** showed normal behavior (the nitro groups were necessary to obtain readily measurable reactivities). The reason in **6** could be the low basicity of the ring nitrogen (pK_a 5-nitroquinoline, 2.73;[8] pK_a quinoline, 4.94[8]), but the results for **7** suggest an additional reason. The lack of a base effect is in accord with the postulated mechanism. The NH and ring nitrogen are not conjugated and a transition state analogous to **8** cannot be written.

The presence of the aza group in the other ring, as in **5**, produces no catalytic effect, as anticipated from the proposed mechanism.

Experimental Section

Compounds. Amines were commercial samples except 2-amino-4-methoxypyridine,[12,13] 8-amino-5-nitroquinoline,[14] and 8-aminoquinoline.[15]

Benzoylations were generally carried out using benzoyl chloride in pyridine.[16] The following were prepared in this way.

N-3-Pyridinylbenzamide, mp 113–114 °C (lit.[17] mp 118 °C). *N*-4-Pyridinylbenzamide, mp 207–209 °C (lit.[17] mp 202 °C). *N*-(4-Methyl-2-pyridinyl)benzamide (**4d**), mp 114 °C (lit.[18] mp 114 °C). *N*-(5-Methyl-2-pyridinyl)benzamide (**4e**), mp 102–104 °C (EtOH–H_2O); Anal. ($C_{13}H_{12}N_2O$) C, H, N. *N*-(5-Bromo-2-pyridinyl) benzamide (**4g**), mp 119–120 °C (EtOH–H_2O); Anal. ($C_{12}H_9BrN_2O$) C, H, N. *N*-(6-Methyl-2-pyridinyl)benzamide (**4c**), mp 86–88 °C (lit.[19] mp 90 °C). *N*-(4-Methoxy-2-pyridinyl)benzamide (**4f**), mp 100–103 °C (EtOH–H_2O) (low yield reaction); exact mass identical with that of the isomer, 4-methoxy-*N*-2-pyridinylbenzamide.[20] *N*-(5-Nitro-8-quinolinyl)benzamide (**6**), mp 204–205 °C ($CHCl_3$–MeOH); Anal. ($C_{16}H_{11}N_3O_3$) C, H, N.

This method, when applied to 2-amino-3-methylpyridine, gave a product which differed from that previously reported (lit.[15] mp 127–128 °C). Material, mp 58–62 °C, was first obtained. This was a hydrate and, after azeotropic distillation with benzene, *N*-(3-methyl-2-pyridinyl)benzamide (**4b**), mp 87–88 °C (benzene–ligroin) was obtained: Anal. ($C_{13}H_{12}N_2O$) C, H, N; NMR (CCl_4) δ 2.30 (s, CH_3), 6.8–8.1 (m, 8 H, ring H), 9.1 (s, NH). The mass spectrum showed the same fragmentation pattern as for the other methyl isomers,[21] and in the kinetic measurements, the infinity spectrum agreed with that of the authentic product mixture.

3-Nitro-*N*-(8-quinolinyl)benzamide (**7**), mp 166–168 °C (EtOH), was prepared by reaction of 8-aminoquinoline with 3-nitrobenzoyl chloride by the general method.[16] Anal. ($C_{16}H_{11}N_3O_3$) C, H, N.

N-Phenyl-2-pyridinecarboxamide[22] was nitrated[23] and the crude product, on being recrystallized from ethanol, gave *N*-(4-nitrophenyl)-2-pyridinecarboxamide (**5**), mp 222–224 °C. Anal. ($C_{12}H_9N_3O_3$) C, H, N.

N-2-Pyridinylbenzamide (**4a**), mp 78–80 °C (lit.[24] mp 82–83 °C), was prepared via the dibenzoyl compound.[24]

Rate Measurements. These were carried out in methanol as described previously.[25] The analytical wavelengths and species moni-

tored are indicated in Tables I and II. In all cases, infinity spectra matched those of authentic product mixtures.

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Hydrolysis Mechanism of BH_4^- in Moist Acetonitrile[1]

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Abstract: Acetonitrile solutions containing up to 0.6 M H_2O do not hydrolyze BH_4^- measurably over a period of days. However, 10^{-3} M CF_3SO_3H in acetonitrile completely hydrolyzes BH_4^- in less than 10 s. The hydrolysis of BH_4^- in acetonitrile containing acetic acid is first order in BH_4^-, and the apparent first-order constant k_1 is given by $k_1 = [k_0 + k_{H_2O}(H_2O)][K(CH_3COOH)/1 + K(CH_3COOH)]$ where K is the equilibrium constant for the formation of a complex between acetic acid and BH_4^-. It has a value of $1.6 \pm 0.3 \times 10^2$. This suggests the rate-determining step involves breakdown of the complex by an unpromoted and a water-promoted route at competitive rates. Acceleration by a tertiary amine suggests that the latter path involves nucleophilic attack by water on the complex. ^{11}B NMR shows no exchange of H for D on boron in interrupted reactions using D_2O in place of H_2O, indicating the acetate ion remains firmly attached to one proton until the complex undergoes reaction. The complex is a rare example of a hydrogen bond not involving either unpaired electrons or a π bond. These observations are consistent with the existence of BH_5 as an intermediate in the hydrolysis of BH_4^- in water, but some differences are apparent.

The hydrolysis of BH_4^- in aqueous solution apparently involves BH_5 as an intermediate[2] with water acting as a proton relay.[3] In accordance with this conclusion, the proton catalytic coefficient, k_{H^+}, is lower in dimethyl sulfoxide (Me_2SO) than in water by a factor of 10^6.[4] The purpose of the present work was to compare acetonitrile (AN) with water and Me_2SO as solvents. Like Me_2SO, AN is a nonhydroxylic solvent, so it should be incapable of functioning as a relay for the proton or as a hydrogen bond donor. Unlike Me_2SO, it is also a poor hydrogen bond acceptor,[5] which should reduce the energy required to break solvent bonds to the proton. This work will provide some insight into the effect of these structural parameters on the mechanism.

Experimental Section

Materials. Acetonitrile (99%) was obtained from the Aldrich Chemical Co. The only detectable impurity was water. Unpurified solvent and acetonitrile which had been dried by the method of Coetzee[6] gave indistinguishable rates. In most experiments the solvent was used as supplied and analyzed for water during the course of the experiment. Tetraethylammonium tetrahydridoborate ("borohydride") was obtained from the Ventron Corporation and was used without further purification. *N,N,N',N''*-Pentamethyldiethylenetriamine (PMDETA) was obtained from Ames Laboratories and was redistilled under vacuum. β-Nicotinamide adenine dinucleotide (NAD^+) and tris(hydroxymethyl)aminomethane (Tris) were obtained from the Sigma Chemical Co. The Tris buffers were prepared by titration with perchloric acid to the desired pH. Tetramethylammonium biacetate (homoconjugate) was prepared from tetramethylammonium hydroxide (20% solution in methanol, Aldrich Chemical Co.) by potentiometric titration with glacial acetic acid. Two equivalents of acid were added for each equivalent of base, and the methanol was carefully removed on a rotary evaporator at 0.5 mm vacuum and room temperature. The resulting residue was twice taken up in AN and restripped. The final crystalline product was stored in a desiccator.

Kinetic Method. Two 50-mL AN solutions were prepared: one containing the known amount of tetraethylammonium borohydride and the other a measured amount of acetic acid and any added water. At time zero the two solutions were mixed in a bottle fitted with a plunger designed to eject a known volume of solution. Five-milliliter aliquots were ejected at recorded time intervals into bottles containing 20 mL of 0.15 M KOH to quench further reaction. For reaction solutions containing 0.1 M acetic acid (the highest concentration employed) this would result in a solution containing 20% AN and 0.10 M KOH. The amount of unreacted BH_4^- in the quenched solutions was determined by a modification in the procedure reported by Werner et al.[7] Within 30 min of quenching, suitable aliquots from the quench solutions (normally 0.3 mL for BH_4^- concentrations of 2×10^{-3} M in the original reaction mixture) were transferred to 3.0 mL of a solution containing 0.0030 M NAD^+ and 0.050 M Tris buffer, adjusted to have a final pH, after addition of the quenched borohydride solution, of 8.5 ± 0.1. Under these conditions NAD^+ quantitatively oxidizes BH_4^- and is itself reduced to NADH and its isomers