Mechanism of Hydrolysis of *O*-Imidomethyl Derivatives of Phenols

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Three series of *O*-imidomethyl derivatives of para-substituted phenolic compounds were synthesized and their rates of hydrolysis were studied. Saccharin, phthalimide, and succinimide served as the imide portions of the derivatives. Their rates of hydrolysis were found to be first order with respect to hydroxide from pH 7.0 to 10 or 11 and dependent on the acidity (leaving group potential) of both the imide and the phenol portions. The more acidic the imide or the phenol, the faster the rate of hydrolysis. However, the rates of hydrolysis were more sensitive to the acidity of the phenol. Trapping experiments with cyanide also suggested that the phenol anion was functioning as the leaving group in what is apparently an S_N2 reaction. An amide derivative was found to hydrolyze more slowly than predicted from the analogous imide series and the pK_a of the amide. This result is apparently due partially to stereoelectronic constraints in the imide series that cause the CH_2–O bond to be oriented more nearly perpendicular to the plane of the C(=O)N group and hence more accessible to nucleophilic attack.

Introduction

Recently a novel ElcB-like mechanism for the hydrolysis of *O*-benzamidomethyl (acylaminomethyl) derivatives of phenols was reported. The hydrolysis apparently involved elimination of the phenol from the corresponding conjugate base of the amide which was relatively rapid [$t_{1/2}$ = 285 min in pH 7.4 buffer at 37 °C for 4-(benzamidomethoxy)-acetanilide][1] and was not affected by plasma enzymes.[2] By contrast, an oxy analogue which did not hydrolyze by an ElcB-like mechanim was much more stable in buffer [$t_{1/2}$ = >3400 h in pH 7.0 buffer at 25 °C for 4-[(pivaloyl-oxy)methoxy]acetanilide],[3] but hydrolyzed with a half-life of only about 25 min under the same conditions in the presence of 5% rat plasma.[3] The investigations of the acylaminomethyl and acyloxymethyl derivatives are part of a systematic investigation of potentially enzymatically or nonenzymatically labile "soft-alkyl" derivatives of thiol groups[4] and of hydroxy groups that could serve as prodrugs of phenolic drugs.[5,6] The common structural feature in the acyloxy- and acylaminomethyl promoieties is a methylene group substituted with two heteroatoms, one of which is acylated. Conceptually, the substitution of the two heteroatoms on the methylene group introduces the potential for hydrolytic lability into such derivatives which is triggered when the stabilizing acyl or acylhetero group is chemically or enzymatically cleaved.

One of the novel aspects of the acylaminomethyl type of prodrug derivative was the fact that it did not require enzymatic hydrolysis to release the parent drug efficiently, and hence was not subject to biological variability in its hydrolysis. However, for the acylaminomethyl derivatives to function as efficient prodrugs, an ionizable NH group was required so that the ElcB-like mechanism was possible. Substitution of the NH group by an N-alkyl group so that the ElcB-like mechanism was not possible slowed the rate of hydrolysis of acylaminomethyl derivatives by a factor of about 10000.[1] On the other hand, substitution on the acylamine portion by another acyl group to give a diacylamine (imide) might increase the leaving group ability of that portion of the promoiety so that an S_N2 type mechanism of hydrolysis might become operative. If it did, regeneration of the parent phenol from such derivatives might also be independent of biological variability. In order to explore this possibility and to continue the systematic investigation of "soft-alkyl" derivatives of phenol, the synthesis of three series of *O*-imidomethyl derivatives of phenols using saccharin, phthalimide, and succinimide as representative diacylamine (imide) groups and the determinations of their rates of hydrolysis were undertaken. The results of those studies are reported here.

Results and Discussion

Synthesis. The appropriate imides were allowed to react with aqueous formaldehyde solution to give the *N*-hydroxymethyl adducts.[7-9] The adducts were halogenated with thionyl chloride or phosphorus pentachloride to give the corresponding *N*-chloromethyl intermediates,[7,9,10] which were subsequently allowed to react with phenol anions to give the corresponding *O*-imidomethyl derivatives, 1–13 (Table I). The possible products from the reaction of cyanide with intermediates in the hydrolysis reactions were synthesized from the reaction of bromoacetonitrile with the appropriate imide or phenol anions.

Hydrolysis Mechanism. The pH versus log k_{obs} profiles from pH 7 to 10 or 11 for the hydrolyses of the

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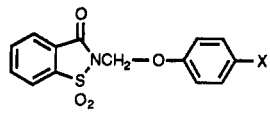
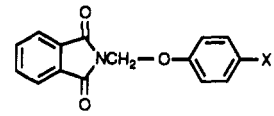
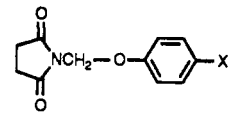
Table I. Compounds Synthesized



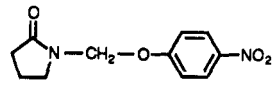
compd	X
1	NO_2
2	H
3	OCH_3
4	Cl
5	$COCH_3$
6	$NHCOCH_3$



compd	X
7	NO_2
8	H
9	OCH_3
10	$NHCOCH_3$



compd	X
11	NO_2
12	H
13	OCH_3
-	-
-	-
-	-



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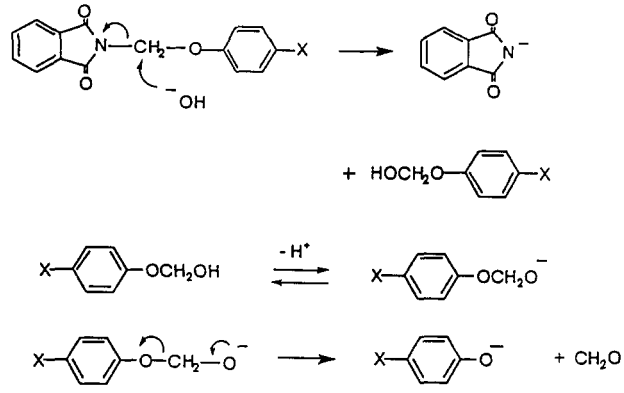
individual imidomethyl derivatives were determined. At pH values above 7, the slopes were all approximately unity (R^2 = 0.97–0.99).[2] This behavior suggests that one hydroxide ion is present in the rate-determining step and that specific base catalysis is occurring. Also, since hydroxide is involved in the rate-determining step, of the two possible substitution mechanisms, the mechanism has to be S_N2 and not S_N1.

For an S_N2 reaction, electron-withdrawing para substituents on the phenol portion of the imidomethyl derivatives should make the phenol anion a better leaving group thereby increasing the rate of a reaction in which the phenol portion is displaced. Similarly, the more electron-withdrawing and the more acidic the imide portion of the derivative becomes, the better leaving group it becomes in a substitution reaction in which the imide portion is displaced. On the other hand, development of greater electron-withdrawing potential in the phenol or in the imide portion (or in both portions) of the derivative will lead to destabilization of any positive charge that builds up on the methylene group between the phenol oxygen and the imide nitrogen in the transition state of the S_N2 reaction. The result is a more reactive electrophilic center. Thus, some of the rate enhancement of the reaction of hydroxide with the imidomethyl derivatives will be due to the effect of the electron-withdrawing ability of each portion on increasing the electrophilic character of the methylene group and not necessarily due to an increase in the nucleofugicity of the phenol or imide anion. In fact, the two effects should be synergistic. For example, in a reaction in which the phenol anion functions as the nucleofuge, the rate of the reaction will increase with increasing electron-withdrawing ability of the imide portion because of the increasing electrophilic character of the methylene group caused by the imide. Thus, there are two equally probable S_N2 mechanisms: one in which the phenol anion and the other in which the imide anion functions as the nucleofuge.

Either mechanism is compatible with rate-determining formation of phenol. In the mechanism where phenol anion functions as the nucleofuge, it is obvious that decomposition of the *O*-imidomethyl derivative leads directly to the formation of phenol. In the mechanism where the imide functions as the nucleofuge, the ionized imide and the hemiacetal of formaldehyde and phenol are formed (Scheme I). This hemiacetal can ionize in a diffusion-controlled step and spontaneously decompose to formaldehyde and phenol. These latter two steps should

Scheme I. S_N2 Reaction of Hydroxide on Compound 8 with Phthalimide Acting as Nucleofuge



be much faster than the initial S_N2 step. For example, the formaldehyde hemiacetal of trifluoroethanol, which exhibits a pK_a of 12.4, hydrolyzes with a rate constant of 8×10^5 s^{-1} analogous to the last two steps in Scheme I.[11] Since phenol exhibits a pK_a of about 10, its formaldehyde hemiacetal should hydrolyze at an even faster rate than that of trifluoroethanol.

In order to determine which mechanism was operating, trapping experiments with cyanide ion were run on the hydrolysis of two representative imidomethyl derivatives: 1 and 7. In the case where phenol anion was functioning as the nucleofuge, cyanomethyl imides (compounds 15 and 16) should be obtained from the competing reaction with cyanide, whereas, if the imide anion was functioning as the nucleofuge, (*p*-nitrophenoxy)acetonitrile (compound 17) should be obtained. Both types of compounds were stable in aqueous solution and could be identified by HPLC analysis of the reaction mixtures spiked with 15–17. However, in all the nonspiked reaction mixtures that were analyzed by HPLC, only peaks corresponding to the cyanomethyl imides were observed. When the reaction products were extracted and then concentrated and analyzed by ^1H NMR, only NCH_2CN absorptions were observed. None of the expected (*p*-nitrophenoxy)acetonitrile was observed by HPLC or ^1H NMR. In each case the yield of cyanide-trapped product was approximately 1% of the yield of the phenol. In addition, mixtures of the imides, formaldehyde, *p*-nitrophenol, and cyanide were stirred together in phosphate

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Table II. Influence of Para-Substituents on Rates of Hydrolysis of Compounds (pH 9.0, 0.10 M, μ = 0.15, 25 °C)

phenol			log k_{obs}[a] (compound)		
X	σ^- [b]	pK_a[c]	1–6	7–10	11–13
NO_2	1.25	7.14	−0.037 (1)	−0.85 (7)	−1.03 (11)
H	0.00	9.95	−0.86 (2)	−1.44 (8)	−1.60 (12)
OCH_3	−0.12	10.2	−1.10 (3)	−1.57 (9)	−1.66 (13)
Cl	0.24	9.38	−0.50 (4)	–	–
$COCH_3$	0.82	8.05	−0.44 (5)	–	–
$NHCOCH_3$	0.19[d]	9.55[e]	−0.57 (6)	−1.20 (10)	–

[a] Rate constants in min^{-1}. [b] Exner, O. *Correlation Analysis of Chemical Data*; Plenum Press: New York, 1988. [c] Jencks, W. P.; Regenstein, J. In *Handbook of Biochemistry and Molecular Biology: Physical and Chemical Data*, 3rd ed.; Fasman, G. D., Ed.; CRC Press, Inc: Cleveland, 1976; Vol. I, pp 305–351. [d] Determined from plot of pK_a of phenol versus σ^- values for the other substituents (R^2 = 0.999). [e] Fairbrother J. E. In *Analytical Profiles of Drug Substances*; Florey, K., Ed.; Academic Press, Inc: New York, 1974; Vol. 3, pp 1–110.

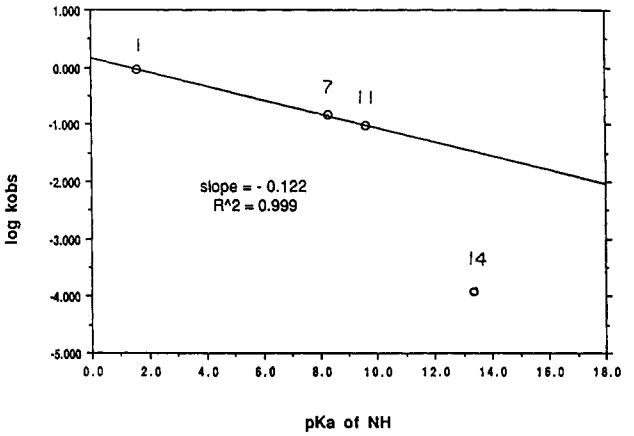

Figure 1. Pseudo-first-order rate constants (min^{-1}) versus acidic pK_a of parent imide for the hydrolyses of compounds 1, 7, 11, and 14: saccharin pK_a = 1.6,[12] phthalimide pK_a = 8.3,[13] succinimide pK_a = 9.6,[14] and pyrrolidinone pK_a = 13.3[15] (pH = 9.0, 0.10 M, μ = 0.15, 25 °C).

buffer and analyzed by HPLC for the formation of cyanide-trapped products generated in situ. None were observed. Thus, the trapping experiments suggest that the mechanism is S_N2 with phenol anion functioning as the nucleofuge.

The kinetics of the hydrolyses of the imidomethyl derivatives also support an S_N2 hydrolysis mechanism in which phenol functions as the leaving group. In all the examples studied, the hydrolyses of O-imidomethyl derivatives were pseudo-first-order with regard to the derivatives. The acidities of the phenol portions of the derivatives were directly proportional to their rates of hydrolysis. The more acidic the phenol the faster the rate of hydrolysis (Table II). Plots of log k_{obs} for the hydrolysis of compounds 1–13 versus the pK_a values of the parent phenols for the saccharin, phthalimide, and succinimide series gave slopes of −0.279 (R^2 = 0.84), −0.218 (R^2 = 0.96) and −0.206 (R^2 = 0.99), respectively (plots not shown). The rates of hydrolysis of the O-imidomethyl derivatives of 4-nitrophenol (1, 7, and 11) as shown in Figure 1 and of phenol (2, 8, and 12) and 4-methoxyphenol (3, 9, and 13) in Figure 2 were also directly proportional to the acidity of the imide. The more acidic the imide[12–15] the faster the

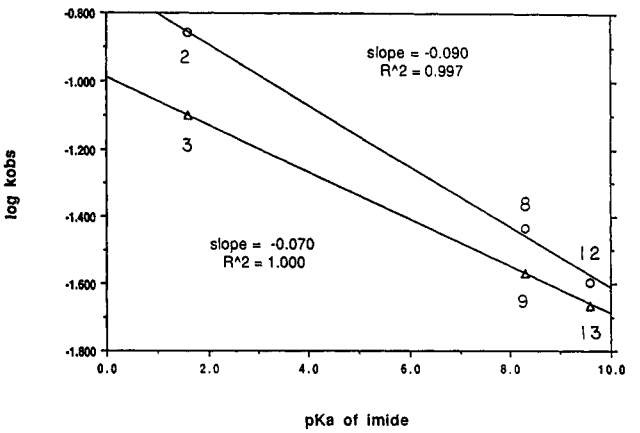

Figure 2. Pseudo-first-order rate constants (min^{-1}) versus acidic pK_a of parent imides for the hydrolyses of compounds 2, 8, and 12 (○) and 3, 9, and 13 (△) (pH = 9.0, 0.10 M, μ = 0.15, 25 °C).

rate. The slopes of the linear plots of log k_{obs} versus pK_a in Figures 1 and 2 indicate the sensitivity of the hydrolysis to the electron-withdrawing character of the imide. None of the hydrolyses were very sensitive to changes in the pK_a of the imide with the 4-nitrophenol derivatives being the most sensitive (slope = −0.122), the phenol derivatives being less sensitive (slope = −0.090), and the 4-methoxyphenol derivatives being the least sensitive (slope = −0.070). A comparison of the two sets of data show that the rates of hydrolysis of the derivatives are more than twice as sensitive to the pK_a of the phenol than to the pK_a of the imide. Thus, the greater sensitivity of the hydrolysis reactions to the acidity of the phenol than to the acidity of the imide suggests that the phenol is functioning as the nucleofuge and supports the results from the trapping experiments.

The effect of the substituents on the phenol portion of k_{obs} was also quantitated from various Hammett plots of substituent constants for the phenol portion of the derivatives versus log k_{obs}. The use of the Yukawa and Tsuno two-parameter approach[16] or the Swain and Lupton dual-parameter approach[17] gave somewhat better correlation coefficient values for their treatment of the data than a plot of σ^- substituents versus log k_{obs}. However, none of the approaches apparently added any significant insight into the mechanism of the hydrolysis. It should be noted, though, that the rates of hydrolysis of the derivatives based on saccharin were more sensitive to the substituent effect than those based on phthalimide or succinimide. For example, from the plots of σ^- versus log k_{obs} (plots not shown) ρ = +0.64 (R^2 = 0.86) for the saccharin derivatives 1–6, ρ = +0.50 (R_2 = 0.92) for the phthalimide derivatives 7–10, and ρ = +0.47 (R^2 = 1.00) for the succinimide derivatives 11–13. All the ρ valves were positive as expected for an S_N2 reaction.

Included in Figure 1 is data for the hydrolysis of a representative O-(N-alkylamido)methyl derivative of 4-nitrophenol (14),[1] which showed that 14 hydrolyzed much slower than predicted based on the relationship observed between pK_a of the imide or amide and log k_{obs} for the imidomethyl derivatives. The lesser electron-withdrawing ability of the N-alkylamido portion of 14 (i.e., the very

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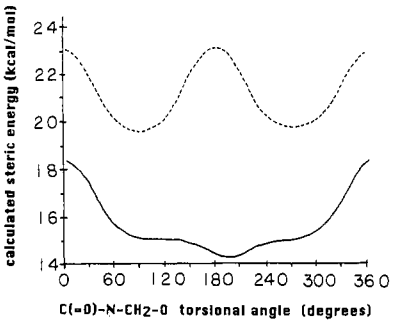

Figure 3. Torsional angle of C(=O)–N–CH_2–O versus calculated steric energy for phthalimide-based compound 8 (- - -) and pyrrolidinone-based compound 14 (—).

high acidic pK_a of the pyrrolidinone NH, pK_a = 13.3)[15] does not fully explain the low observed rate constant when compared to the imidomethyl derivatives in which the imide portions are much more acidic, i.e., pK_a = 1.6–9.6.[12-14]

Therefore, stereoelectronic factors were considered as possibly contributing to the difference in reactivity of **14** compared to **1–13**. Energy-minimized structures were calculated for compounds **2**, **8**, **12**, and **14**, and torsional angles for the C(=O)–N–CH_2–O group were obtained for the minimized conformations. A torsional angle of 180° would indicate that the atoms are in the same plane but with the C(=O)–N bond anti to the CH_2–O bond. The derivatives based on saccharin, phthalimide, and succinimide (**2**, **8**, and **12**) exhibited torsional angles of 80°, 92°, and 88°, respectively (see Figure 3 for phthalimide-based derivative **8**), indicating the CH_2–O bond is twisted out of the C(=O)–N–CH_2 plane. This is a result of minimization of the interaction between the two unshared pair of electrons on the ether oxygen and the unshared pair of electrons on either of the imide carbonyl oxygens. On the other hand, the energy minimum for the pyrrolidinone-based derivative **14** is very broad, i.e., 60–300°, although there is a second shallow minimum of <1 kcal/mol which gives a C(=O)–N–CH_2–O torsional angle close to planarity (195°, see Figure 3). The plots for both **8** and **14** in Figure 3 show an energy barrier of about 3.5 kcal/mol corresponding to conformations in which the ether oxygen's two unshared pairs of electrons approach carbonyl groups. The difference between **2**, **8**, and **12**, on one hand, and **14** on the other, is that there is a second energy barrier (about 3.5 kcal/mol) corresponding to close approach of the ether oxygen's unshared pairs to the other carbonyl group for **2**, **8**, and **12**, but a shallow minimum (<1 kcal/mol) for the conformation of **14** in which the unshared pairs are farthest from the single carbonyl group.

The conformation of **14** (torsional angle = 195°) which minimizes the interaction of the unshared pair of electrons on the ether oxygen with that of the single amide carbonyl group also orients the unshared pair of electrons on the amide carbonyl oxygen toward the backside of the CH_2–O bond. Then, since an S_N2 reaction requires backside attack of the methylene group by the nucleophile, the unshared pair of electrons of the carbonyl group in **14** will inhibit nucleophilic attack, and the rate of hydrolysis of **14** will be slower than predicted from trends based on the rates of hydrolysis of imidomethyl derivatives. However, only about 1 kcal/mol of energy is required for **14** to rotate to a C(=O)–N–CH_2–O torsional angle of about 90° (or 270°) where **14** could assume the same minimum-energy conformation from which **2**, **8**, and **12** undergo S_N2 hydrolysis. This energy difference can account for a difference in rates between imide type derivatives and **14** of about 5 times. Thus, it is clear that differences in energy of conformations of **14** may only partially account for the slower rate of hydrolysis of **14**.

Finally, the hydrolyses of **1**, **7**, and **11** in 80% human plasma and in heat-denatured human plasma were run to determine if the hydrolyses of the *O*-imidomethyl-type derivatives were sensitive to enzymatic catalysis. Compounds **7** and **11** hydrolyzed at the same rate in buffer, plasma, and heat-denatured plasma.[2] On the other hand, compound **1** did hydrolyze somewhat faster (8–6 times) in plasma than in buffer or heat-denatured plasma, respectively.[2] However, since there was no dramatic increase in the rate of hydrolysis of **1**, it has been concluded that as a group the *O*-imidomethyl-type derivatives are not sensitive to enzymatic catalysis.

Conclusions

The *O*-imidomethyl type of derivative is another example of a soft-alkyl type derivative which exhibits physicochemical properties that are complementary to the previously described *O*-amidomethyl and *O*-acyloxymethyl soft-alkyl types of derivatives. Although the hydrolyses of the *O*-amidomethyl derivatives followed an ElcB mechanism, the *O*-imidomethyl derivatives of phenols followed an S_N2 mechanism where the phenol anion functioned as the nucleofuge. Even the incorporation of a highly acidic amide such as saccharin, in which it was expected that the leaving group potential was maximized, was not sufficient to change the mechanism of the hydrolysis to one in which imide anion functioned as the leaving group. However, the rates of hydrolysis of the *O*-imidomethyl derivatives were sensitive to the electron-withdrawing ability of the imide. Thus, different rates of release of a specific phenol from these soft-alkyl derivatives can be achieved for specific conditions of hydrolysis by using *O*-imidomethyl derivatives derived from imides exhibiting different pK_a values. For example, the half-life of the *O*-imidomethyl derivative of a representative phenol drug, acetaminophen, is 100 min at pH 7.4 and 25 °C if saccharin (compound **6**) comprises the imide portion of the derivative, whereas the half-life is 436 min if phthalimide (compound **10**) comprises the imide portion.

This flexibility can be a valuable asset if it becomes necessary to design a derivative to protect a phenol drug from premature metabolism during absorption from an oral dose, but it is not obvious what release rate is necessary to ensure biological activity, i.e. for the derivative to function as a prodrug. Preliminary data for the saccharin-based *O*-imidomethyl derivative of estradiol[18] suggests that it functions as a prodrug which is about 8 times more potent than an equimolar oral dose of estradiol.

The inverse relationship between the pK_a of the imide and the rate of hydrolysis of the *O*-imidomethyl derivatives can not be extrapolated to *O*-(*N*-alkylamido)methyl derivatives based on the results for the hydrolysis of a single cyclic example, **14**. The difference between these two types of soft-alkyl derivatives apparently is due at least partially to a difference in the orientation of the CH_2–O bond. The implications of this result for the design of other soft-alkyl derivatives which hydrolyze more slowly than the

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O-benzamidomethyl, O-imidomethyl, or O-acyloxymethyl derivatives is currently under investigation.

Experimental Section

Equipment and Materials. The buffer solutions were prepared according to tables in Perrin and Dempsey.[19] The ionic strengths were adjusted to $\mu = 0.15$ through the addition of KCl. A Radiometer pH meter Model 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 the limits of detection (0.02 units). NBS-traceable standard buffer solutions (phthalate, borate, carbonate) were used to calibrate the instrument. TLC plates (0.25 mm, silica UV_{254} fluorescent) were obtained from Sybron/Brinkman.

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 reverse-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. The molecular modeling was performed using Chem 3D Plus version 3.0, Cambridge Scientific Computing, Inc.

Proton ^{1}H NMR spectra were obtained with a Varian EM-390 90-MHz spectrometer. Infrared spectra were recorded with a Perkin-Elmer 1420 Ratio Recording IR spectrometer. Melting points were determined using a Mel-Temp capillary melting point apparatus and are uncorrected. 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 the compound dissolved in acetonitrile to a 1-cm quartz cuvette containing 0.60 mL of methanol and 2.4 mL of the appropriate buffer at 25 °C or 3.0 mL of 80% human plasma and 20% phosphate buffer at 37 °C. 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 the 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 six half-lives. The rate constants were determined from the average of three identical 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 a 1.0 mg/mL stock solution to a flask containing 2 mL of CH_3OH and 8 mL of buffer solution. The final concentration of substrate 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) tetrabutylammonium 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 the imides with the solvent front. No de novo synthesis of the starting compound from the reaction products alone nor formation of side products was observed. In all cases the hydrolyses were allowed to proceed to completion.

Trapping Experiments. In a typical experiment 10 mL of a 0.1 M phosphate buffer solution containing 10 mg of sodium cyanide was adjusted to pH 8. To this mixture was added 1.0 mL of methanol in which 10 mg of the compound of interest had been dissolved. The resulting total cyanide concentration was about 10^{-2} M. The reaction mixture was stoppered, placed in a fume hood, and allowed to stand at room temperature for a time period sufficient for complete hydrolysis of the compound (>7 half-lives). At pH 8.0 the amount of free cyanide ion was about 10^{-4} M, so there was about a 100-fold excess of cyanide. The reaction mixtures were analyzed by HPLC (mobile phase, 30:70, MeOH/pH 8.0 phosphate buffer). The chromatograms were compared to compounds 15–17 as well as to the usual hydrolysis products obtained in the absence of cyanide ion. In addition, the reaction mixtures were extracted with chloroform and concentrated, and ^{1}H NMR spectra were obtained. The products of hydrolysis and cyanide ion trapping were distinguished by the chemical shift of their methylene protons. These experiments were performed on representative compounds: 1 and 7.

Synthesis. The O-imidomethyl derivatives based on saccharin were synthesized from N-(chloromethyl)saccharin and the corresponding 4-substituted phenols. The N-(chloromethyl)saccharin was obtained from saccharin by first allowing saccharin to react with aqueous formaldehyde to give N-(hydromethyl)-saccharin[7] [mp 119–123 °C, lit. mp 125–126 °C, ^{1}H NMR ($CDCl_3$) δ 5.21 (d, 2, J = 3 Hz, NCH_2OH)] and then allowing the N-(hydroxymethyl)saccharin to react with PCl_5 in ether to give N-(chloromethyl)saccharin[7] [mp 145–146 °C, lit. mp 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 5.49 (s, 2, NCH_2Cl)].

Compounds 1–6. Equimolar amounts (0.01 mol) of N-(chloromethyl)saccharin, potassium carbonate, sodium iodide, and the appropriate phenol were added to 20 mL of dry acetone and stirred overnight. The mixture was diluted with 125 mL of methylene chloride and filtered. The filtrate was extracted with 20 mL of 0.5% NaOH solution. The organic phase was collected, dried over sodium sulfate, filtered, and concentrated. The resulting oil solidified upon standing. The solid was triturated with ether and filtered. The product was recrystallized from acetone to give the following compounds.

Compound 1: mp 160–162 °C; yield 1.07 g (3.3 mmol, 33%); ^{1}H NMR ($CDCl_3$) δ 5.92 (s, 2, NCH_2O). Anal. $C_{14}H_{10}N_2O_6S$: Calcd (found) %C 50.29 (50.21), %H 3.02 (3.03), %N 8.38 (8.33). TLC (EtOAc), R_f = 0.5.

Compound 2: mp 119–120 °C; yield 560 mg (1.9 mmol, 19%); ^{1}H NMR ($CDCl_3$) δ 5.86 (s, 2, NCH_2O). Anal. $C_{14}H_{11}NSO_4$: Calcd (found) %C 58.13 (57.98), %H 3.83 (3.85), %N 4.84 (4.76). TLC (EtOAc), R_f = 0.53.

Compound 3: mp 118–120 °C; yield 560 mg (1.8 mmol, 18%); ^{1}H NMR ($CDCl_3$) δ 5.80 (s, 2, NCH_2O). Anal. $C_{15}H_{13}NSO_5$: Calcd (found) %C 56.24 (56.19), %H 4.41 (4.33), %N 4.37 (4.30). TLC (EtOAc), R_f = 0.56.

Compound 4: mp 102–103 °C; yield 320 mg (0.99 mmol, 10%); ^{1}H NMR ($CDCl_3$) δ 5.73 (s, 2, NCH_2O). Anal. $C_{14}H_{10}NSO_4Cl$: Calcd (found) %C 52.13 (52.20), %H 3.11 (3.23), %N 4.33 (4.35). TLC (EtOAc), R_f = 0.53.

Compound 5: mp 138–139 °C; yield 500 mg (1.50 mmol, 15%); ^{1}H NMR ($CDCl_3$) δ 5.81 (s, 2, NCH_2O). Anal. $C_{16}H_{13}NO_5S$: Calcd (found) %C 58.00 (57.75), %H 3.95 (3.75), %N 4.23 (4.32). TLC (Et_2O), R_f = 0.65.

Compound 6: mp 160–162 °C; yield 500 mg (1.44 mmol, 14%); ^{1}H NMR ($CDCl_3$) δ 5.70 (s, 2, NCH_2O). Anal. $C_{16}H_{14}N_2O_6S$: Calcd (found) %C 55.49 (55.52), %H 4.07 (4.10), %N 8.10 (8.29). TLC (Et_2O), R_f = 0.46.

The O-imidomethyl derivatives based on phthalimide were synthesized from N-(chloromethyl)phthalimide and the corresponding 4-substituted phenols. The N-(chloromethyl)phthalimide was obtained from phthalimide by first allowing phthalimide to react with aqueous formaldehyde to give N-(hydroxymethyl)phthalimide[7] [mp 141–142 °C; lit. mp 141–142 °C; ^{1}H NMR ($CDCl_3$) δ 5.01 (d, 2, J = 3 Hz, NCH_2OH)] and then allowing the N-(hydroxymethyl)phthalimide to react with PCl_5 in ether to give N-(chloromethyl)phthalimide[10] [mp 130–132 °C, lit. mp 133–135 °C, ^{1}H NMR ($CDCl_3$) δ 5.50 (s, 2, NCH_2Cl)].

Compounds 7–10. N-(Chloromethyl)phthalimide (2.1 g, 0.01 mol), sodium iodide (1.5 g, 0.01 mol), potassium carbonate (1.4 g, 0.01 mol), and 20 mL of dry acetone were combined and stirred for 15 min, after which 0.01 mol of the appropriate phenol was added. The reaction mixture was stirred for 2 days and then it was diluted with 100 mL of methylene chloride and filtered. The

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filtrate was concentrated to give a solid which was recrystallized from acetone. The resulting crystals were filtered and vacuum-dried overnight.

Compound 7: mp 160–161 °C; yield 1.44 g (4.8 mmol, 48%); ^{1}H NMR ($CDCl_3$) δ 5.80 (s, 2, NCH_2O). Anal. $C_{15}H_{10}N_2O_5$: Calcd (found) %C 60.20 (60.33), %H 3.34 (3.43), %N 9.36 (9.32). TLC (Et_2O), R_f = 0.45.

Compound 8: mp 140–143 °C; lit. mp 133–135 °C;[20] yield 900 mg (3.6 mmol, 36%); ^{1}H NMR ($CDCl_3$) δ 5.72 (s, 2, NCH_2O). Anal. $C_{15}H_{11}NO_3$: Calcd (found) %C 71.14 (71.23), %H 4.38 (4.41), %N 5.53 (5.49). TLC (Et_2O), R_f = 0.45.

Compound 9: mp 149–150 °C; yield 1.33 g (4.7 mmol, 47%); ^{1}H NMR ($CDCl_3$) δ 5.58 (s, 2, NCH_2O). Anal. $C_{16}H_{13}NO_4$: Calcd (found) %C 67.84 (67.89), %H 4.63 (4.66), %N 4.94 (4.93). TLC (Et_2O), R_f = 0.48.

Compound 10: mp 149–150 °C; yield 1.33 g (4.3 mmol, 43%); ^{1}H NMR ($CDCl_3$) δ 5.72 (s, 2, NCH_2O). Anal. $C_{17}H_{14}N_2O_4$: Calcd (found) %C 65.80 (65.89), %H 4.55 (4.66), %N 9.03 (8.93). TLC (CH_2Cl_2), R_f = 0.48.

The *O*-imidomethyl derivatives based on succinimide were synthesized from *N*-(chloromethyl)succinimide and the corresponding 4-substituted phenols. The *N*-(chloromethyl)succinimate was obtained from succinimide by first allowing succinimide to react with aqueous formaldehyde to give *N*-(hydroxymethyl)-succinimide[9] [mp 64–66 °C, lit. mp 66 °C; ^{1}H NMR ($CDCl_3$) δ 4.96 (d, 2, J = 3 Hz, NCH_2OH)] and then by allowing the *N*-(hydroxymethyl)succinimide to react with $SOCl_2$ in ether to give *N*-(chloromethyl)succinimide[9] [mp 46–52 °C, lit. mp 58 °C; ^{1}H NMR ($CDCl_3$) δ 5.20 (s, 2, NCH_2Cl)].

Compounds 11–13. *N*-(Chloromethyl)succinimide (1.6 g, 0.01 mol), 1.38 g (0.01 mol) of potassium carbonate, and 1.44 g (0.01 mol) of sodium iodide were combined in 20 mL of acetone and stirred for 15 min after which 0.01 mol of the appropriate phenol was added. The reaction mixture was stirred at room temperature for 2 days. The mixture was diluted to 150 mL with methylene chloride and filtered. The filtrate was concentrated to give a solid which was recrystallized from acetone.

Compound 11: mp 156–158 °C; yield 1.00 g (4.0 mmol, 40%); ^{1}H NMR ($CDCl_3$) δ 5.6 (s, 2, NCH_2O). Anal. $C_{11}H_{10}N_2O_5$; Calcd (found) %C 52.80 (52.76), %H 4.03 (4.04), %N 11.20 (11.16). TLC (Et_2O), R_f = 0.17.

Compound 12: mp 88–91 °C; yield 1.20 g (5.8 mmol, 58%); ^{1}H NMR ($CDCl_3$) δ 5.50 (s, 2, NCH_2O). Anal. $C_{11}H_{11}NO_3$; Calcd (found) %C 64.39 (64.19), %H 5.40 (5.46), %N 6.83 (6.77). TLC (Et_2O), R_f = 0.29.

Compound 13: mp 86–88 °C; yield 700 mg (3.3 mmol, 33%); ^{1}H NMR ($CDCl_3$) δ 5.43 (s, 2, NCH_2O). Anal. $C_{13}H_{13}NO_4$: Calcd (found) %C 61.28 (61.19), %H 5.40 (5.62), %N 6.00 (5.89). TLC (Et_2O), R_f = 0.45.

Compounds 15–17. Equimolar amounts (0.016 mmol) of imide or phenol, 2-bromoacetonitrile, and potassium carbonate were allowed to react in 30 mL of acetone overnight at room temperature. A white precipate formed. The suspension was diluted with 100 mL of dichloromethane and filtered. The filtrate was extracted twice with 10 mL of water. The organic fraction was separated, dried over sodium sulfate, and concentrated. The residue was purified by crystallization or by column chromatography to give the desired compounds.

Compounds 15 [*N*-(Cyanomethyl)saccharin]: 51% yield; mp 137–139 °C; ^{1}H NMR ($CDCl_3$) δ 4.63 (s, 2, NCH_2CN). Anal. $C_9H_6N_2O_3S$: Calcd (found) %C 48.65 (48.45), %H 2.72(2.74), %N 12.61 (12.49).

Compound 16 [*N*-(Cyanomethyl)phthalimide]: 63% yield, mp 121–123 °C, ^{1}H NMR ($CDCl_3$) δ 4.55 (s, 2, NCH_2CN). Anal. $C_{10}H_6N_2O_2$: Calcd (found) %C 64.51 (64.51), %H 3.25 (3.21), %N 15.05 (14.99).

Compound 17 [4-(Nitrophenoxy)acetonitrile]: 21% yield; mp 73–75 °C; ^{1}H NMR ($CDCl_3$) δ 4.93 (s, 2, OCH_2CN). Anal. $C_8H_6N_2O_3$: Calcd (found) %C 53.93 (54.01), %H 3.40 (3.38), %N 15.73 (15.77).

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