JOC The Journal of Organic Chemistry
Cite This: J. Org. Chem. XXXX, XXX, XXX−XXX
Article
pubs.acs.org/joc

N-(Hydroxybenzyl)benzamide Derivatives: Aqueous pH-Dependent Kinetics and Mechanistic Implications for the Aqueous Reactivity of Carbinolamides

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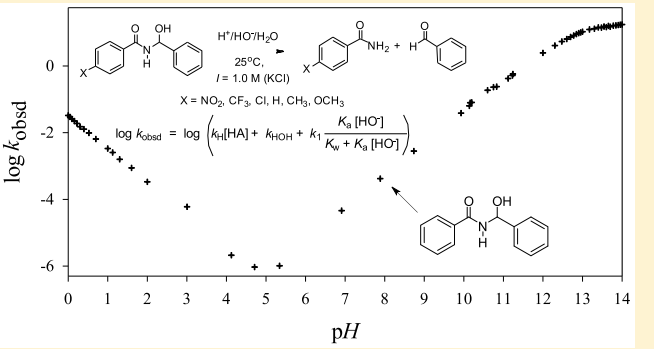
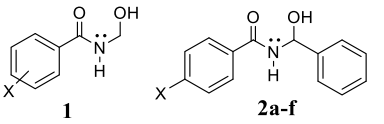
Supporting Information

ABSTRACT: The rate constants for the aqueous reaction, between pH 0 and 14, have been determined for a series of amide substituted *N*-(hydroxybenzyl)benzamide derivatives, in H_2O, at 25 °C, I = 1.0 M (KCl). The *N*-(hydroxybenzyl)-benzamide derivatives were found to react via three distinct mechanisms with the kinetically dominant mechanism being dependent on the pH of the reaction solution. It has been shown that the carbinolamides react via a specific-base-catalyzed mechanism (E1cB-like) under basic and pH neutral conditions. At lower pH values, an acid-catalyzed mechanism was kinetically dominant and, last, a water reaction was postulated at pH values where neither the hydroxide-dependent nor the general-acid-catalyzed mechanism was dominant. Contrary to earlier studies with *N*-(hydroxymethyl)benzamide compounds, no evidence for mechanistic variation based upon the nature of the amidic substituent was observed for any of the *N*-(hydroxybenzyl)benzamide derivatives studied between pH values of 0−14. The rate for the acid-catalyzed reaction (k_H, ρ = −1.17), the apparent second-order hydroxide rate constant (k'_1, ρ = 0.87), the hydroxide-independent rate (k_1, ρ = 0.65), and the pK_a's of the hydroxyl group of the carbinolamide (ρ = 0.23) are reported.



INTRODUCTION

At first appearance, carbinolamides are structurally similar to a variety of carbonyl derivatives that possess a broad range of reactivity.[1] Coupled to the problem of a broad potential reactivity range within this family of functionalities is a lack of information concerning reactions having an amide group acting as a leaving group.[2−7] Additionally, there are aspects of the mechanism of reaction of carbinolamides that are still not well understood, and this is surprising given that the first report of compounds possessing this functionality appeared in the literature as early as the 1870s.[8] One could rationalize this statement as being the result of the rarity of the functionality within our world. If one accepts this argument, it would be surprising to learn of the diverse roles that carbinolamide containing compounds have in a broad variety of venues. For example, an increasing number of compounds possessing this functionality have been discovered and are being developed that have interesting pharmaceutical applications.[9−23] Carbinolamides have also been found to be intermediates in an array of biological venues with both positive[24−28] and negative[29−31] outcomes for the associated organism. Our studies, to date, have focused on the mechanisms and methods of catalyzing the reaction of these compounds and the role that structure plays in their reactivity patterns.[7,32−35] Much of the work that has been performed, in our group, on the *N*-(hydroxymethyl)-benzamide derivatives (**1**) has been published, with several interesting observations having been reported.[7,32−35] A valid question that has resulted from these studies is how characteristic of "normal" carbinolamide reactivity patterns are the *N*-(hydroxymethyl)benzamide derivatives given the well-known electrophilicity of formaldehyde[36−38] vs other aromatic aldehydes?[39−43] To broaden the understanding of the effects of structure on the aqueous reactivity of carbinolamides, the aqueous kinetics for a series of *N*-(hydroxybenzyl)-benzamide derivatives (**2**) were investigated in H_2O, as a function of pH, at 25 °C, I = 1.0 M (KCl).



a = -NO_2 **d** = -H
b = -CF_3 **e** = -CH_3
c = -Cl **f** = -OCH_3

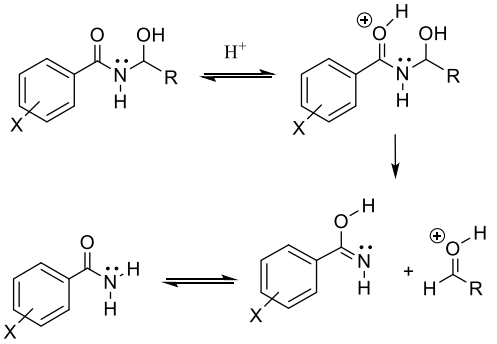
The studies involving *N*-(hydroxymethyl)benzamide derivatives (**1**) led to a number of somewhat unexpected outcomes, one of which was the reexamination of the generally accepted reaction pathways at different pH values.[7,32−35] The previously accepted mechanism for the acid-catalyzed reaction was thought to involve a specific-acid protonation of the carbinolamide, followed by rate-limiting decomposition into

Received: November 7, 2019
Published: December 12, 2019

DOI: 10.1021/acs.joc.9b02812
J. Org. Chem. XXXX, XXX, XXX−XXX

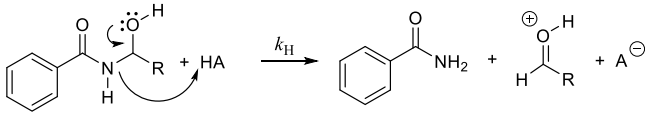
the tautomer of the amide and protonated aldehyde (Scheme 1).[32,44,45] This proposed mechanism was invalidated by the

Scheme 1. Previously Accepted Specific-Acid-Catalyzed Breakdown of Carbinolamides

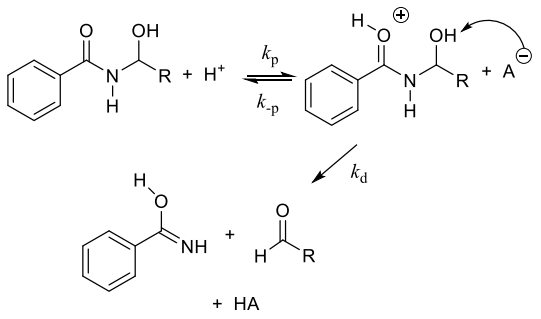


observation of buffer catalysis in the acid-catalyzed region of the pH−rate profile for the derivatives of **1**.[34,35] Buffer catalysis provided evidence for an acid-dependent reaction which involved rate-determining proton transfer.[33,34] This provided a new complication, as two kinetically equivalent mechanisms could be proposed for the acid-catalyzed reaction that involve rate-determining proton transfer. These mechanisms are general-acid catalysis (Scheme 2) and a specific-acid followed by a general-base mechanism (Scheme 3).[33,34]

Scheme 2. General-Acid-Catalyzed Mechanism

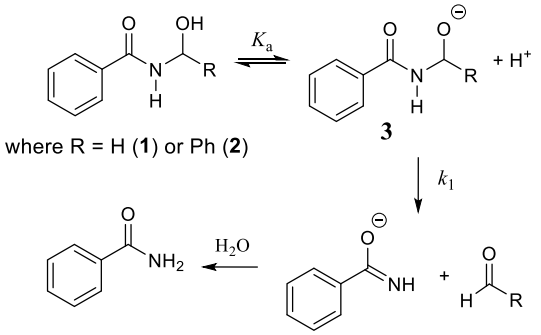


Scheme 3. Specific Acid Followed by General Base



A second outcome, stemming from the work focused on the reactivity of derivatives of **1**, occurred in the high [HO^-] region of the pH−rate profile for those compounds bearing electron-donating groups. The generally accepted mechanism for the breakdown of carbinolamides under basic conditions involves a specific-base-catalyzed deprotonation of the hydroxyl group of the carbinolamide, followed by rate-limiting breakdown of the conjugate base into the aldehyde and an amidate (Scheme 4).[7,32,35,44−48] Experimental evidence for the mechanism, shown in Scheme 4, involved a lack of buffer catalysis and the existence of a pH-independent region at high [HO^-] where the carbinolamide would be fully deprotonated. However, it was found that derivatives of **1**, bearing strongly electron-donating groups on the amidic portion of the carbinolamide structure, reacted faster than anticipated based

Scheme 4. Specific-Base-Catalyzed Reaction



upon the trends observed for those compounds having electron-withdrawing substituents or having no substituent (apparent break in the Hammett plot).[7,32,35] Product analysis of the reaction products of the derivatives of **1**, bearing strongly electron-donating groups, showed the presence of large amounts of carboxylate product present.[35] That is, there was more hydrolyzed amide present than could be explained by carbinolamide breakdown followed by amide hydrolysis, based upon the conditions of the reaction (H_2O, 25 °C, I = 1.0 M (KCl)).[35] These observations led to the conclusion that the decrease in the nucleofugality of the benzamidate, upon the addition of the electron-donating groups, increased the stability of the conjugate base of the carbinolamide (**3**), where R is an H (see Scheme 4), to the degree that alternative reaction pathways became energetically competitive.[35] Would this observation hold true for the carbinolamides not generated from formaldehyde?

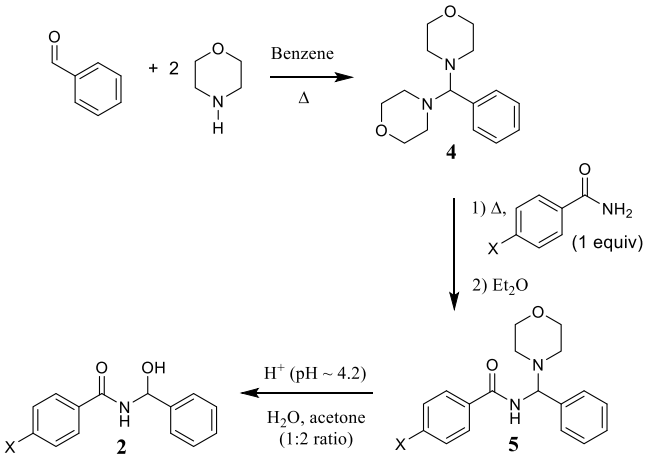
These observations, which form the foundation of what is currently known about the reactivity of carbinolamides, were determined as a result of studies of the *N*-(hydroxymethyl)-benzamide derivatives (**1**). It should be noted that the derivatives of **1** are a unique class of carbinolamides, as they are the product of the reaction of a benzamide derivative with formaldehyde. The electrophilicity of formaldehyde results in the conjugated base of the carbinolamide (**3**) not having strong electronic assistance to the departure of the benzamidate leaving group in the breakdown of the carbinolamide.[36−38] The results for the *N*-(hydroxybenzyl)benzamide derivatives represent a series of compounds where the nucleofugality of the benzamidate leaving groups was the same as the studies with **1**, but the electronic assistance to the departure of the benzamidate, by the less electrophilic aromatic aldehydes, should be greater.[39,40] What effect will this have on the reactivity of the derivatives of **2** vs **1**, and will the mechanisms of reaction remain the same? Reported here are the kinetics of the aqueous reaction of *N*-(hydroxybenzyl)benzamide and the amide substituted derivatives as a function of pH at 25 °C, I = 1.0 M (KCl), and the implications of these results on the accepted reaction mechanisms of carbinolamides under aqueous conditions.

RESULTS

The carbinolamides used in the studies described here were synthesized from the amide and aldehyde starting materials (see Scheme 5). The morpholine aminal of benzaldehyde (**4**) was reacted with the benzamide derivatives, using a solvent-free method, to generate the monoacylaminal synthetic intermediate (**5**).[49] The monoacylaminals were then subjected to solvolysis conditions, maintained at "pH" ∼4.2 in an

DOI: 10.1021/acs.joc.9b02812
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 5. Synthesis of Carbinolamide Compounds



acetone/water solution (2:1, respectively), which was a modification of a method used by Bundgaard et al. and led to the synthesis and eventual isolation of the target carbinolamides.[44,49]

All kinetic experiments were performed in H_2O at 25 °C and I = 1.0 M (KCl) and were initiated by the injection of concentrated solution of the carbinolamide, in DMSO, into the reaction solution to yield a final [substrate] of ~1×10^{-4} M. Rate constants for experiments between pH values of 0−4 and 6−9 were obtained by following the change in absorbance as a function of time, utilizing a UV−vis spectrophotometer. Between pH values of 10 and 14, a stopped-flow apparatus was used to perform the kinetic studies, as the reactions were too fast to follow by other means. The stopped-flow experiments were performed similarly to the studies described above; however, the stock solution of substrate was injected into H_2O or 1 M KCl solution and these solutions were mixed with the hydroxide solutions, in the stopped-flow, to obtain k_{obsd} at a specific [HO^-]. All of the carbinolamides studied exhibited good first-order kinetics with stable infinity absorbancies. Reactions quenched, prior to the completion of the reaction, showed only starting material, amide, and benzaldehyde by HPLC analysis. At all pH values, the reaction of the carbinolamides was much more rapid than subsequent hydrolysis of the benzamide based upon available data.[50,51]

For experiments performed in the pH range from 4 to 6, HPLC was used to monitor the reaction progress as a function of time. The chromatogram showed separate peaks for the carbinolamide, amide, and benzaldehyde so that the disappearance and appearance of each component could be followed independently. The rate of reaction was obtained using eq 1, where A_{car} was the area of the peak for the carbinolamide at some time t and A_{ald} was the area of the benzaldehyde peak at the same time. The observed area of the benzaldehyde peak was corrected by R_x to account for differences in the molar extinction coefficients of benzaldehyde and the carbinolamides.[52] (The R_x values used are reported in Table S1 of the Supporting Information.)

$$\ln\left(\frac{A_{car}}{(A_{car} + (R_x)(A_{amide\ or\ ald}))}\right) = k_{obsd}t \quad (1)$$

Shown in the graphical abstract is the pH−rate profile for **2d** (see the pH−rate profiles for the other compounds in the Supporting Information). Three distinct regions are present in the pH−rate profile, and the equation that fits this data is also shown: the acid-dependent reaction, the hydroxide-dependent reaction, and, at higher pH, a hydroxide-independent reaction. Previous studies also reported a region, between the acid- and hydroxide-dependent reactions, where there was no change in rate as the pH of the solution was modified.[32,44,45,53] The reaction, in this region of the pH−rate profile, was said to be reacting via a water-catalyzed reaction. The derivatives of **2** discussed here show only a very small region that might be called the water reaction as compared to previous studies involving derivatives of **1**.[32]

Figures 1 and 2 show the effects of changes in the hydronium ion concentration on the observed rate of carbinolamide breakdown and the effect of buffer concentration on k_{obsd}, respectively, in H_2O at 25 °C and I = 1.0 M (KCl). The second-order rate constants for the acid-dependent reaction (k_H) from the plots in Figure 1 are reported in Table 1. For studies between pH values of 2 and 6, the acid-dependent reaction was buffer-catalyzed with k_{obsd}, at a specific pH value, being determined by extrapolation to zero [buffer] (see Figure 2). Extensive investigations of the second-order

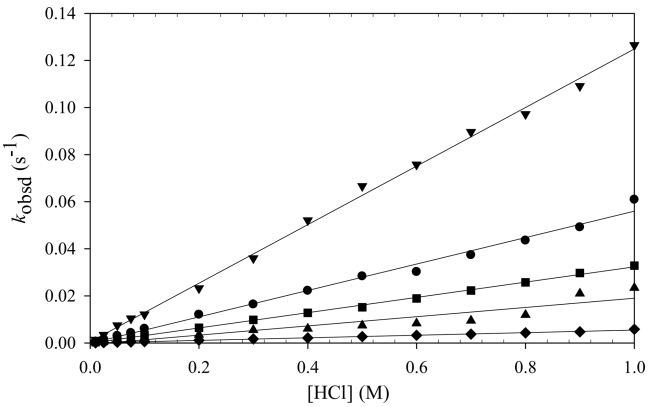


Figure 1. Plot of the effect of [hydronium ion] (M) on the observed rates of reaction (k_{obsd}, s^{-1}) for *N*-(hydroxyphenylmethyl)-4-nitrobenzamide (◆), *N*-(hydroxyphenylmethyl)-4-chlorobenzamide (▲), *N*-(hydroxyphenylmethyl)benzamide (■), *N*-(hydroxyphenylmethyl)-4-methylbenzamide (●), and *N*-(hydroxyphenylmethyl)-4-methoxybenzamide (▼) in H_2O, at 25 °C, I = 1.0 M (KCl).

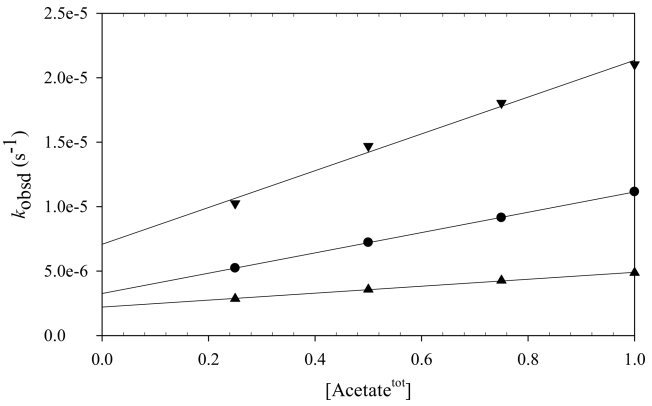


Figure 2. Plot of the effect of acetate buffer (M) of the observed rates of reaction (k_{obsd}, s^{-1}) at pH 4.0 for *N*-(hydroxyphenylmethyl)-4-chlorobenzamide (▲), *N*-(hydroxyphenylmethyl)-4-methylbenzamide (●), and *N*-(hydroxyphenylmethyl)-4-methoxybenzamide (▼) in H_2O, at 25 °C, I = 1.0 M (KCl).

DOI: 10.1021/acs.joc.9b02812
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Table 1. Constants for the Aqueous Reaction of *N*-(Hydroxybenzyl)benzamide and Derivatives and Their pK_a's in Water at 25 °C, I = 1.0 (KCl)

compound	k_H (10^{-2} M^{-1} s^{-1})	k_1' (M^{-1} s^{-1})[a]	k_1 (s^{-1})[b,c]	K_a (10^{-13} M)[b]	pK_a[d]	k_{rel}[e]
2a	0.55 ± 0.02	1.35×10^3	71.4 ± 0.8	1.93 ± 0.05	12.71	3.92
2b	–	7.4×10^2	36.8 ± 0.6	1.97 ± 0.05	12.71	2.02
2c	2.0 ± 0.1	4.0×10^2	28.9 ± 0.6	1.31 ± 0.05	12.88	1.59
2d	3.2 ± 0.1	2.5×10^2	18.2 ± 0.4	1.39 ± 0.05	12.86	1.0
2e	5.6 ± 0.2	1.9×10^2	15.6 ± 0.4	1.14 ± 0.05	12.94	0.86
2f	12.0 ± 0.1	1.6×10^2	13.7 ± 0.4	1.19 ± 0.05	12.92	0.75

[a]Apparent second-order rate constant for the hydroxide-dependent breakdown of the carbinolamides in water calculated from k_1 and K_a using $k_1' = (k_1K_a)/K_w$ and $K_w = 1 \times 10^{-14}$ M^2. [b]Errors obtained from nonlinear least-squares fits of k_{obsd} vs [HO^-] according to eq 2. [c]First-order rate constant for the pH-independent breakdown of the deprotonated carbinolamide. [d]Ionization constant for the hydroxyl group of the carbinolamide. [e]Calculated by dividing k_1 for **2d** into the k_1 value for each amide.

rates of buffer catalysis were not pursued, and at most pH values, the buffer concentrations were kept quite low (0.05–0.1 M) and this, ultimately, limited the utility of the second-order buffer catalysis constants obtained under these experimental conditions.

Shown in Figure 3 is the effect of [HO^-] on k_{obsd} for carbinolamide breakdown into amide and benzaldehyde in

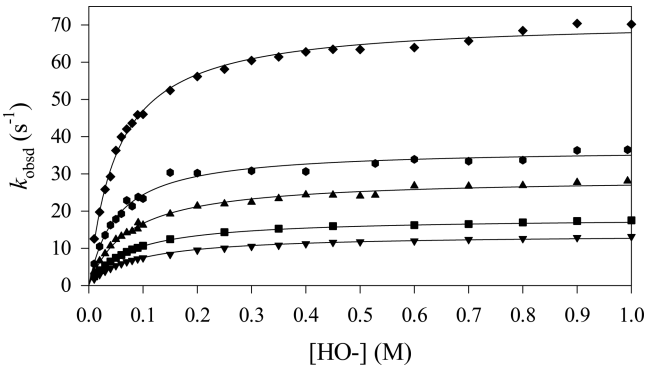

Figure 3. Plot of the effect of [hydroxide] (M) of the observed rates of reaction (k_{obsd}, s^{-1}) for *N*-(hydroxyphenylmethyl)-4-nitrobenzamide (◆), *N*-(hydroxyphenylmethyl)-4-(trifluoromethyl)benzamide (●), *N*-(hydroxyphenylmethyl)-4-chlorobenzamide (▲), *N*-(hydroxyphenylmethyl)-benzamide (■), and *N*-(hydroxyphenylmethyl)-4-methoxybenzamide (▼) in H_2O, at 25 °C, I = 1.0 M (KCl).

H_2O, at 25 °C and I = 1.0 M (KCl). No evidence for buffer catalysis was observed between pH values of 5 and 12, but in most cases, the buffer concentrations were kept low (0.01–0.05 M total buffer). From Figure 3, low [HO^-] yielded a first-order dependence between [HO^-] and k_{obsd}, while at higher [HO^-], the rate of the reaction was independent of the [HO^-]. The dependence of k_{obsd} on [HO^-] can be fit by eq 2 (see Scheme 4), to obtain the limiting rate of reaction (k_1) and the K_a of the hydroxyl group (see Table 1).

$$(k_{obsd})^{HO} = k_1 \frac{K_a[HO^-]}{K_w + K_a[HO^-]} \quad (2)$$

DISCUSSION

While carbinolamides have been known for quite some time,[8,54] the structural diversity of the known compounds is not as broad as might be expected, as the majority of the isolated synthetic compounds result from the reaction of amides with highly electrophilic aldehydes, such as formaldehyde and chloral.[55] The first studies, from our group, with this functionality, were focused on the *N*-(hydroxymethyl)-benzamide derivatives (**1**), as these compounds represented the most straightforward access to the carbinolamide functionality.[7,32−35] The synthesis of carbinolamides using less electrophilic aldehydes remained problematic, although biological systems seem to be quite able to make such compounds.[9−17]

It was shown, by Bundgaard and co-workers,[44] that *N*-(hydroxybenzyl)benzamide could be synthesized by an adaptation of a procedure from Macovski and Backmeyer wherein the morpholine monoacylaminal was synthesized from a 1:1:1 mixture of benzamide, benzaldehyde, and morpholine.[56] The monoacylaminal formed was subsequently hydrolyzed to yield **2d**. Unfortunately, for the purposes of the work described here, the monoacylaminal formation reaction was most successful with benzamide and other benzamide derivatives yielded poor to nonexistent amounts of monoacylaminals for reasons that we did not explore. The development of a solvent-free method to synthesize the monoacylaminals from the morpholine aminal of benzaldehyde and the amide, followed by hydrolysis, provided a route to the compounds discussed herein (see Scheme 5).[49,57]

Initial kinetic studies, by Bundgaard and co-workers, were focused on the aqueous reaction of carbinolamides having a broad variety of structures, with their primary interest directed toward the utility of carbinolamides as pro-drugs.[44−48] As such, the Bundgaard studies focused on pH ranges and at a temperature that were relevant for biological systems.[44−48] Bundgaard et al. did perform studies with *N*-(hydroxybenzyl)-benzamide (**2d**) in the pH range from 2 to 10.[44] The second-order rate constant for the acid-catalyzed reaction (k_H = 0.13 M^{-1} s^{-1}) and the apparent second-order rate constant for the hydroxide-dependent reaction (k_1' = 3.0×10^2 M^{-1} s^{-1} in H_2O, I = 0.5 M and 37 °C) were reported.[44] No substituted derivatives of **2d** were investigated, and kinetic data points leading to the k_H for **2d** were limited.[44]

Acid-Catalyzed Studies. Shown in Figure 1 are the plots of k_{obsd} vs [HCl] for five of the derivatives of **2**. All five compounds show a linear dependence on the acid concentration, and the second-order rate constants for the acid-catalyzed reaction are reported in Table 1. From Figure 1 and Table 1, the methoxy derivative (**2f**) reacts most quickly and the compound bearing the nitro group (**2a**) reacts more slowly than the others studied. This substituent effect suggests that the rate-limiting step of the reaction involves a species with a positive charge or a developing positive charge that would be destabilized by electron-withdrawing groups. The effect of the substituents is better illustrated in Figure 4, which shows the

DOI: 10.1021/acs.joc.9b02812
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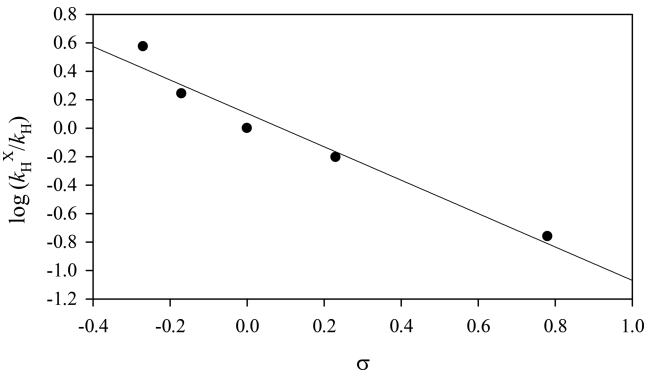

Figure 4. Hammett plot of $\log(k_H^X/k_H^H)$ for the acid-catalyzed reaction of a series of *N*-(hydroxybenzyl)benzamide derivatives in H_2O, at 25 °C, I = 1.0 M (KCl) vs σ.

Hammett plot of the k_H values. The linear correlation, shown in Figure 4, supports the conclusion that all five of the compounds react via a similar mechanism. The plot, shown in Figure 4, has a ρ value of −1.17.

The negative ρ value for the acid-dependent rates is an indication that there is buildup of positive charge on the amidic portion of the carbinolamide in an intermediate or during the rate-determining step of the reaction. (It is unlikely that the positive charge is on the hydroxyl portion of the carbinolamide, as it has been shown and will be shown later, during the discussion of the hydroxide-dependent reaction, that the substituents on the amide portion of the structure have only a minor effect on the pK_a of the hydroxyl group of the carbinolamide.)[7,32] The effect of the substituents on the reactivity of the derivatives of **2** is similar to that observed for the derivatives of **1**.[32] The observed substituent effects support a mechanism of the type shown in Scheme 1; however, the observation of buffer catalysis in the acidic portion of the pH−rate profile indicates that proton transfer must be occurring during the rate-limiting step of the acid-catalyzed reaction (see Figure 2).

Shown in Figure 2 is the effect of [buffer] on the rate of the acid-catalyzed reaction with acetate buffer at a single pH value. The same observation was made with both acetate and chloroacetic acid which were the only two buffers used in the acid region of these studies. The k_{obsd} value for the buffer-independent rate at each pH value was obtained from the *y*-intercept values of the plots shown in Figure 2. For most of the studies performed, total [buffer] ($[B_{tot}]$) was kept quite low (<0.05 M = $[B_{tot}]$), resulting in limited data concerning the second-order rate for buffer catalysis for the compounds discussed here. The important conclusion connected to the observation of buffer catalysis was the reaction must be occurring via a mechanism involving proton transfer during the rate-determining step.

From above, two mechanisms have been proposed based upon the observation of buffer catalysis in the aqueous acid-dependent reaction of carbinolamides (see Schemes 2 and 3).[33] Shown in Scheme 2 is the general-acid catalysis reaction where the rate-determining step involves proton transfer from an acid source as the carbinolamide decomposes into the amide and protonated aldehyde. The atom being protonated during the decomposition step is arbitrary, as it could be either the nitrogen or the oxygen of the amidic species. The rate expression for the reaction shown in Scheme 2 is as shown in eq 3, where $(k_{obsd})^H$ is the observed rate for the acid-dependent reaction.

$$(k_{obsd})^H = k_H[HA] \tag{3}$$

The second proposed mechanism for the acid-catalyzed reaction is shown in Scheme 3. The mechanism involves an initial protonation of the carbonyl oxygen (specific-acid catalysis).[32] The protonated species then undergoes rate-determining general-base-catalyzed decomposition with a base removing the hydroxyl proton during breakdown. The rate expression for the mechanism in Scheme 3 is shown in eq 4 and has the same dependence on [HA], as seen in eq 3. (Equations 3 and 4, where K_a^{HA} is the K_a of the buffer catalyst and $k_d[A^-]$ can be dropped from the denominator of the rate expression, as it would be slow compared to k_{-p}.) The mechanism shown in Scheme 3 resembles the accepted specific-acid-catalyzed mechanism for the breakdown of acetals.[58,59] It is acknowledged that, given the available data, no conclusion concerning which mechanism dominates can be made based upon the results presented here, but we have argued in a previous publication that it is the mechanism shown in Scheme 3 that is the acid-dependent reaction.[33]

From Table 1, the k_H values are similar to that reported by Bundgaard et al. for **2d** with Bundgaard's value being ∼4-fold faster. The difference between the values in Table 1 for k_H of **2d** and that reported by Bundgaard can be rationalized due to differences in the experiment temperatures (37 °C vs 25 °C) and ionic strength (0.5 vs 1.0) at which the studies were performed vs the studies reported herein.

The similarity of the rate expressions for the reactions shown in Schemes 2 and 3 does not allow for a definitive conclusion with respect to the mechanism of the acid-catalyzed reaction. What is clear is that all of the derivatives of **2** react via the same mechanism (see Figure 4), and at a much faster rate than that observed for the derivatives of **1**. Very little work on the acid-catalyzed reaction of carbinolamides has been published; however, the rate constants for the acid-catalyzed reaction of **1** and the 4-chloro substituted derivative of **1** have been reported to be $k_H = 7.3 \times 10^{-6}$ M^{-1} s^{-1} and $k_H = 5.7 \times 10^{-6}$ M^{-1} s^{-1}, respectively.[32,33] These rate constants, for **1** and its derivative, are ∼4000-fold slower than that for the similarly substituted derivatives of **2** (see Table 1). The relative reactivity of **1** vs **2** mirrors the relative electrophilicity of formaldehyde (K_{Hyd} = 2420)[36−38] vs benzaldehyde (K_{Hyd} = ∼0.01),[40,43] as measured by the hydration constant.

$$(k_{obsd})^H = \frac{k_p k_d[H^+][A^-]}{k_{-p} + k_d[A^-]} = \frac{k_p k_d K_a^{HA}[HA]}{k_{-p}} \tag{4}$$

Hydroxide-Dependent Reaction. From the graphical abstract and Figure 3, at lower [hydroxide], there is a linear dependence between k_{obsd} and the $[HO^-]$, but at higher $[HO^-]$, k_{obsd} becomes independent of hydroxide. Such observations are consistent with a specific-base-catalyzed reaction where, at lower $[HO^-]$, the first-order dependence on hydroxide is a result of the shift in equilibrium between **2** and **3** (in Scheme 4). As the K_a value of the hydroxyl group of **2** is approached, with increasing pH, the k_{obsd} dependence on $[HO^-]$ transitions from first-order to zero-order as the equilibrium is fully shifted to **3** and further increases in hydroxide have no effect on the concentration of the reactive species in solution. This observation supports the conclusion

DOI: 10.1021/acs.joc.9b02812
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that the rate-determining step is the decomposition of **3** into benzaldehyde and the benzamidate leaving group.

Further evidence for a mechanism of the type shown in Scheme 3 was provided by the lack of buffer catalysis for the kinetic studies for pH values between 5 and 12. Each of the reactions for pH values between 5 and 12 were performed at, at least, three [buffer], at the same pH, and no evidence for buffer catalysis was observed for any of the buffers that were utilized. This observation indicates that proton transfer does not occur during the rate-determining step of carbinolamide breakdown under conditions when the hydroxide-dependent mechanism dominates. The rate expression for the hydroxide-dependent reaction is shown in eq 2, where K_w is the dissociation constant of water. The observed rate data for the hydroxide-dependent reaction was fit to eq 2, yielding the limiting rate constant (k_1) and the K_a of the hydroxyl group of the carbinolamide (see Table 1).[60]

From Figure 3 and Table 1, the effect of the substituents on the hydroxide-dependent reaction are the opposite of that observed for the acid-catalyzed reaction. The derivatives of **2** bearing electron-withdrawing substituents react more quickly than those having electron-donating substituents. Such an observation would be in accord with the type of mechanism shown in Scheme 4, as electron-withdrawing groups would more effectively stabilize the developing negative charge on the benzamidate leaving group during the rate-determining step. (Benzamide pK_a data is limited, but available data suggests a pK_a range of ∼16−21 for the benzamide derivatives studied herein.[36])

$$(k_{obsd})^{HO} = \frac{k_1 K_a [HO^-]}{K_w} \quad (5)$$

Previous studies of the reaction of **2d**, performed by Bundgaard and co-workers, under aqueous conditions were completed at 37 °C and I = 0.5 M.[44] Due to the limited range of pH over which this study was performed, only the linear portion of the effect of hydroxide on the rate of reaction was investigated. As a result, the authors only reported an apparent second-order rate constant (k_1', see eq 5 where $k_1K_a/K_w = k_1'$) for the effect of hydroxide on the rate of reaction.[44] Reported in Table 1 are the apparent second-order rate for the hydroxide reaction for compounds **2a**−**f**. From Table 1, **2d** has an apparent second-order rate constant of k_1' = 250 M^{-1} s^{-1} at 25 °C, I = 1.0 M (KCl), as compared to k_1' = 300 M^{-1} s^{-1} reported by Bundgaard et al. at 37 °C and I = 0.5 M.[44] Given the difference in the experimental conditions, the two results are similar to one another, showing that the temperature and ionic strength have a smaller effect on the hydroxide-dependent reaction than that observed for the acid-catalyzed reaction.

From eq 5, it is apparent that k_1' incorporates the effects of the substituents on both the K_a of the hydroxyl group and the limiting rate of the breakdown of **3**. There is a rate enhancement of ∼10-fold on moving from the 4-methoxy (**2f**) to the 4-nitro compound (**2a**). The Hammett correlation of the apparent second-order rate constants for the derivatives of **2** is linear (see the Supporting Information) with a ρ value of 0.87. This value is the same as that found for the Hammett plot of the apparent second-order rate constants for the derivative *N*-(hydroxymethyl)benzamide (**1**) (ρ = 0.87) bearing electron-withdrawing groups.[7,35] While there is an approximate 3 orders of magnitude difference between the apparent second-order rates for the derivatives of **1** vs **2**, the effect of the substituents on the leaving group ability of amidate remains the same.[7,35]

The linearity of the Hammett plot of k_1', for the derivatives of **2**, was not unexpected, as all of the derivatives of **1** also reacted by a single mechanism at lower [HO^-]. It was only at higher [HO^-] that the derivatives of **1** bearing electron-donating groups began to exhibit mechanistic variation.[35]

Substituent Effect on K_a. The K_a values for the derivatives of **2** were determined by the nonlinear least-squares fit of eq 2 to the dependence of k_{obsd} upon the [hydroxide]; see Figure 3. The K_a values determined in this manner are listed in Table 1, and these values show a greater dependence upon the nature of the substituent attached to the ring than was observed for the derivatives of **1**, which had a ρ value of 0.07, albeit over a smaller substituent range.[7] However, like the derivatives of **1**, no significant changes in pK_a of the derivatives of **2** were observed. The pK_a of the hydroxyl group of **2d** (pK_a = 12.9) was essentially the same as the pK_a reported for the hydrate of benzaldehyde (pK_a = 12.8).[40] A similar observation between the pK_a of the hydroxyl group of **1** and the pK_a of the hydrate of formaldehyde was noted previously.[7] These two observations would suggest that the inductive effect of the benzamide group in the carbinolamide is similar to that of a hydroxyl group in hydrates of aldehydes.

The Hammett correlation of the K_a values of the derivatives of **2** was linear (see the Supporting Information) and had a ρ value of 0.23. The plot was linear over all of the compounds that were studied, which contrasted with studies of the derivatives of **1** which underwent a substituent-dependent mechanism change for the hydroxide-dependent reaction which yielded odd variations in the K_a when k_{obsd} was incorrectly used to fit the [HO^-] using eq 2.[7,35] For the derivatives of **2**, the substituent-dependent change on the pK_a of the hydroxyl group of the carbinolamide was larger than that found for **1** (ρ = 0.07). The change in K_a seen for the derivatives of **2** was more in line with the expected effect of the addition of methylene units between the carbon bearing the ionizable group and the aromatic ring.[37,61]

While the changes in the K_a of the hydroxyl group are more substantive for derivatives of **2** as compared to those observed for **1**, there is no clear rationale for this observation, as the only difference is the presence of an aromatic ring in the aldehyde portion of the carbinolamide structure. It was noted in the previous studies of **1** that substituents in the ortho position of the aromatic ring also did not have any apparent effect on the K_a of the hydroxyl group, which was in contrast to the effect of ortho substituents on the K_a of benzoic acids which tend to be quite significant.[7] This result further illustrated the oddity of the invariance of the K_a values for the derivatives of **1**.[7] The K_a values shown in Table 1 for the derivatives of **2** show an effect of the magnitude expected based upon other studies studying the effect of remote substituents on K_a in other molecular structures.[37,61]

Limiting Rate (k_1). It has been proposed that the rate-limiting step for the breakdown of carbinolamides under the hydroxide-dependent mechanism is the departure of an amidate leaving group and the formation of the aldehyde product (see Scheme 4). This proposal was based upon a lack of buffer catalysis in the region of the pH−rate profile where the hydroxide-dependent reaction dominated and a change from a first-order to zero-order dependence on the [hydroxide] in this same region. The reaction can be thought of as an E1cb-

DOI: 10.1021/acs.joc.9b02812
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like reaction and represents a unique form of reactivity wherein an amide (amidate) acts as a leaving group. The properties of amides acting as leaving groups is not something that has received a great deal of attention.[7,26,29]

The k_1 values or limiting rates, shown in Table 1, follow a similar trend to that observed for the apparent second order rates (k_1'). That is, the amidic functionality bearing electron-withdrawing groups undergoes elimination more quickly than those bearing electron donating groups. This result is in accord with the previous studies involving derivatives of **1** and was attributed to electron-withdrawing groups providing better stabilization of the developing negative charge of the amidate as it departs.[7,32,35] Figure 5 shows the Hammett plot of limiting

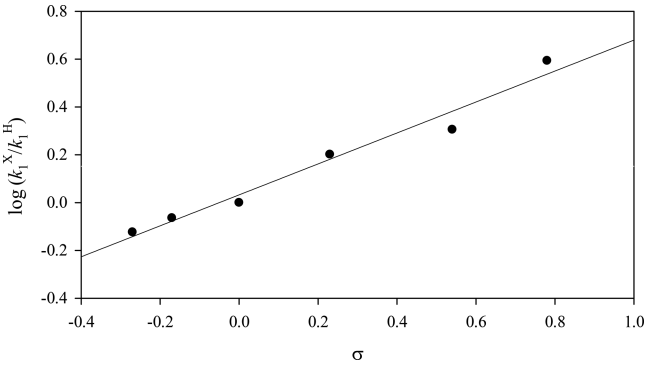

Figure 5. Hammett plot of $\log(k_1^X/k_1^H)$ for the hydroxide-dependent reaction of a series of *N*-(hydroxybenzyl)benzamide derivatives in H_2O, at 25 °C, I = 1.0 M (KCl) vs σ.

rate constants. The plot is linear, indicating a single mechanism over the range of compounds reported here, and the ρ value is 0.65. The ρ value found for the derivatives of **1** had a ρ value of 0.67.[7]

The linearity of the plot in Figure 5 provides evidence that the mechanism is the same over the six compounds studied which is in contrast to studies involving derivatives of **1**.[7,26,29] It has been shown that all derivatives of **1** react via a single mechanism at moderate [HO^-] (Hammett plot of the apparent second-order rate constants (k_1', see above)), but at higher concentrations of [HO^-], those derivatives of **1** bearing electron-donating groups transitioned to a different mechanism.[7,26,29] Product analysis of the derivatives of **1** bearing electron-donating groups showed large amounts of amide hydrolyzed product both at 50% reaction and after reaction completion, relative to those derivatives of **1** bearing electron-withdrawing groups which only showed the presence of amide after reaction completion.[35] A second observation, for derivatives of **1** bearing electron-donating groups, was that the limiting rate (k_1) became invariant with addition of strong electron-donating groups.[35] These observations were rationalized as the hydrolytic mechanism becoming competitive with the normal carbinolamide reaction due to the poor nucleofugality of the amidate bearing electron-donating groups.[35] The linearity of the plot shown in Figure 5 supports the conclusion that all of the derivatives of **2** studied react by the same mechanism and the hydrolysis route, observed for those derivatives of **1** bearing electron-donating groups, does not become energetically competitive as compared to the accepted specific-base-catalyzed reaction for the derivatives of **2** studied. Presumably, this observation is the result of the greater electrophilicity of formaldehyde vs benzaldehyde;[36−43] thus, benzaldehyde provides better electron assistance to the departure of the benzamidate leaving group. Implicit in this statement is the idea that the energetics of the amidic hydrolysis pathway for carbinolamide breakdown would not change too dramatically between **1** and **2**.

In addition, the similarity of the two ρ values found for the derivatives of **1** (ρ = 0.67) and **2** (ρ = 0.65) indicates that the substituents have the same relative effect on the rate-limiting breakdown of the conjugate base of the carbinolamide. This result provides further evidence that the substituent effect is solely on the departure of the leaving group and that the extent of charge stabilization on the benzamidate leaving group, in the transition state, must be similar for **1** and **2**. This result may seem to be curious given the difference in the relative limiting rates of reaction for the derivatives of **1** vs **2**. When the limiting rates for **2a**, **2b**, and **2d** are compared to their related *N*-(hydroxymethyl)benzamide derivative, the derivatives of **2** react, on average, 430 times faster than their related derivatives of **1**. The effect of the aromatic ring on the carbinol portion of **2** must provide significant stabilization/assistance during the departure of the benzamidate, leading to a rate enhancement vs derivatives of **1**.

CONCLUSIONS

Presented here are the results of studies investigating the mechanism of the aqueous reaction of amide substituted derivatives of *N*-(hydroxybenzyl)benzamide as a function of the pH of the solution. The *N*-(hydroxybenzyl)benzamide derivatives (**2**) show much greater reactivity than their *N*-(hydroxymethyl)benzamide derivative (**1**) counterparts. The degree of the reactivity difference was dependent on the pH-dependent mechanism, but the derivatives of **2** were 400−4000 times more reactive than the derivatives of **1**. These studies were undertaken to broaden the understanding of the aqueous reactivity of carbinolamides as a function of the structure of the carbinolamide itself. Very little information is available in the literature concerning the reactivity of carbinolamides derived from less electrophilic aldehyde sources,[38−42] and the data presented herein represents the first complete pH−rate profile study of compounds of this type. The studies were performed between pH values of 0 and 14 with buffers used to maintain pH between 2 and 12. The pH−rate profile for **2** can be seen in the graphical abstract, and four distinct regions are evident. There was an acid-catalyzed reaction, hydroxide-dependent reaction, hydroxide-independent reaction, and water reaction (see the equation in the graphical abstract). As with the derivatives of **1**, the hydroxide-dependent reaction dominated the largest portion of the pH−rate profile.

The acid-catalyzed reaction was observed between pH values of 0 and ∼4 with electron-donating groups increasing the rate relative to electron-withdrawing groups (ρ value = −1.17). The reaction itself was buffer-catalyzed, and two kinetically equivalent mechanisms can be proposed. Both a general-acid-catalyzed reaction (Scheme 2) and a specific-acid followed by general-base-catalyzed reaction (Scheme 3) can be postulated. The results presented here cannot distinguish which mechanism was energetically more favorable; however, all of the compounds studied react via a single mechanism (see Figure 4) and the derivatives of **2** mirror the observations reported for **1**, while being much more reactive than similar derivatives of **1**. For the acid-catalyzed reaction, the data supports a common mechanism for both the derivatives of **1** and **2**.

DOI: 10.1021/acs.joc.9b02812
J. Org. Chem. XXXX, XXX, XXX−XXX

For the hydroxide-dependent reaction, the data reported supports a specific-base-catalyzed process for all of the derivatives of **2** studied ($(E1cb)_R$-like reaction). Once again, the derivatives of **2** react much faster than their related derivatives of **1** but show similar substituent effects to the derivatives of **1** bearing electron-withdrawing groups. The change in reactivity can, in part, be explained by a minor difference in the pK_a of the hydroxyl group of **2** vs **1**. The derivatives of **1** had pK_a values of ∼13.1, whereas those compounds discussed herein had pK_a values of ∼12.8. This difference in pK_a would lead to a larger concentration of the conjugate base of **2** vs **1** in solution at a specific pH and resulting in a relative rate increase. The remainder of the difference in rates between **1** vs **2** was due to differences in the limiting rate (k_1) between the two types of carbinolamides.

The limiting rates (k_1) for derivatives of **2** were much larger than similarly substituted derivatives of **1**. Presumably, this pattern of reactivity was as a result of the greater electrophilicity of formaldehyde vs benzaldehyde, as the leaving groups in both studies are the same. Further, the similarity of the ρ values between **1** and **2** indicates that the transition state/charge development must be similar between the two sets of compounds, with the benzamidate leaving group having similar charge development in the transition state for both **1** and **2**. The most significant divergence between the derivatives of **1** and **2** was that all derivatives of **2** react via the same mechanism under all conditions where the hydroxide-dependent reaction dominates.

It becomes more apparent with each group of carbinolamides studied that the acid-catalyzed reaction occurs with rate-limiting proton transfer. The problem is which of the two mechanisms (general-acid vs specific-acid followed by general-base) is the actual mechanism of the acid-dependent reaction? Additionally, was it the stability of **3** for the derivatives of **1** that led to the competitive amide hydrolysis reaction? At what point does the electrophilicity of the aldehyde involved in the formation of the carbinolamide lead to this amide hydrolysis mechanism becoming energetically competitive? Lastly, by which mechanism does the PAL enzyme catalyze the breakdown of the carbinolamide? The acid-catalyzed reaction involves rate-limiting proton transfer but also requires relatively acidic conditions with only moderate returns in reactivity. The hydroxide-dependent reaction yields much larger catalysis potential (see graphical abstract), but how would the enzyme affect the reactivity of the conjugate base of the carbinolamide (**3** in Scheme 4) to achieve catalysis?

EXPERIMENTAL SECTION

All chemicals were reagent grade from commercial sources and were used without further purification unless otherwise noted. HCl, potassium acetate, potassium hydrogen phosphate, potassium carbonate, potassium chloride, potassium pyrophosphate, chloroacetate acid, and potassium hydroxide were obtained from commercial sources. The water used in the kinetic and HPLC studies was house DI-water that was then passed through a water purification system. Standard potassium hydroxide and HCl solutions were obtained by dilution of concentrated solutions with the final hydroxide or HCl concentration obtained by titration to the phenolphthalein end point using standard HCl and hydroxide solutions, respectively.

All melting points are uncorrected. The NMR spectra were obtained in deuterated DMSO or $CDCl_3$ utilizing a 400 or 500 MHz instrument.

Synthesis. All of the derivatives of *N*-(hydroxybenzyl)benzamide were synthesized using the general pathway shown in Scheme 5.

Benzamides. Benzamide, 4-(trifluoromethyl)benzamide, and 4-chlorobenzamide were obtained from commercial sources and used without further purification. In general, the other benzamide derivatives were synthesized from the reaction of their benzoic acid precursors with PCl_5 to yield the acyl halide intermediate which was subsequently reacted with concentrated ammonium hydroxide, to yield the crude amide product.[62] Crude amide products were then recrystallized and melting points determined: 4-methoxybenzamide (methanol, mp = 166−167 °C, lit. mp = 164−167 °C),[63] 4-methylbenzamide (water, mp = 160−162 °C, lit. mp = 162−163 °C),[64] 4-nitrobenzamide (water, mp = 207−209 °C, lit. mp = 206 °C).[65]

Aminal Synthesis. Dimorpholinophenylmethane (**4**) was synthesized utilizing a standard method[66] with the resulting product requiring no further purification and with mp = 100−102 °C (lit. mp = 105−106 °C).[57]

Monoacylaminal Synthesis. The monoacylaminal derivatives were synthesized using a solvent-free method described in the literature.[49] The general method involved mixing equimolar amounts of the benzamide derivative (∼0.01 mol) and **4** in a 50 mL Erlenmeyer flask. The flask was heated using a Bunsen burner until the two solids melted, yielding a viscous liquid. Heating was continued for 5−7 min, with constant swirling of the flask. After heating was discontinued, the flask was allowed to cool until warm to the touch, whereupon diethyl ether was added to promote crystallization (∼25 mL). The monoacylaminal was isolated by vacuum filtration with the crystals being washed with ice-cold 3:1 diethyl ether and 95% ethanol to remove residual amide.

*N-(Morpholinobenzyl)-4-nitrobenzamide (**5a**).* **5a** with a melting point of 161−164 °C, lit. mp = 161−164 °C.[49]

*N-(Morpholinobenzyl)-4-(trifluoromethyl)benzamide (**5b**).* **5b** was obtained by reacting 1.00 g (5.29×10^{-3} mol) of 4-(trifluoromethyl)benzamide with 1.39 g (5.29×10^{-3} mol) of **4** as described above. The crude product was isolated from ether by vacuum filtration and recrystallized from 1:1 H_2O:95% ethanol. The product was a white powder weighing 0.2967 g (7.88×10^{-4} mol, 15% yield) with a melting point of 187−189 °C. ^1H NMR 500 MHz (DMSO-d_6) δ 9.13 (d, 2H); 8.14 (d, 2H); 7.88 (d, 2H); 7.54 (d, 2H); 7.40 (t, 2H); 7.32 (t, 1H); 5.93 (1H, d); 3.67−3.56 (m, 4H); 2.55−2.49 (m, 4H). $^{13}C\{1H\}$ NMR 125 MHz (DMSO-d_6): δ 166.6, 139.3, 138.6, 131.7 (q, $^2J_{CF}$ = 32 Hz, C−CF_3), 129.1, 128.7, 128.1, 127.9, 125.7, 124.4 (q, $^1J_{CF}$ = 273 Hz, CF_3), 71.9, 66.7, 49.3. HRMS (ESI-TOF) *m*/*z*: Calcd for $C_{19}H_{19}F_3N_2O_2H$ $[M + H]^+$ 365.1471; Found 365.1501.

*N-(Morpholinobenzyl)-4-chlorobenzamide (**5c**).* **5c** with a melting point of 140−143 °C, lit. mp = 140−143 °C.[49]

*N-(Morpholinobenzyl)benzamide (**5d**).* **5d** with a melting point of 160−162 °C, lit. mp = 166−167 °C.[57]

*N-(Morpholinobenzyl)-4-methylbenzamide (**5e**).* **5e** with a melting point of 134−136 °C, lit. mp = 134−136 °C.[49]

*N-(Morpholinobenzyl)-4-methoxybenzamide (**5f**).* **5f** was obtained by reacting 1.012 g (6.70×10^{-3} mol) of 4-methoxybenzamide with 1.74 g (6.62×10^{-3} mol) of **4** as described above. The crude product was isolated from ether by vacuum filtration and recrystallized from 1:1 H_2O:95% ethanol. The product was a white powder weighing 1.273 g (4.0×10^{-3} mol, 60% yield) with a melting point of 158−161 °C. ^1H NMR 400 MHz ($CDCl_3$) δ 7.8 (d, 2H); 7.55 (d, 2H); 7.25−7.45 (m, 3H); 6.95 (d, 2H); 6.4−6.5 (bd, 1H); 5.9 (1H, d); 3.9 (s, 3H); 3.7−3.8 (m, 4H); 3.6−3.7 (m, 2H); 3.5−3.6 (m, 2H). $^{13}C\{1H\}$ NMR 125 MHz (DMSO-d_6): δ 166.9, 162.2, 139.8, 130.1, 129.8, 128.6, 127.9, 126.8, 113.9, 71.6, 66.8, 55.9, 49.4. HRMS (ESI-TOF) *m*/*z*: Calcd for $C_{19}H_{22}N_2O_3H$ $[M + H]^+$ 327.1703; Found 327.1700.

Carbinolamide Synthesis. All *N*-(hydroxybenzyl)benzamide derivatives were synthesized using a similar general method based upon a previously published method.[44] Approximately 1 g of the monoacylaminal was dissolved in 30 mL of a 1:2 mixture of DI-water and reagent grade acetone. The reaction solution was stirred and gently warmed (∼30 °C) for 0.5−1.5 h. The "pH" of the solution, monitored using a pH meter, was maintained at a pH reading between

DOI: 10.1021/acs.joc.9b02812
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4 and 4.5 via the addition of small amounts of 0.10 M HCl or 1.00 M HCl, depending upon the observed rate of change in the "pH" of the reaction solution. As the reaction was nearing completion, changes in the observed "pH" would slow and precipitate would begin to collect in the reaction vessel. When the reaction was complete, the crystals were collected by vacuum filtration and further purified by washing with ice cold 95% ethanol.

*N-(Hydroxybenzyl)-4-nitrobenzamide (**2a**).* **2a** was obtained by reacting 0.830 g (2.43×10^{-3} mol) of **5a** in ~30 mL of a 1:2 mix of DI-water and reagent grade acetone. The pH was monitored, and the pH was maintained between 4 and 4.5 by the addition of 0.1 M HCl or 1.0 M HCl. The product precipitated out of solution as the reaction proceeded. After no further change in pH was observed, the reaction solution was cooled, and the product was collected by vacuum filtration. The product was washed with ice-cold 95% ethanol and dried in a vacuum desiccator. The product was a pale-yellow powder that weighed 0.278 g (1.02×10^{-3} mol, 42% yield) with a melting point of 106−109 °C. ^{1}H NMR 500 MHz (DMSO-d_6): δ 9.44 (d, 1H), 8.23 (d, 2H), 8.07 (d, 2H), 7.44 (d, 2H), 7.31 (t, 2H), 7.23 (t, 1H), 6.49−6.46 (m, 2H). ^{13}C{1H} NMR 100 MHz (DMSO-d_6): δ 164.7, 149.6, 142.4, 140.4, 129.6, 128.5, 128.1, 126.6, 123.9, 74.5. HRMS (ESI-TOF) m/z: Calcd for $C_{14}H_{12}N_2O_4H$ $[M + H]^+$ 273.0869; Found 273.0865.

*N-(Hydroxybenzyl)-4-(trifluoromethyl)benzamide (**2b**).* **2b** was obtained by reacting 0.1835 g (5.04×10^{-4} mol) of **5b** in ~50 mL of a 1:1 mix of DI-water and reagent grade acetone. The pH was monitored, and the pH was maintained between 4 and 4.5 by the addition of 0.1 M HCl. The product precipitated out of solution as the reaction proceeded. After no further change in pH was observed, the reaction solution was cooled, and the product was collected by vacuum filtration. The product was washed with ice-cold 95% ethanol and dried in a vacuum desiccator. The product was a light-yellow powder that weighed 0.1103 g (3.74×10^{-4} mol, 74% yield) with a melting point of 127−128 °C. ^{1}H NMR 500 MHz (DMSO-d_6) δ 9.40 (d, 1H), 8.12 (2H, d), 7.85 (2H, d), 7.51 (2H. d), 7.38 (2H, t), 7.31 (1H, t), 6.56 (1H, dd), 6.52 (1H, d). ^{13}C{1H} NMR 125 MHz (DMSO-d_6): δ 165.2, 142.6, 138.5, 131.7 (q, $^2J_{CF}$ = 32 Hz, C−CF_3), 129.0, 128.5, 128.0, 126.6, 125.7, 124.4 (q, $^1J_{CF}$ = 273 Hz, CF_3), 74.4. HRMS (ESI-TOF) m/z: Calcd for $C_{15}H_{12}F_3NO_2H$ $[M + H]^+$ 296.0893; Found 296.0885.

*N-(Hydroxybenzyl)-4-chlorobenzamide (**2c**).* **2c** was obtained by reacting 0.800 g (2.42×10^{-3} mol) of **5c** in ~30 mL of a 1:2 mix of DI-water and reagent grade acetone. The pH was monitored, and the pH was maintained between 4 and 4.5 by the addition of 0.1 M HCl or 1.0 M HCl. The product precipitated out of solution as the reaction proceeded. After no further change in pH was observed, the reaction solution was cooled, and the product was collected by vacuum filtration. The product was washed with ice-cold 95% ethanol and dried in a vacuum desiccator. The product was a white powder that weighed 0.360 g (1.37×10^{-3} mol, 57% yield) with a melting point of 110−112 °C. ^{1}H NMR 500 MHz (DMSO-d_6): δ 9.23 (d, 1H), 7.96 (d, 2H), 7.54 (d, 2H), 7.50 (d, 2H), 7.38 (t, 2H), 7.30 (t, 1H), 6.54 (dd, 1H), 6.46 (d, 1H). ^{13}C{1H} NMR 125 MHz (DMSO-d_6): δ 165.2, 142.7, 136.7, 133.5, 130.0, 128.7, 128.4, 128.0, 126.6, 74.3. HRMS (ESI-TOF) m/z: Calcd for $C_{14}H_{12}ClNO_2H$ $[M + H]^+$ 262.0629; Found 262.0625.

*N-(Hydroxybenzyl)benzamide (**2d**).* **2d** was obtained in a 75.7% yield with a melting point of 112−114 °C (lit. mp = 114−115 °C).[44] ^{1}H NMR 400 MHz (DMSO-d_6): δ 9.14 (d, 1H), 7.92 (d, 2H), 7.41−7.58 (m, 5H), 7.37 (t, 2H), 7.28 (t, 1H), 6.57 (m, 1H), 6.42 (d, 1H). ^{13}C{1H} NMR 100 MHz (DMSO-d_6): δ 166.5, 143.05, 134.9, 132.0, 128.9, 128.7, 128.3, 128.1, 126.8, 74.5.

*N-(Hydroxybenzyl)-4-methylbenzamide (**2e**).* **2e** was obtained in 51.1% yield with a melting point of 102−105 °C (lit. mp = 105 °C).[67] ^{1}H NMR 400 MHz (DMSO-d_6): δ 9.05 (d, 1H), 7.84 (d, 2H), 7.49 (d, 2H), 7.40 (t, 1H), 7.38 (t, 2H), 7.25 (d, 2H), 6.51−6.58 (m, 1H), 6.42 (d, 1H), 2.35 (s, 3H). ^{13}C{1H} NMR 100 MHz (DMSO-d_6): δ 165.6, 142.4, 141.2, 131.5, 128.8, 128.7, 127.9, 127.6, 126.1, 73.7, 20.9.

*N-(Hydroxybenzyl)-4-methoxybenzamide (**2f**).* **2f** was obtained by reacting 0.704 g (2.17×10^{-3} mol) of **5f** in 30 mL of a 1:2 mix of DI-water and reagent grade acetone. The pH was monitored, and the pH was maintained between 4 and 4.5 by the addition of 0.1 M HCl or 1.0 M HCl. The product precipitated out of solution as the reaction proceeded. After no further change in pH was observed, the reaction solution was cooled, and the product was collected by vacuum filtration. The product was washed with ice-cold 95% ethanol and dried in a vacuum desiccator. The product was a white powder that weighed 0.189 g (7.35×10^{-4} mol, 33% yield) with a melting point of 183−186 °C. ^{1}H NMR 500 MHz (DMSO-d_6): δ 8.87 (d, 1H), 7.85 (d, 2H), 7.40 (d, 2H), 7.27 (t, 2H), 7.20 (t, 1H), 6.89 (d, 2H), 6.45 (dd, 1H), 6.27 (d, 1H), 3.72 (s, 3H). ^{13}C{1H} NMR 125 MHz (DMSO-d_6): δ 165.7, 162.2, 143.0, 130.0, 128.4, 127.8, 126.9, 126.6, 113.9, 74.2, 55.8. HRMS (ESI-TOF) m/z: Calcd for $C_{15}H_{15}NO_3H$ $[M + H]^+$ 258.1124; Found 258.1120.

Kinetics. The rate constants for the aqueous reaction were determined as a function of pH. Since the rates of the aqueous reaction varied by several orders of magnitude over the entire pH−rate profile under examination (see graphical abstract), several techniques were required to follow the breakdown of the carbinolamides studied.

UV−vis Spectroscopy. The kinetic studies observed between pH ~6−9 and 0−4 were followed using a UV−vis spectrophotometer with a temperature-controlled sample transport tray maintained at 25 °C. Experiments were initiated using ~2−3 μL of a 0.1 M stock solution of the carbinolamides dissolved in DMSO, into 3 mL of a thermally equilibrated reaction solution in a quartz cuvette, to yield a final substrate concentration of $\sim 6.67 \times 10^{-5}$ to 1.00×10^{-4} M. The compounds studied were monitored through the change in absorbance at 250 nm as a function of time with k_{obsd} determined using the software supplied with the instrument. For those experiments where buffers were used to maintain the pH of reaction solution, the observed rate constant was determined at, at least, three different buffer concentrations, at the same pH. The observed rate, under buffered conditions at a particular pH value, was determined by the linear extrapolation back to zero [buffer]. The pH values of the kinetic solutions were measured after the reaction was completed via standardized combination glass electrode attached to a pH meter. The reported k_{obsd} at each pH was the average of, at least, three trials at the specific pH value.

The hydroxide concentration was calculated using eq 6 with an apparent activity coefficient for hydroxide of γ^{HO-} = 0.79,[68] determined from the measured pH of known [HO−] in water at I = 1.0 M (KCl) at 25 °C.

$$[HO^-] = \frac{10^{(pH-K_w)}}{\gamma^{HO-}} \quad (6)$$

HPLC Kinetic Studies. The kinetic experiments for pH values between 4 and 6 (pH 2−5 for **2a**) were too slow to be followed conveniently with the UV−vis spectrophotometer. For those experiments, the reaction was followed by means of an HPLC instrument. A general HPLC kinetic experiment commenced with the ~3−4 μL injection of a stock solution of the *N*-(hydroxybenzyl)-benzamide derivative in DMSO (0.1 M) into 4 mL of the reaction solution (with varying buffer concentration) to yield a substrate concentration of $\sim 6.7 \times 10^{-5}$ M. Prior to substrate addition and subsequent to addition, samples were thermally equilibrated throughout the reaction period in an autosampler, maintained at 25 °C. The HPLC utilized had dual pumps and sphotodiode array detector, all remotely controlled by computer. The column was a C-18 reverse phase column with a guard column containing the same material. Reaction progress was monitored by injection of 100 μL volumes of the reaction solution into the instrument at timed intervals. Reaction progress was followed by the observation of the disappearance of the carbinolamide (A_{car}) and the concurrent appearance of the amide (A_{amide}) or aldehyde (A_{ald}), depending on the substrate, as a function of time (s) (see eq 1). The pH of the reaction solutions was determined prior to the initiation of the

DOI: 10.1021/acs.joc.9b02812
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reaction and upon completion of the reaction. No significant changes in pH (>0.05) were ever observed.

The observed rates of the reaction utilizing the HPLC were calculated using eq 1. The areas observed for the amide or aldehyde were statistically corrected for differences in the molar absorptivities between the carbinolamide and the amide or aldehyde product. The correction factor (R_x) was determined by following the reaction by HPLC for ∼2−5 half-lives and determining the differences in the total area changes between the carbinolamide and the amide or aldehyde (R_x values shown in Table S1 of the Supporting Information). The correction factor was determined at, at least, two other pH values, and good agreement between the values was found in all cases.

Stopped-Flow Kinetics. Studies were performed using a stopped-flow spectrophotometer for reactions that were complete in less than 1 min. For all kinetic experiments, the solutions were equilibrated at 25 °C for at least 10 min prior to the initiation of any experiment. Each experiment consisted of injection of a 0.1 M solution of the carbinolamide under study in DMSO into an aqueous solution. The stock solution was injected into the reaction solution (water or 1 M KCl solution) to yield a final concentration of approximately 1×10^{-4} M carbinolamide. All compounds studied were monitored at an absorbance of 250 nm. The observed rate constants were calculated using instrument supplied software, and the k_{obsd} values reported are the average of at least five kinetic experiments.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b02812.

pH−rate profiles and hydroxide plots for all compounds studied and the observed rate constants that were used to determine k_{obsd} at specific pH values (PDF)

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■ ACKNOWLEDGMENTS

This work was supported by the Department of Chemistry and Illinois State University.

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DOI: 10.1021/acs.joc.9b02812
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