2951, 2871, 1465, 1380, 970, 895 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.4 (d, 3 H); 1.9–2.3 (m, 2 H); 3.0–3.4 (m, 3 H). MS (m/e): 120 (M^+), 88, 56.

General Procedure for the Preparation of Cyclic Disulfides. Synthesis of 3,5-Dimethyl-1,2-dithiolane (8).[7,9] Reaction of 1 (1.936 g, 4 mmol) in DMF (5 mL) at 28 °C for 6 h yielded the product which after chromatographic purification using 5% ether/petroleum ether (40–60 °C) as eluent gave a yellow oil. IR (thin film): 2967, 2870, 1466, 1380, 1000–960, 890 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.12–1.22 (d, 6 H); 1.25–1.47 (m, 2 H); 3.06–3.47 (m, 2 H). MS (m/e): 134 (M^+), 90.

4,4-Dimethyl-1,2-dithiolane (11).[9] IR (thin film): 2950, 2870, 1385, 1365, 970, 895 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.18 (s, 6 H); 2.78 (s, 4 H). MS (m/e): 134 (M^+), 119, 70.

1,2-Dithiane (15).[8,11] MP: 28–30 °C (lit.[11] mp 32–33 °C). IR ($CHCl_3$): 2910, 1450, 1280, 745 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.95 (s, 4 H); 2.8 (s, 4 H). MS (m/e): 120 (M^+), 88.

1,2-Dithiepane (17).[11] Bp: 55–60 °C (4 mm) (lit.[11] bp 41 °C (2 mm)). IR ($CHCl_3$): 2910, 1450, 1280, 770 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.73–2.06 (m, 6 H); 2.8 (t, 4 H). MS (m/e): 134 (M^+), 102, 70.

1,2-Dithiacyclooctane (19).[11] BP: 61–63 °C (2 mm) (lit.[11] bp 65.5 °C (2 mm)). IR ($CHCl_3$): 2910, 1450, 770 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.53–1.88 (m, 8 H); 2.56 (t, 4 H). MS (m/e): 148 (M^+), 147, 115, 83.

Compound 21. IR (thin film): 2955, 2920, 2875, 2854, 970, 890 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.18 (s, 4 H); 3.53 (s, 4 H). Anal. Calcd for $C_5H_8Br_2S_2$: C, 20.55; H, 2.74. Found: C, 20.61; H, 2.85.

Compound 22.[13,14] MP: 69–70 °C (lit.[14] mp 70 °C). IR ($CHCl_3$): 2955, 2875, 960, 880 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.18 (s, 8 H). MS (m/e): 196 (M^+), 164, 132, 117, 99, 85.

1,2-Dithianorbornene (24). IR ($CHCl_3$): 3010, 1660 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 1 H); 2.81 (s, 1 H); 4.17–4.3 (br s, 2 H); 5.68 (s, 2 H). MS (m/e): 130 (M^+).

4-Methyl-3,6-dihydro-1,2-dithiin (26).[17a] IR ($CHCl_3$): 3010, 2970, 1600 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.72 (s, 3 H); 3.10–3.14 (m, 4 H); 5.06–5.31 (t, 1 H). MS (m/e): 132 (M^+).

Compound 28.[20] Mp: 78–79 °C (lit.[20] mp 80 °C). IR (KBr): 3060, 2960, 1600 cm^{-1}. ^{1}H NMR (CCl_4): δ 4.03 (s, 4 H); 7.08 (br s, 4 H). MS (m/e): 168 (M^+), 136, 104.

Reaction of Ditosylate 12 with 1. Treatment of 1 (0.242 g, 0.5 mmol) in DMF (10 mL) with compound 12 (0.233 g, 0.5 mmol) in DMF (2 mL) at 28 °C for 12 h gave the crude product which on chromatographic purification using 15% ether/petroleum ether (40–60 °C) as eluent gave the dithiolane 13 (0.051 g, 54%) as a pale yellow oil. IR (thin film): 3080, 1640, 1500, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.04–1.30 (m, 8 H); 1.68–1.96 (m, 2 H); 2.72–2.88 (m, 2 H); 3.0–3.36 (m, 1 H); 4.32–4.64 (m, 2 H); 5.0–5.44 (m, 1 H). MS (m/e): 188 (M^+), 124. Anal. Calcd for $C_9H_{16}S_2$: C, 57.45; H, 8.50. Found: C, 57.81; H, 8.24.

Synthesis of (±)-α-Lipoic Acid (35). To a solution of 1 (0.484 g, 1 mmol) in DMF (10 mL) was added dropwise a solution of the dibromo acid 34 (0.302, 1 mmol) in DMF at 50 °C for 4 h. After the usual workup, the crude product after chromatographic purification on silica gel (25% ethyl acetate–petroleum ether, 60–80 °C) gave α-lipoic acid (35)[21] (0.132 g, 65%) as a solid. Mp: 45–47 °C (lit.[21] m.p. 46–48.5 °C). IR ($CHCl_3$): 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.60 (br s, 8 H); 2.13–2.37 (m, 2 H) 3.08 (t, 2 H); 3.50 (m, 1 H); 10.06 (s, 1 H). MS (m/e): 206 (M^+).

Synthesis of Asparagusic Acid (37). A solution of 1 (0.968 g, 2 mmol) in DMF (10 mL) was allowed to react with a solution of dibromo acid 36[25] (0.492 g, 2 mmol) in DMF (10 mL) at 28 °C for 5 h. It was worked up as described earlier to yield asparagusic acid (37)[14,22] (0.182 g, 77%), after chromatographic purification on silica gel (20% ethyl acetate–petroleum ether 60–80 °C), mp 74–76 °C (lit.[14] mp 75.5–76.5 °C). IR ($CHCl_3$): 3500, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.95–3.08 (m, 1 H); 3.22–3.29 (d, 4 H); 10.43 (s, 1 H). MS (m/e): 150 (M^+).

Acknowledgment. We thank the Department of Science and Technology, New Delhi, for financial support of this work.

Registry No. 1, 56181-21-6; 2, 109-64-8; 3, 33087-69-3; 4, 107-80-2; 5, 138152-58-6; 6, 55487-20-2; 7, 19398-53-9; 8, 55487-21-3; 9, 35196-66-8; 10, 5434-27-5; 11, 58375-01-2; 12, 115948-55-5; 13, 138152-59-7; 14, 110-52-1; 15, 505-20-4; 16, 111-24-0; 17, 6008-51-1; 18, 629-03-8; 19, 6008-69-1; 20, 3229-00-3; 21, 138152-60-0; 22, 176-02-3; 23, 17040-70-9; 24, 115018-95-6; 25, 138152-61-1; 26, 18655-86-2; 27, 91-13-4; 28, 3886-39-3; 30, 59697-70-0; 32, 138283-89-3; 33, 138152-62-2; 34, 138152-63-3; 35, 1077-28-7; 36, 41459-42-1; 37, 2224-02-4; $CH_3COCH_2CO_2Et$, 141-97-9; $H_2C{=}CH(CH_2)_3Br$, 1119-51-3; tungstic acid, 7783-03-1; piperidine, 110-89-4; H_2S, 7783-06-4.

Supplementary Material Available: Experimental details and spectral data for compounds 3, 5, 12, and 30–34 (5 pages). Ordering information is given on any masthead pages.

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Mechanism of Hydrolysis of Benzamidomethyl Derivatives of Phenols and Its Implications for Prodrug Design

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Received July 22, 1991

A series of *O*-benzamidomethyl derivatives of phenols was synthesized, and their rates of hydrolysis were investigated. The hydrolyses of the compounds follow pseudo-first-order kinetics resulting in quantitative and rapid regeneration of the phenol. The rates of hydrolysis were shown to be dependent on phenol nucleofugicity as well as the pK_a of the amide. The mechanism of hydrolysis apparently involves an elimination of the phenol anion from the conjugate base of the amide (E1cB-like).

Introduction

The most convenient, safest, and least expensive method of drug delivery is through oral ingestion. However, many drugs cannot be administered orally due to rapid metabolism by enzymes in the intestinal tract and liver.[1] The prodrug approach can be successful in improving the oral bioavailability of a drug by chemically modifying a functional group on the drug molecule that is particularly

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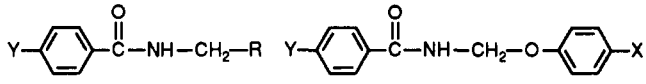
Table I. Compounds Synthesized



compd	Y	R	compd	Y	X
1a	H	OH	**3a**	H	H
1b	Cl	OH	**4a**	H	NO_2
1c	OCH_3	OH	**4b**	NO_2	NO_2
1d	NO_2	OH	**4c**	Cl	NO_2
2a	H	Cl	**5a**	H	OCH_3
2b	Cl	Cl	**6a**	H	Cl
2c	OCH_3	Cl	**7a**	H	$NHCOCH_3$
2d	NO_2	Cl			

Table II. Hydrolysis Rates of Compounds

compd	K ($\times 10^3$) min^{-1}	half-life[a] (min)	half-life[b] (min)
3a	5.80	120	
4a	1390	0.496	6.40
4b	3850	0.179	
4c	1750	0.394	
5a	3.67	190	
6a	28.4	24.4	
7a	18.9	36.7	285
8	0.120	5780	

[a] pH 9.0 buffer, 25 °C. [b] pH 7.4, 37 °C.

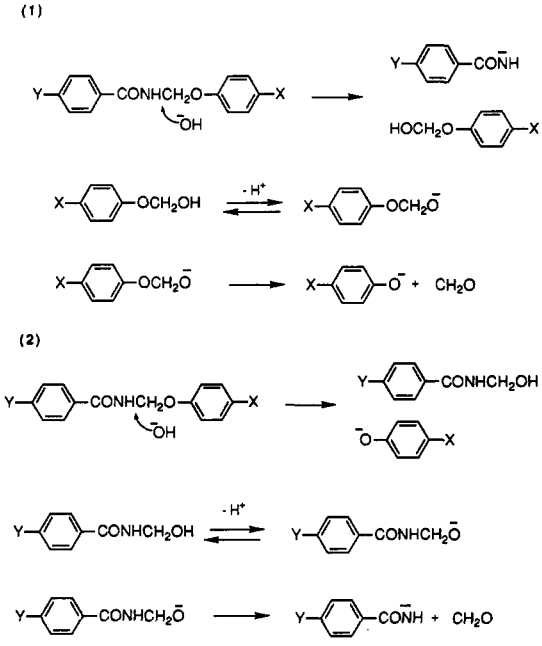
susceptible to enzymatic attack. This eliminates a primary metabolic path and allows the prodrug to enter the systemic circulation where the active drug species is released to exert its pharmacological effect. Many examples of this technique can be found in the literature.[2,3] Most require enzymatic hydrolysis (e.g., by plasma esterases) to produce active drug species and hence are subject to biological variability. However, some prodrugs, such as the benzamidomethyl derivatives of carboxylic acids,[4] hydrolyze so quickly (half-lives of less than 1 min at pH 7.4) that no enzymatic facilitation is required. The proposed *O*-benzamidomethyl derivatives of phenols were designed by analogy to the carboxylic acid derivatives to be chemically labile and therefore not dependent on enzymes or subject to biological variabilities. The following study addresses the suitability of this novel promoiety for the derivatization of drugs containing the phenol functional group.

Discussion and Results

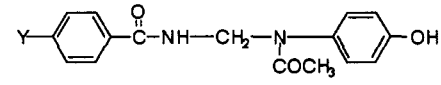
Synthesis. The compounds synthesized are shown in Table I. Benzamide was allowed to react with aqueous formaldehyde solution to give **1a**. Recrystallization of the product was not possible, so crude **1a** was allowed to react with thionyl chloride to form compound **2a**. Besides **2a**, dimeric side products, $(PhCONHCH_2)_2O$ [^1H NMR ($CDCl_3$) δ 4.90, d, 4, J = 6 Hz] and $(PhCONH)_2CH_2$ [^1H NMR ($CDCl_3$) δ 5.00, t, 2, J = 9 Hz], also were obtained. Dehydrohalogenation of **2a** in the solid state led to the formation of $(PhCONHCH_2)_2O$ even if **2a** was stored in a desiccator. Thus, it was necessary to prepare fresh alkylating agent, **2a**, before each reaction. Compounds **4a**, **5a**, and **6a** were formed by the addition of the alkylating agent to the potassium salt of the appropriate phenol in acetone. For compounds **3a**, **4b**, **4c**, and **7a**, it was necessary to pre-form the *N*-acylimine of **2a** by allowing it to react with triethylamine and then to add the phenol.

In the case of the synthesis of compound **7a**, amidomethylation of the acetanilide nitrogen to give **7b**, and not

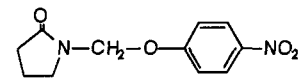
Scheme I



7a, occurred if the potassium salt of 4-hydroxyacetanilide was allowed to react with **2a**. Compound **7b** was characterized by ^1H NMR, IR, and UV. The ^1H NMR spectrum of compound **7a** exhibited a doublet at δ 5.38 for the methylene protons. The position of the absorption for the same protons for the other O-alkyl compounds ranged from δ 5.60 to 5.43. On the other hand, the *N*-amidoalkyl product **7b** exhibited the corresponding absorption at δ 5.20. A UV spectrophotometric titration showed no change in the spectrum of compound **7a** but revealed that an ionization occurred with an estimated pK_a of 9.51 for **7b**. The reported pK_a of the hydroxyl group of 4-hydroxyacetanilide is 9.51.[5] Infrared spectroscopy showed a C–O–C asymmetric stretch (1265 cm^{-1}), C–O–C symmetric stretch (1110 cm^{-1}), and NH wag (805 cm^{-1}) similar to those seen in 4-ethoxyacetanilide; C–O–C asymmetric stretch 1250 cm^{-1}, C–O–C symmetric stretch 1050 cm^{-1}, and NH wag 850 cm^{-1}.[6] Lastly, the N-amindomethylated product **7b** was stable under conditions which caused compound **7a** and the other *O*-amidomethyl products to hydrolyze.



Compound 7b



Compound 8

Hydrolysis Mechanism. At pH 8–9 the slope of the plot of pH versus log rate of hydrolysis of the *O*-benzamidomethyl phenols typically approaches unity suggesting that one hydroxyl ion is present in the rate-determining step (specific base catalysis or its kinetic equivalent). At pH of about 6, stability of the compounds apparently becomes pH independent.

Several mechanisms for base catalyzed hydrolysis of the *O*-benzamidomethyl phenol derivatives can be proposed. Scheme I (1) shows one possibility: an S_N2 reaction in

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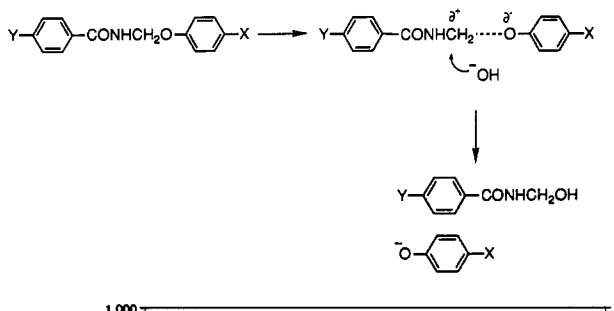
Scheme II



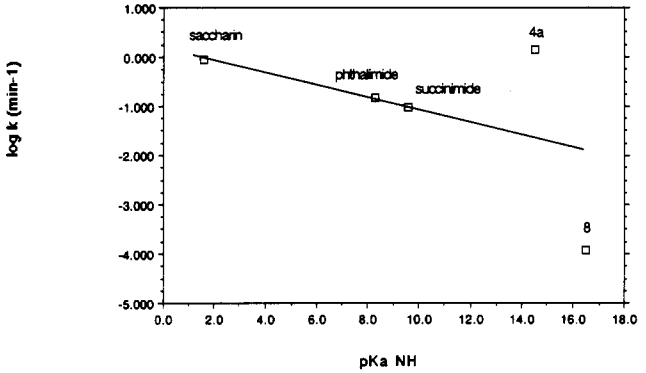
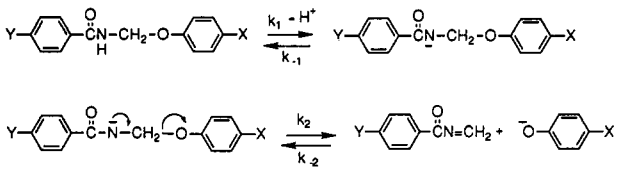


Figure 1. Pseudo-first-order rate constant for the hydrolysis of the prodrugs vs the acidic pK_a of the parent nitrogen compound (pH 9.0, 0.10 M, μ = 0.15, 25 °C).

which hydroxide acts as a nucleophile in displacing the benzamide anion to give an *O*-hydroxymethyl phenol. This hemiacetal structure could then rapidly lose a proton to the solvent and the unstable anion decompose to the parent phenol and formaldehyde.[7] Alternately, hydroxide attack on the methylene carbon could result in expulsion of the phenol anion as shown in Scheme I (2). This would lead to the formation of the *N*-hydroxymethyl benzamide compound **1a**, which subsequently hydrolyzes to give benzamide and formaldehyde. Because the phenol exhibits a lower pK_a, the phenol anion is potentially a better leaving group than the benzamide anion, so the latter mechanism is the more likely of the two S_N2 mechanisms. Scheme II shows an S_N1 type mechanism in which the CH_2–O bond undergoes solvolysis. This requires the stabilization of a full negative charge by the phenol and the formation of a stable *N*-acyliminium intermediate. This putative intermediate could undergo addition of H_2O, ionization of the N–CH_2–OH and loss of formaldehyde.

Evidence that an elimination rather than a substitution mechanism is found in the hydrolysis of the benzamidomethyl ethers comes from studies of similar types of phenolic prodrugs. A series of model compounds derived from imides as opposed to the amides of this study have been synthesized and investigated.[8] A strong dependence of the rate of hydrolysis on the ability of the parent imide to stabilize a negative charge was seen. A plot of the rate vs imide pK_a is shown in Figure 1. The lack of an ionizable NH group in the cyclic structure of the imide derivatives precludes the formation of the *N*-acylimine so a β-elimination reaction is not possible for these compounds. Extrapolation of the data from Figure 1 to pK_a 14.5 for a benzamide-type nitrogen leaving group gives an estimated half-life for the benzamide derivative of about 30 min at pH 9.0, 25 °C. The half-life was determined experimentally to be 0.5 min (for **4a**). By contrast, the *O*-amidomethyl derivative of 4-nitrophenol, **8**, formed from the cyclic amide 2-pyrrolidinone (pK_a 16.5) which does not contain an ionizable NH, can only hydrolyze by a substitution mechanism and was very slow to hydrolyze ($t_{1/2}$ = 96.3 h, pH 9.0, 25 °C). This illustrates that a substitution hydrolysis mechanism for amidomethyl derivatives of phenols is not particularly facile. Obviously, a different mechanism is operating for the benzamide-based structures compared to the imide-based structures, one that results in faster than expected hydrolysis and depends on the presence of the ionizable N–H in the benzamide portion of the prodrug. Thus, an elimination rather than the S_N2 mechanism seen with imidomethyl derivatives seems to be operative in the hydrolysis of the *O*-benzamidomethyl derivatives of phenols.

Scheme III



Elimination mechanisms may be unimolecular or bimolecular. Because elimination reactions consume base, they are not strictly speaking base catalyzed but they are analogous to specific (or general) base-catalyzed reactions and show similar pH profiles. In an E1 mechanism the leaving group (e.g., the phenol) could depart, followed by abstraction of the amide proton. This mechanism can be precluded due to the relatively poor nucleofugicity of the phenol anion. In rare cases, the β-H (NH in this case) is very acidic allowing total ionization to occur prior to elimination. Therefore, the departure of the leaving group becomes rate limiting. This mechanism ($(E1)_{anion}$) can be excluded due to the relatively high pK_a of the amide (pK_a $\approx$15).

A more likely hypothesis is an E1cB-like mechanism by which compounds having an ionizable H and a relatively poor leaving group undergo a stepwise reaction involving an initial ionization step and subsequent elimination. Depending on the degree of separation between the conjugate acid and the anion as well as the relative magnitudes of the rate constants, three discrete mechanisms may be described by this reactive sequence; $(E1cB)_{reversible}$, $(E1cB)_{irreversible}$, and $(E1cB)_{ion\ pair}$.[9] Scheme III illustrates an E1cB-type elimination for the 4-(benzamidomethoxy)benzene compounds in which the "conjugate base" eliminates the phenol anion and the transient *N*-acylimine undergoes hydration with subsequent loss of formaldehyde.

Often, with compounds that contain a reasonably good leaving group, elimination reactions occur by way of a bimolecular or E2 mechanism. The E2-type elimination lies between the mechanistic extremes of the E1 and E1cB mechanisms. That is, the proton and the leaving group depart in a more concerted fashion with N- -H bond and C- -O bond breakage occurring nearly simultaneously in a symmetrical transition-state intermediate.[10] The reaction is second order (first order in base and in substrate), and the rate is dependent on the nature of the leaving group. Several of the E1cB mechanisms are also second order and are therefore difficult to distinguish from an E2 mechanism.

Increased rates of hydrolysis for compounds with electron withdrawing groups in the para position of the phenol

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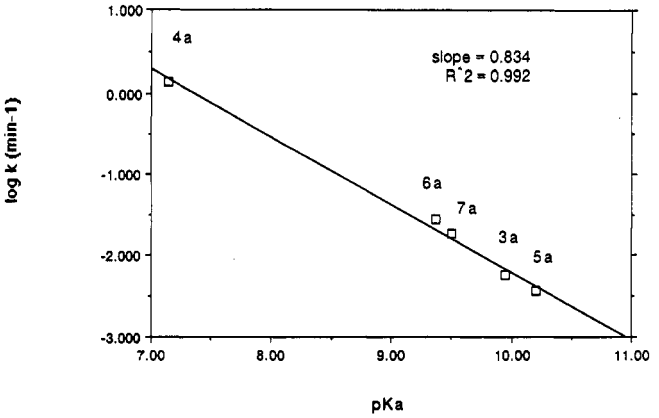

Figure 2. Pseudo-first-order rate constants for the hydrolysis of prodrugs vs the acidity of the phenol (pH 9.0, μ = 0.15 M, T = 25 °C).

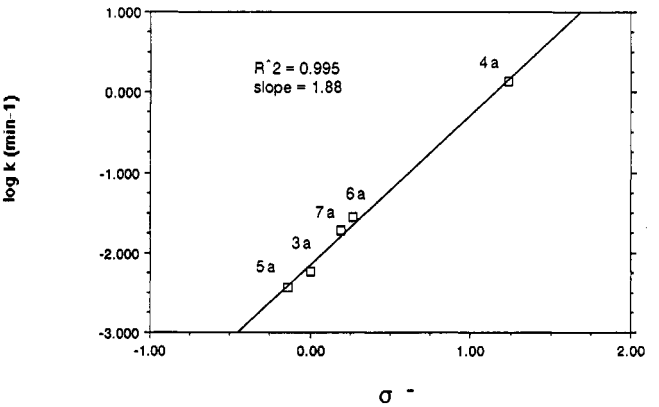

Figure 3. Pseudo-first-order rate constants for the hydrolysis of prodrugs vs the Hammett σ^- values of the phenol substituents (pH 9.0, 0.10 M, μ = 0.15, T = 25 °C).

were observed (Figure 2). In addition, a linear free energy relationship was seen between the rates of hydrolyses and σ^- values of the phenols (Figure 3). A reaction sensitivity value (ρ) of 1.90 indicates that an area of electron density is being generated in the transition state. This observation argues against the $(E1cB)_{irreversible}$ mechanism which should not show an effect of phenol substituent on the rate because proton abstraction, not elimination of phenol, is the rate-determining step. This leaves the $(E1cB)_{reversible}$ and E2 mechanisms as possibilities.

The rates of hydrolysis of a series of compounds with substituents in the para position of the benzamide (compounds **4a**, **4b**, and **4c**) were shown to depend on the Hammett σ values of the substituents. A positive ρ value was obtained from a plot of their psuedo-first-order rate constants for hydrolysis versus Hammett σ para (σ_p) values. This suggests the formation of an N-anion in the transition state and favors a "conjugate base" mechanism over a bimolecular elimination. Finally, the rates of hydrolysis of **4a** were measured in phosphate buffer solutions ranging in concentration from 0.01 to 0.10 M at constant buffer ratio. No rate increase was seen at the higher buffer concentrations; hence, general base catalysis was not observed with phosphate. This provides further support for the $(E1cB)_{reversible}$ mechanism which, of all the mechanisms considered, involves specific base catalysis only. The results indicate that the hydrolysis of these benzamidomethoxy compounds is by an $(E1cB)_{reversible}$ mechanism.

Conclusions

The *O*-benzamidomethyl phenols have been shown to hydrolyze at a faster rate than expected for a simple S_N2 or S_N1 mechanism due to a reversible "conjugate base" elimination mechanism. The half-life of the benzamidomethyl derivative of a representative phenol drug, acetaminophen, is about 5 h, so that the derivative is stable enough that a significant portion of it would be absorbed intact under physiological conditions. The subsequent quantitative release of the phenol under physiologic conditions makes α-benzamidoalkyl derivatives of phenols attractive prodrug candidates when it is desirable that release of the drug be independent of enzymes.

Experimental Section

Equipment. The buffer solutions were prepared according to tables in Perrin and Dempsey.[11] The ionic strengths were adjusted to μ = 0.15 through the addition of KCl. A Radiometer pH meter 26 was used to measure the pH at the appropriate temperature. An RC GK 2320 C electrode was used to check pH before and after experiments. In no case did the pH change within our detectable limits (0.02 units). NBS traceable standard buffer solutions (phthalate, borate, carbonate) were used to calibrate the instrument.

Hydrolysis of the compounds was measured by the change in UV–vis absorption spectra with time. A thermostated Cary 410 spectrophotometer equipped with a Fisher Model 80 Isotemp constant temperature circulator was used for the measurements. In addition, a reversed-phase high-performance liquid chromatography system was used to verify the identities of the products and identify any nontransient intermediates or side reaction products, as well as corroborate the UV-derived kinetic data. The system was comprised of a Beckman 110 A solvent metering pump with a model 153 analytical UV (254 nm) detector. An Applied Science Adsorbosphere 10-μm octylsilyl column was used for separation. Data acquisition was handled by a Hewlett-Packard 3392A integrator and a Fisher Recordall Series 5000 strip chart recorder.

Proton NMR spectra were obtained with a Varian EM-360 90-MHz spectrometer. Infrared spectra were done with a Perkin-Elmer 1420 Ratio Recording IR spectrometer. Melting points were determined using a Mel-Temp capillary melting point apparatus and are corrected. Differential scanning calorimetry was done with a Perkin-Elmer DSC-7. Microanalysis was performed by Atlantic Microlabs, Norcross GA. All chemicals and solvents were reagent grade and were used without additional purification.

Kinetic Procedures. The hydrolysis reactions were initiated by the addition of 30 μL of a 1.0 mg/mL stock solution of compound dissolved in acetonitrile to a 1-cm quartz cuvette containing 0.60 mL of methanol and 2.4 mL of appropriate buffer. This resulted in a final concentration of about 10^{-5} M. The cuvettes were magnetically stirred. Serial overlay scans were recorded, and isosbestic points were observed in each case. The wavelength where maximum change in absorbance occurred was used in determining rates. Plots of $-\ln(A_\infty - A)$ or $-\ln(A - A_\infty)$ vs time were made, and pseudo-first-order rate constants were determined according to the method of least-squares. All reactions were allowed to complete at least 6 half-lives. Three runs were performed for each experiment. The rate constants were determined by the average of the three runs. The coefficient of variation for each was less than 1%.

For HPLC analyses, the reactions were initiated by the introduction of 0.50 mL of 1.0 mg/mL stock solution to a flask containing 2 mL of MeOH and 8 mL of buffer solution. Final concentration was about 10^{-4} M. At various time intervals a sample was withdrawn and injected onto the column (20-μL sample loop). The mobile phase consisted of 40% MeOH, 60% 7.1 pH phosphate buffer (0.1 M), and 2% (w/v) tetrabutyl ammonium sulfate. The flow rate was 1.5 mL/min. Retention times for the intact ethers were about 6 min. The phenols were eluted at about 3 min and benzamide with the solvent front. No de novo synthesis of the starting compound nor formation of side products was observed. In all cases the hydrolyses were allowed to proceed to completion.

(11) Perrin, D.; Dempsey, B. *Buffers for pH and Metal Ion Control*; J. Wiley & Sons: New York, 1974.

Syntheses. 1a. *N*-(Hydroxymethyl)benzamide. Benzamide (7.0 g, 0.058 mol) was suspended in a mixture of 20 mL (0.25 mol) of 37% aqueous formaldehyde solution, 10 mL of water, and 0.2 g (0.001 mol) of potassium carbonate. The suspension was heated until it cleared, and then it was allowed to cool to room temperature. A white precipitate formed overnight which was filtered and vacuum dried. The product was not recrystallized; mp 90–115 °C. Typical yield was 4.5 g (33 mmol, 57%): NMR ($CDCl_3$) δ 4.93 (d, 2, J = 6 Hz, $NHCH_2O$).

2a. *N*-(Chloromethyl)benzamide. *N*-(Hydroxymethyl)-benzamide (4.0 g, 0.026 mol) was suspended in 40 mL of methylene chloride. Thionyl chloride (7 mL, 0.08 mol) was added dropwise with stirring to the suspension. The resulting clear solution was poured into 150 mL of heptane. A fine white precipitate immediately formed. The mixture was quickly filtered and washed with heptane to give 2.0 g (11.7 mmol, 45%) of **2a** as a typical yield; mp 90–91 °C: NMR ($CDCl_3$) δ 5.24 (d, 2, J = 6 H, $NHCH_2Cl$).

4a. 1-Nitro-4-(benzamidomethoxy)benzene. *N*-(Chloromethyl)benzamide (1.65 g, 0.009 mol) was dissolved in 20 mL of dry acetone. Potassium *p*-nitrophenolate (1.39 g, 0.01 mol) was added and stirred at room temperature for 15 h. The mixture was diluted to 150 mL with methylene chloride and filtered. The filtrate was extracted 3 times with 5 mL of 0.1 N aqueous potassium carbonate solution. The organic fraction was dried over anhydrous sodium sulfate and evaporated in vacuo to give a pale yellow solid. Recrystallization of the solid from acetone gave 400 mg (1.5 mmol, 15%) of **4a**; mp 142–144 °C: NMR ($CDCl_3$) δ 5.60 (d, 2, J = 9 Hz, NCH_2O). Anal. Calcd (found) for $C_{14}H_{12}N_2O_4$; C, 61.76 (61.83); H, 4.44 (4.47); N, 10.29 (10.32). DSC purity estimation was 98.98%.

5a and 6a were synthesized in a similar fashion. For **5a** (1-methoxy-4-(benzamidomethoxy)benzene) 460 mg (1.76 mmol, 22%) of white crystals were obtained from diethyl ether; mp 112–114 °C: NMR ($CDCl_3$) δ 5.43 (d, 2, J = 9 Hz, NCH_2O). Anal. Calcd (found) for $C_{14}H_{12}NO_2Cl$: C, 70.02 (69.83); H, 5.88 (5.93); N, 5.44 (5.43). DSC purity estimate 99.36%. For **6a** (1-chloro-4-(benzamidomethoxy)benzene) 440 mg (1.70 mmol, 17% yield) of white crystals were obtained from diethyl ether; mp 119–121 °C: NMR ($CDCl_3$) δ 5.47 (d, 2, J = 9 Hz, NCH_2O). Anal. Calcd (found) for $C_{14}H_{12}N_2O_4$: C, 61.76 (61.83); H, 4.44 (4.47); N, 10.29 (10.32). DSC purity estimation was 98.64%.

3a. 1-(Benzamidomethoxy)benzene. *N*-(Chloromethyl)-benzamide (5.5 g, 0.03 mol) was added to 3.6 g (0.036 mol) of triethylamine in 100 mL of methylene chloride. A white precipitate immediately formed. An additional 50 mL of solvent was added and the suspension filtered. To the filtrate was added 2 g (0.02 mol) of phenol. The mixture was stirred for 5 h and then evaporated in vacuo to give an oil. The oil was chromatographed on silica with ethyl acetate as eluent and then crystallized from acetone to give 300 mg (1.37 mmol, 4.4%) of **3a** as white crystals; mp 120–122 °C: NMR ($CDCl_3$) δ 5.50 (d, 2, J = 9 Hz, NCH_2O). Anal. Calcd (found) for $C_{14}H_{12}NO_2$: C, 73.99 (74.20); H, 5.76 (5.79); N, 6.17 (5.91). DSC purity estimation was 99.39%.

4b, 4c, and 7a were synthesized in a similar manner. 1-Nitro-4-(4′-nitrobenzamidomethoxy)benzene, **4b**, was obtained as 350 mg of white crystals after recrystallization from acetone-/hexane; mp 142–146 °C: NMR ($CDCl_3$) δ 5.65 (d, 2, J = 9 Hz, NCH_2O). Anal. Calcd (found) for $C_{14}H_{11}N_3O_6$: C, 53.00 (53.15); H, 3.50 (3.53); N, 13.25 (13.13). 1-Nitro-4-(4′-chlorobenzamidomethoxy)benzene, **4c**, was obtained as 300 mg of white crystals from acetone/hexane; mp 169–172 °C: NMR ($CDCl_3$) δ 5.63 (d, 2, J = 9 Hz, NCH_2O). Anal. Calcd (found) for $C_{14}H_{11}N_2O_4Cl$: C, 54.83 (55.03); H 3.62 (3.67); N, 9.13 (9.02). 1-(Acetylamino)-4-(benzamidomethoxy)benzene, **7a**, was obtained as 560 mg of white crystals from acetone; mp 169–172 °C: NMR ($CDCl_3$) δ 5.30 (d, 2, J = 9 Hz, NCH_2O). Anal. Calcd (found) for $C_{16}H_{16}N_2O_3$: C, 67.59 (67.53); H, 5.69 (5.72); N, 9.72 (9.85).

7b. 4-Hydroxy-*N*-(benzamidomethyl)acetanilide. *N*-(Chloromethyl)benzamide (1.85 g, 0.01 mol) was added to a suspension of 1.50 g (0.001 mol) of the potassium salt of 4-hydroxyacetanilide in 50 mL of tetrahydrofuran. Dimethylformamide (1.5 mL) was added to the suspension. The reaction was stirred overnight at room temperature. The suspension was filtered, and the filtrate was concentrated in vacuo to a solid which was resuspended in acetone and filtered. The filtrate was chromatographed on silica using 1% methanol in diethyl ether as the eluent. The product was crystallized from acetone as a white solid; mp 174–175 °C: NMR ($CDCl_3$) δ 5.20 (d, 2, J = 9 Hz, NCH_2N). Anal. Calcd (found) for $C_{16}H_{16}N_2O_3$: C, 67.59 (67.40); H, 5.69 (5.70); N, 9.72 (9.80).

8. 1-Nitro-4-[(2′-oxopyrrolidin-1′-yl)methoxy]benzene was prepared by allowing 1.9 g (0.01 mol) of *N*-(chloromethyl)-pyrrolidinone to react with 1.5 g of potassium 4-nitrophenolate in 25 mL of methylene chloride and 2 mL of triethylamine. The (chloromethyl)pyrrolidinone was synthesized by the method of Bohme.[12] The reaction was stirred for 16 h at room temperature then condensed in vacuo to a yellow oil. This oil was chromatographed on silica gel using diethyl ether as the eluent. The product was crystallized from methylene chloride/diethyl ether to give 100 mg of **8** as a white solid; mp 89–90 °C: NMR ($CDCl_3$) δ 5.32 (s, NCH_2O). Anal. Calcd (found) for $C_{11}H_{12}N_2O_4$: C, 55.92 (56.00); H, 5.12 (5.12); N, 11.86 (11.93).

Registry No. **1a**, 6282-02-6; **2a**, 38792-42-6; **3a**, 82212-42-8; **4a**, 134697-00-0; **4b**, 138722-59-5; **4c**, 138722-60-8; **5a**, 138722-57-3; **6a**, 138722-58-4; **7a**, 82212-43-9; **7b**, 138722-61-9; **8**, 138722-62-0; benzamide, 55-21-0; formaldehyde, 50-00-0; potassium *p*-nitrophenolate, 1124-31-8; phenol, 108-95-2; potassium *p*-methoxyphenolate, 1122-93-6; potassium *p*-chlorophenolate, 1121-74-0; benzamidomethyl ether, 113660-19-8; dibenzamidomethane, 1575-94-6; potassium *p*-acetamidophenolate, 35719-43-8; *N*-(chloromethyl)pyrrolidinone, 31282-95-8.

(12) Bohme, H.; Driessen, G.; Schünmen, D. *Arch. Pharm. (Weinheim, Ger)* **1961**, *294*, 341.