Kinetics of Hydrobenzamide Formation from
p-Dimethylaminobenzaldehyde and Ammonia.   Role of the Imine
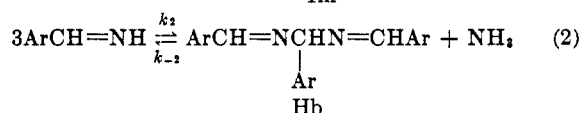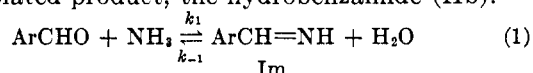
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The rate of reaction of ammonia with p-dimethylaminobenzaldehyde, in methanol at 25°, has been measured by spectrophotometry and dilatometry. The predominant product in solution is the imine, ArCH=NH, which trimerizes with loss of ammonia to the slightly soluble hydrobenzamide. The reverse reaction of hydrobenzamide with ammonia, to form imine, is second order and appears to involve protonated substrate except at very high pH.

The simplest example of the condensation product RR'C=NR'', from a carbonyl compound and an amine, is the type obtained from ammonia, RR'C=NH. Although ketimines are known, aliphatic aldimines RCH=NH are less stable than various other reaction products and the corresponding aromatic imines have been prepared only at high ammonia concentrations (liquid ammonia)[2] or very low aldehyde concentrations (dilute methanol solution).[3] Under those conditions, as the following equations show, the imine (Im) would be favored over the commonly and easily isolated product, the hydrobenzamide (Hb).

$$ArCHO + NH_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{Im}{ArCH=NH} + H_2O \tag{1}$$

$$3ArCH=NH \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{\substack{|\\Ar\\Hb}}{ArCH=NCHN=CHAr} + NH_3 \tag{2}$$

Extending our previous work on the kinetics of Schiff base formation in methanol to the ammonia reaction and using the rate of simple imine formation in dilute solution[3] as a starting point, we have now studied the reaction of p-dimethylaminobenzaldehyde (ArCHO) with ammonia in the concentration range where reaction 2 become appreciable.[4] The rates of formation of other hydrobenzamides have been determined by Dobler[5] and by Ogata, Kawasaki, and Okumura,[6] but the imine intermediate, which we will show to be higher in concentration at all times than the hydrobenzamide, was not recognized.

Experimental Section

Materials.—The solvent was Mallinckrodt reagent grade methanol. Ammonia solutions, prepared by passing the gas into methanol, were titrated for water (Karl Fischer method in glacial acetic acid),[7] a typical result being 0.42 g/l. The water concentration of aldehyde solutions and of reaction mixtures was calculated by adding the measured water content of the solvent to any additional amount of water purposely introduced.

The hydrobenzamide (ArCH=N)₂CHAr, where Ar is p-dimethylaminophenyl, was prepared[8] in 79% yield by adding 2 g of ArCHO to 50 ml of 3.5 M ammonia in methanol. After 40 hr the crystals were filtered off, dissolved in chloroform,

precipitated with ether, collected, and dried in a desiccator; mp 194–196° (lit.[8] mp 193°).

Anal. Calcd for $C_{27}H_{33}N_5$: C, 75.84; H, 7.78; N, 16.38. Found: C, 75.55; H, 7.56; N, 16.62.

p-Dimethylaminobenzaldehyde (ArCHO) was recrystallized from water. Glacial acetic acid was dried by azeotropic distillation with benzene.

Apparatus and Procedure.—The tapless dilatometer[9] had a volume of 43.48 ml, and the rise, *h*, in the two 0.01-cm diameter capillaries was observed by thermal expansion of methanol to be 4.96 cm per 1-ml volume increase. The temperature in all the experiments described in this paper was 24.85°, constant to 0.003°.

Infrared spectra were taken on a Perkin-Elmer Model 21 spectrophotometer, using a 0.025-mm Irtran-2 cell, or on an Infracord with a 0.1-mm sodium chloride cell. Beckmann DU and DK-2 ultraviolet spectrophotometers were used.

Liquid densities were determined with a Weld pycnometer. To obtain the solubility of hydrobenzamide, the solid was shaken 6 hr or more with methanolic sodium methoxide and a sample of the liquid phase was acidified and subsequently analyzed for acetal. The solubility in ammonia was determined by weighing the portions of solute added.

Results

Spectra of the Hydrobenzamide.—The ultraviolet absorption spectrum of Hb in 0.01 M sodium methoxide is stable and shows maxima at 261 mμ (ε 1.42 × 10⁴) and 334 (5.5 × 10⁴). The first clearly arises from the >CHAr group, comparable to the acetal ArCH(OCH₃)₂ (λmax 261 mμ (ε 1.88 × 10⁴)) or to ArCH₃ (λmax 254 (ε 3 × 10⁴)). The maximum at 334 mμ is due to the ArCH=N groups which also occur in the imine ArCH=NH (λmax 327 mμ (ε 2.28 × 10⁴))[3] and in the Schiff base, ArCH=NC₄H₉ (λmax 329 (ε 2.47 × 10³)).[10]

In dilute methanolic hydrogen chloride, there is an absorption maximum at 392 mμ (ε 8.7 × 10⁴) which shifts within 2 min to 386 mμ. This latter wavelength indicates that HbH⁺ has been converted to HIm⁺, an inference which is confirmed by making the solution alkaline and observing peaks at 327 and 261 mμ arising from a 2:1 mole ratio of imine and acetal. The reaction causing the shift in acidic medium is given in reaction 3. Aromatic aldehydes are completely con-

$$\underset{Hb}{(ArCH=N)_2CHAr} + 2CH_3OH_2^+ \rightarrow$$
$$\underset{HIm^+}{2ArCH=NH_2^+} + ArCH(OCH_3)_2 \tag{3}$$
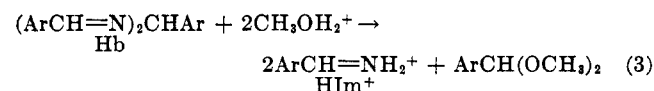
verted to acetals in acidic methanol[10] and the imine formed by reaction 3 meets the same fate within a day.

Practically all the —CH=N— nitrogens in Hb are

(1) Shell Foundation Fellow, 1960–1961, DuPont Teaching Assistant, 1961–1962.
(2) H. H. Strain, *J. Am. Chem. Soc.*, **49**, 1558 (1927).
(3) R. K. McLeod and T. I. Crowell, *J. Org. Chem.*, **26**, 1094 (1961).
(4) R. K. McLeod, Ph.D. Dissertation, University of Virginia, Charlottesville, Va., 1962.
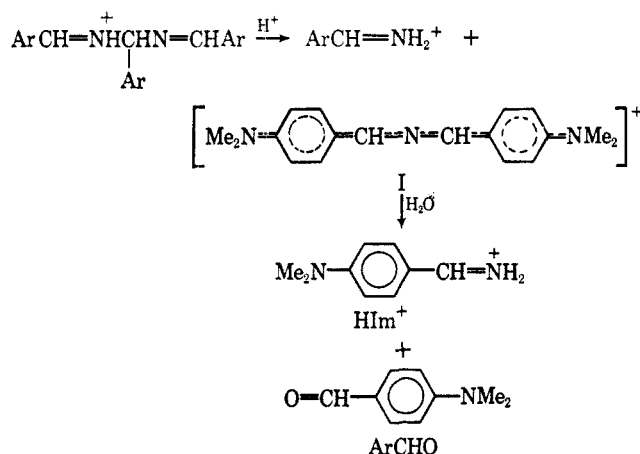(5) F. Dobler, *Z. Physik. Chem.* (Leipzig), **101**, 1 (1922).
(6) Y. Ogata, A. Kawasaki, and N. Okumura, *J. Org. Chem.*, **29**, 1895 (1964).
(7) J. R. Mitchell and P. M. Smith, "Aquametry," Interscience Publishers, Inc., New York, N. Y., 1948, p 264.
(8) F. Sachs and P. Steinert, *Ber.*, **37**, 1733 (1904).

(9) G. A. Benford and C. K. Ingold, *J. Chem. Soc.*, 929 (1938).
(10) G. M. Santerre, C. J. Hansrote, Jr., and T. I. Crowell, *J. Am. Chem. Soc.*, **80**, 1254 (1958).

protonated in 5.1×10^{-5} M methanolic hydrogen chloride but not at lower concentrations. Partial protonation occurs even in pure methanol. These facts suggest that pK_a is about 4.8 for $HbH_2{}^{2+}$ and considerably higher for HbH^+. The λ_{max} 392 mμ for the protonated species indicates that the imine, not the amine nitrogens, is protonated to give greater electron delocalization, as in HIm^+ and protonated Schiff base.[3]

Glacial acetic acid solutions of Hb are a brilliant green, with absorption peaks at 383, 435 and 650 mμ. Within 45 min at room temperature, the green color changes to the yellow (383 mμ) of HIm^+ as the peak at 435 mμ disappears. This process is greatly accelerated by adding water, methanol, or concentrated sulfuric acid to the acetic acid. A plausible explanation of these phenomena is the formation of the cation I.

$$ArCH{=}\overset{+}{N}H\underset{|}{\overset{}{C}}HN{=}CHAr \xrightarrow{H^+} ArCH{=}NH_2{}^+ +$$
$$\hspace{2.2cm} Ar$$

$$\left[Me_2N{-}\langle\bigcirc\rangle{=}CH{-}N{=}CH{-}\langle\bigcirc\rangle{-}NMe_2 \right]^+$$

$$I$$
$$\downarrow H_2O$$

$$Me_2N{-}\langle\bigcirc\rangle{-}CH{=}\overset{+}{N}H_2$$
$$HIm^+$$
$$+$$
$$O{=}CH{-}\langle\bigcirc\rangle{-}NMe_2$$
$$ArCHO$$

The infrared spectrum of Hb, in chloroform, between 1150 and 1600 cm^{-1} was quite similar to that of the Schiff base in methanol, with strong absorption at 1170, 1366, 1532, 1610, and 1633 cm^{-1}. This last frequency, which in Hb appears as a shoulder on the 1610-cm^{-1} peak, is due to C=N stretching. Hb does not absorb strongly at the C=O stretching frequency of 1670 cm^{-1} exhibited by ArCHO, a fact used in the kinetic work.

The central, benzylic proton of Hb and the CH=N protons appear in the nmr spectrum (CDCl$_3$) at τ 4.20 and 1.54, respectively. The methyl frequencies (τ 7.08) are split due to the two electronically different species of benzene ring, and for the same reason the aromatic protons appear as two independent A_2X_2 systems at the resolution attained.

Accumulation of Imine.—The solubility of Hb in methanol is quite low, about 0.002 M, though it readily forms supersaturated solutions. In many reaction mixtures, however, the concentration of product in solution, known from the rate of ArCHO consumption to be many times larger than 0.002 M, is not Hb but some other compound, presumably the imine. The ultraviolet spectra of such solutions, observed either in a 0.1-mm cell or by dilution into a stabilizing sodium methoxide solution, show the characteristics of imine–aldehyde mixtures to an extent which would obscure any absorption at 261 mμ expected of Hb.

It was necessary to estimate the equilibrium constant K_2 for reaction 2, given by $K_2 = [Hb][NH_3]/[Im]^3$. Methanolic ammonia solutions were equilibrated with solid Hb. The ammonia greatly increased

the apparent solubility of the solid by converting it to imine. In one experiment, 50 ml of 0.46 M ammonia dissolved nearly 0.225 g of Hb. Assuming [Hb] = 0.0017, the saturation value, and that the rest is converted to Im, one calculates [Im] = 0.0264 and $K_2 = (0.0018)(0.46)/(0.0264)^3 = 45$. A second series of reaction mixtures was prepared, containing ArCHO, ammonia, and water. After sufficient time for reaction, the solutions were seeded with crystals of Hb. A borderline case, in which only a slight precipitate was formed (0.082 M ArCHO, 1.0 M NH$_3$, 0.55 M H$_2$O), was used to calculate K_2, assuming the equilibrium constant K_1 for reaction 1 to be 0.416.[3] The value obtained was 48. In subsequent calculations, K_2 was assumed to be 45, though the experimental methods and the cubed term in the denominator cause considerable uncertainty in this equilibrium constant.

Rate of Imine Formation.—The rate of reaction 1, easily followed by observing the $ArCH{=}NH_2{}^+$ absorption at 386 mμ in acidified solutions,[3] was redetermined under new conditions with the following results.

The rate constants $10^5 k_1$ at water concentrations of 0, 0.555, and 1.11 M were 4.47, 4.58, and 4.59 M^{-1} sec^{-1}, respectively, showing a negligible effect on the rate of imine formation. (Schiff base formation was accelerated 18% by 5.1 M H$_2$O.[11]) The ammonia concentration was 0.572 M and the aldehyde concentration was 4×10^{-4} M.

Higher aldehyde concentrations (0.201 M ArCHO, 1.021 M NH$_3$) depressed k_1 to 3.3×10^{-5} M^{-1} sec^{-1}.

To rule out any effect of the acidification method on the calculated rate, for example, dehydration of stable tetrahedral intermediates, one run was followed simply by observing the change in absorption at 340 mμ. The value 4.2×10^{-5} was obtained for k_1.

Reaction of Hydrobenzamide with Ammonia.—Since hydrobenzamide appeared to be in equilibrium with the imine (eq 2), we investigated the kinetics of the reaction. Hydrobenzamide (10^{-3} M) in 0.184 to 0.733 M methanolic ammonia followed a pseudo-first-order course to the imine, as evidenced by the decrease in the Hb absorption at 261 mμ and the shift of the 334-mμ peak to 327. The final intensity at this last wavelength was equal to the predicted value for 3 molar equiv of imine ($\pm 1\%$, 8 runs). The reaction is first order in both Hb and ammonia and moreover is decelerated by sodium methoxide. Figure 1 shows the dependence of k_{-2} on the methoxide ion concentration and also on the calculated hydrogen ion concentration; the rate equation is $d[Hb]/dt = -k_{-2} [NH_3]\cdot$ [Hb] with k_{-2} (M^{-1} sec^{-1}) = $7.3 \times 10^{-5} + 1.1 \times 10^{11}\cdot$ [H$^+$], assuming [H$^+$][OCH$_3{}^-$] = $10^{-16.7}$.

Rate of the Forward Reaction.—Although the reaction of ammonia with p-dimethylaminobenzaldehyde, at concentrations high enough to form hydrobenzamide, could probably be followed by the ultraviolet spectra described above, infrared spectrophotometry and dilatometry were used instead.

The decrease in the carbonyl absorption at 1670 cm^{-1} was observed in a solution initially containing 0.178 M ArCHO, 1.74 M NH$_3$, and 0.02 M H$_2$O. Very little aldehyde remained at equilibrium, subject to the error in estimating the base line. The rate

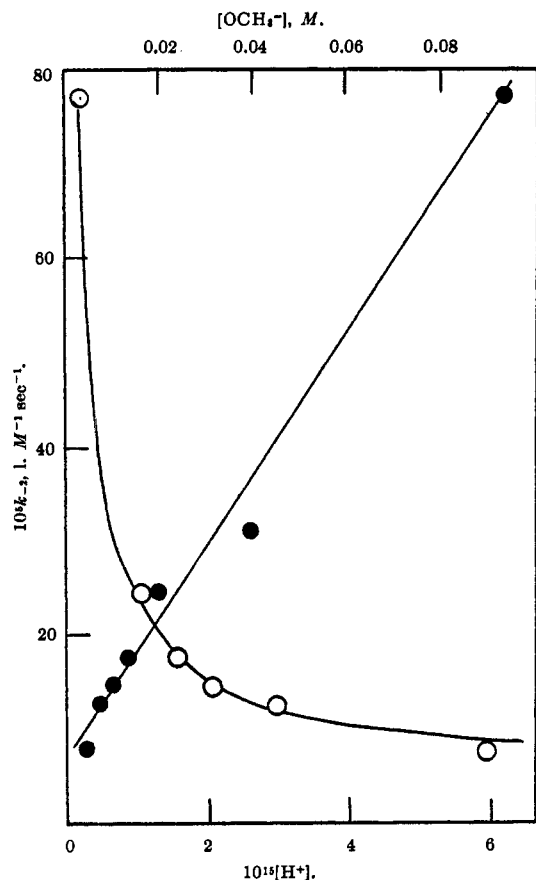(11) R. L. Hill and T. I. Crowell, J. Am. Chem. Soc., 78, 2284 (1956).

[OCH₄⁻], M.

Figure 1.—Dependence of rate of ammonolysis of hydrobenzamide on methoxide ion concentration (O) or hydrogen ion concentration (●).
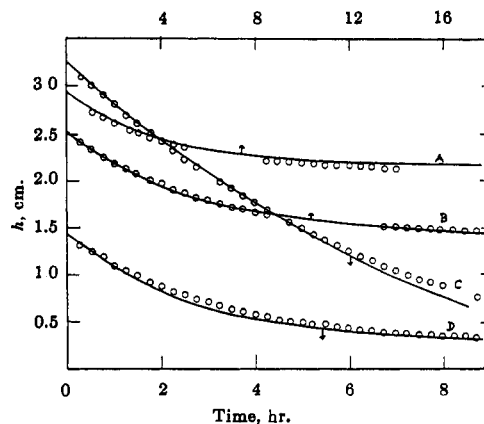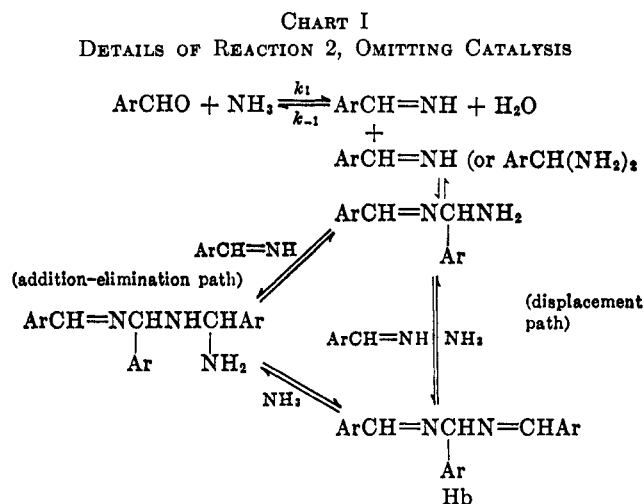

Figure 2.—Typical dilatometer data (O) and calculated curves. Initial concentrations (A_0, B_0, W_0): run A—0.09, 0.75, 0.57; run B—0.09, 0.75, 0.29; run C—0.18, 0.86, 0.02; run D—0.09, 1.8, 0.57 M.

constant, calculated from the slope of a plot of log $(A - A_\infty)$ vs. time, was 3.5×10^{-5} M^{-1} sec^{-1}. Hydrobenzamide precipitated near the end of the reaction, but the presence of methanol prevented any direct spectral measurement of its concentration.

The most precise measurements were made by dilatometry. The rate as well as the total volume change in a reaction, ΔV_∞, was reproducible. The reaction was clearly first order in aldehyde and reversed by water. The rate was increased by increasing the ammonia concentration or by adding ammonium salts but was insensitive to ionic strength. Typical plots of h vs. time are shown in Figure 2 and their interpretation described in the Discussion section.

From the measured densities of methanolic solutions and plots of volume vs. molality,[12] the following partial molal volumes were obtained (ml/mole): ammonia, 24.1; water, 14.9; p-dimethylaminobenzaldehyde, 124; p-dimethylaminobenzylidene-n-butylamine, 200; n-butylamine, 93.9.

Discussion

Since the main product of the ammonia–aromatic aldehyde reaction, before precipitation of hydrobenzamide, is imine, this obviously accounts for the fact that the rate constant for aldehyde consumption $(3.5 \times 10^{-5}$ M^{-1} sec^{-1} by infrared) is very close to k_1 for imine formation. If hydrobenzamide were the

(12) G. N. Lewis and M. Randall, "Thermodynamics," revised by K. S. Pitzer and L. Brewer, McGraw-Hill Book Co., Inc., New York, N. Y., 1961, p 206.

only product, these figures would strongly suggest rate-controlling imine formation followed by rapid trimerization with loss of ammonia, and would rule out the rapid reaction of imine with free aldehyde postulated by Ogata and co-workers,[6] a mechanism which would double or triple the rate. Although the accumulation of imine complicates matters, hydrobenzamide formation through the imine is still the simplest mechanism consistent with our observations. Any faster mechanism can moreover be invalidated because the hydrobenzamide so formed would react with ammonia to produce imine at the higher rate, which is contrary to fact.

The mechanism may then be formulated as in Chart I. The many possible protonated species are omitted for simplicity, since the extremely detailed data necessary to elucidate catalysis in so complex a system are lacking.

CHART I
DETAILS OF REACTION 2, OMITTING CATALYSIS

$$ArCHO + NH_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArCH=NH + H_2O$$

$$+$$

$$ArCH=NH \ (or \ ArCH(NH_2)_2$$

$$\updownarrow$$

$$ArCH=NCHNH_2$$

(addition–elimination path) ArCH=NH

(displacement path)

$$ArCH=NCHNHCHAr \quad ArCH=NH \ | \ NH_3$$

$$| \qquad | \qquad Ar \qquad NH_2 \qquad$$

$$NH_3$$

$$ArCH=NCHN=CHAr$$

$$|$$

$$Ar$$

$$Hb$$

The observed lyonium ion catalysis of the reverse of reaction 2, however, could arise from attack of ammonia (k_4) on protonated hydrobenzamide. If so, k_{-2} would be equal to $k_4[H^+]/K_{HbH^+}$ with $k_4/K_{HbH^+} = 1.1 \times 10^{11}$ M^{-2} sec^{-1}. This would be quite possible if, for example, $K_{HbH^+} = 10^{-9}$ and $k_4 = 100$. The rate constant for attack of ammonia on Hb would then be 7.3×10^{-5} M^{-1} sec^{-1}, the attack by the amide ion on HbH$^+$ being a kinetically indistinguishable alterna-

tive. At lower pH and ammonia concentration than those used, it is also possible that the cation I is an intermediate. In Chart I, displacements on carbon (plausible only with protonation of the leaving group) are formulated as well as the addition–elimination paths which predominate in the reactions of carbonyl compounds.

Let us now estimate how rapidly equilibrium is established between imine and hydrobenzamide in 0.5 M ammonia, without sodium methoxide. At this pH, k_{-2} is calculated to be $2.7 \times 10^{-3} M^{-1} \sec^{-1}$. The reaction of Hb with this large excess of ammonia is pseudo first order with a rate constant $0.5k_{-2}$ or $1.3 \times 10^{-3} \sec^{-1}$. At any imine concentration much larger than the corresponding equilibrium hydrobenzamide concentration (for example, [Im] = 0.02 M for which $[Hb]_e = 45(0.02)^3/0.5 = 0.0007$), the concentration of imine is practically unchanged by partial conversion to hydrobenzamide. It follows that the rate of conversion is constant and the half-time of attainment of equilibrium is less than $(\ln 2)/1.3 \times 10^{-3} \sec^{-1}$ or 9 min. Since the kinetic runs lasted many hours, it is a fair (but not excellent) approximation to consider reaction 2 at equilibrium.

The differential equation for the system is then

$$dx/dt = k_1(A - x)(B - x + y) - k_{-1}(x - 3y)(W + x) \quad (4)$$

where

$$y(B - x + y)/(x - 3y)^3 = K_2 \quad (5)$$

In these equations, $x = [ArCHO]_0 - [ArCHO]$, $y = [Hb]$, $A = [ArCHO]_0$, $W = [H_2O]_0$, $B = [NH_3]_0$. The imine concentration is $x - 3y$. Equation 4 was integrated by simple summation, computing the equilibrium concentration of y at each time increment by use of eq 5.[13] The constants used were $k_1 = 3.5 \times 10^{-5}$, $k_{-1} = 9.1 \times 10^{-5}$, and $K_2 = 45$. This computation, which gave [Im] and [Hb] as a function of time during the ammonia–aldehyde reaction, as shown in Figure 3, was also used to correlate the dilatometer experiments.

The dilatometric data were fitted to the kinetic scheme (eq 4 and 5) by letting $\Delta V_1 = -10.2$ ml/mole for imine formation (eq 1) and $\Delta V_2 = -15.3$ ml/mole of Hb for hydrobenzamide formation (eq 2). Examples of the fit are shown in Figure 2, in which the experimental points are compared with the calculated curves. The data are consistent with the assumed mechanism and support the values of k_1, k_{-1}, and ΔV_1. The data do not, however, necessarily provide evidence for the correctness of k_2 and ΔV_2, because hydrobenzamide formation is a relatively small part of the observed reaction. In fact, a direct dilatometric measurement of ΔV_2, carried out with a 0.001 M solution of hydrobenzamide in methanolic ammonia, showed $\Delta V_2 \sim 0$. The value of ΔV_2, although used as a curve-fitting parameter, may therefore be incorrect.

An observable such as volume in a dilatometer, which depends on the concentration of all species, is
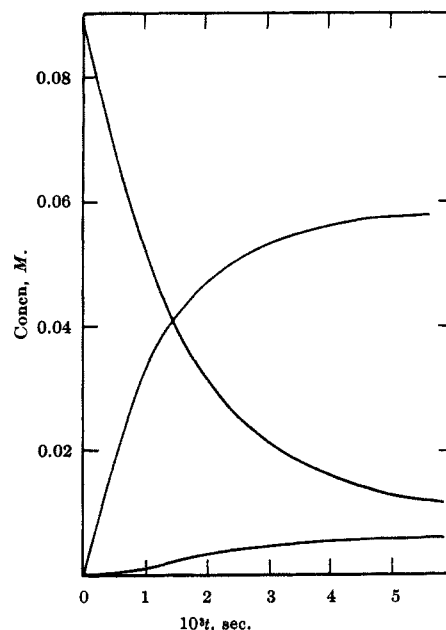
Figure 3.—Calculated reactant and product concentrations during a run with initial concentrations $A_0 = 0.089$, $B_0 = 1.5$, $W_0 = 0.025 M$; upper curve, ArCHO; middle curve, imine; lower curve, hydrobenzamide.

easily misinterpreted. The values of ΔV_∞ for anhydrous runs were independent of the ammonia concentration, which at first led us to the erroneous conclusion that reaction 2 had gone to completion! Guggenheim plots using this ΔV_∞ were generally straight, though the rates appeared markedly depressed by water. These artifacts of the inadequate mechanism disappeared when evidence for the successive production of imine and hydrobenzamide was obtained and used. One feature of both Guggenheim and simple first-order (log V vs. time) plots for anhydrous solutions was a slight downward concavity in the first few hours. This was reproduced in the computer analysis and may therefore be due to the effect of hydrobenzamide formation on the equilibrium 1.

It is interesting that the partial molal volume change, ΔV_1, for imine formation, -10.2 ml/mole, can be largely accounted for by the difference (-9.2) in the partial molal volumes of ammonia (24.1) and water (14.9) in methanol. The ΔV for Schiff base formation, calculated from the measured partial molal volumes, is -3 ml/mole.

Our conclusion that only small quantities of hydrobenzamide, relative to imine, are formed in solution is valid only for the particular case of p-dimethylaminobenzaldehyde. We would expect that other substituents with higher σ constants would favor the less highly conjugated hydrobenzamide and increase K_2. If the effect were large enough, the assumptions of Ogata and co-workers that hydrobenzamide predominates could be true for the cases they studied. This question must be settled experimentally.