Hydrolytic Behavior of *N*-Acyl Phthalimides

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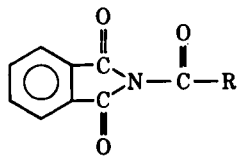
Abstract □ The hydrolysis of *N*-acyl phthalimides was studied to determine the effect of the *N*-acyl moiety on the hydrolytic rate and hydrolytic products, *i.e.*, whether hydrolysis leads to the regeneration of the parent phthalimide or to formation of the corresponding *N*-acyl phthalamic acid. A series of *N*-acyl phthalimides was prepared and their hydrolysis was observed in the neutral to alkaline pH range at 25°. It was found that *N*-acetyl-, *N*-propionyl-, *N*-(ethoxycarbonyl)-, and *N*-(morpholinocarbonyl)phthalimides gave their corresponding *N*-acyl phthalamic acid as their major hydrolytic product while *N*-chloroacetyl- and *N*-bromoacetylphthalimides gave phthalamide and the corresponding carboxylic acid. The change in path depending on the *N*-acyl group was rationalized in terms of the susceptibility of the appropriate carbonyls to attack.

Keyphrases □ *N*-Acyl phthalimides—hydrolysis, effect of *N*-acyl moiety on rate and formation of phthalimide parent or *N*-acyl phthalamic acid □ Phthalimides, *N*-acyl—hydrolysis, effect of *N*-acyl moiety on rate and formation of phthalimide parent or *N*-acyl phthalamic acid □ Hydrolysis of *N*-acyl phthalimides—effect of *N*-acyl moiety on rate and phthalimide or phthalamic acid products □ Imides (phthalimides)—formation by hydrolysis of *N*-acyl phthalimides

Imides form a group of compounds which have found wide use in the pharmaceutical and chemical industries. The major pharmaceuticals having the imide functionality within their structural formulas are glutethimide and thalidomide (sedatives), ethosuximide and phensuximide (anticonvulsants), bemegride (barbiturate antagonist), and a number of antibiotic, antiviral, and carcinostatic agents (1).

The present study was concerned with the hydrolysis of *N*-acyl phthalimides (I) and the possible use of acylimides as prodrugs of imides. The aim of the work was to observe the effect of the *N*-acyl moiety on the hydrolytic rate and hydrolytic products of *N*-acyl phthalimides, *i.e.*, whether hydrolysis leads to the regeneration of the imide or to formation of the corresponding *N*-acyl phthalamic acid. If *N*-acyl imides are to be considered for prodrugs of imides, they must regenerate the imide on hydrolysis.

The solvolysis and aminolysis of *N*-acyl cyclic imides under various conditions were the subjects of a limited number of studies (2–9), most of which were intended as observations of the acylating power of the acylated imides; however, no quantitative kinetic data were presented. There also appears to be some confusion as to the mechanism of reaction because the products vary depending on the nucleophile, solvent, and temperature of reaction.



I

R = alkyl, alkoxy, or amino

EXPERIMENTAL

Equipment—A recording spectrophotometer[1], with a thermostated cell compartment maintained at 25 ± 0.1°, was used for all kinetic and product measurements. NMR spectra were obtained using spectrometers[2] with all spectra run in $CDCl_3$. IR spectra were acquired using an IR spectrometer[3]. All pH measurements were obtained on a research pH meter[4] at 25°, standardized with standard phosphate and borate buffers.

Reagents and Materials—Dioxane and phthalimide were purified according to the method of Perrin *et al.* (10). All other chemicals were of analytical or reagent grade and were used without further purification. A TLC sorbent[5] was used. *N*-Ethoxycarbonylphthalimide (II) was obtained commercially[6], and all other phthalimide derivatives studied were synthesized.

Synthesis of *N*-Acetylphthalimide (III)—Five grams (0.034 mole) of phthalimide was dissolved in 25 g. (0.250 mole) of acetic anhydride. The solution was refluxed for 2 hr. and then fractionally distilled (30-cm. vigreux column). The first distillate was collected at 123° (acetic acid plus acetic anhydride), and the reaction was terminated when the distillate temperature rose to 138°. The residue was then taken up in toluene, hot filtered through charcoal, and, on cooling, diluted with 50 ml. of ether. The resulting white precipitate was recrystallized three times from the toluene–ether mixture to give a solid of m.p. 136–137° [lit. (11) m.p. 135–136°]. NMR showed a symmetrical A_2B_2 pattern at 7.92 and 7.98δ (four protons) and a singlet at 2.69δ (three protons), confirming *N*-acylation. The IR spectrum gave a large peak area between 1800 and 1600 $cm.^{-1}$, and the UV spectrum gave peaks at 270 and 295 nm.

Synthesis of *N*-Propionylphthalimide (IV)—This was prepared in a similar manner to *N*-acetylphthalimide, except that propionic anhydride was used in place of acetic anhydride. A product of m.p. 153–155° was obtained [lit. (12) m.p. 143–144°]. NMR showed a symmetrical A_2B_2 pattern at 7.92 and 7.96δ (four protons), a triplet at 1.29δ (three protons), and a quartet at 3.10δ (two protons), confirming *N*-acylation. The IR spectrum gave a large peak area between 1800 and 1600 $cm.^{-1}$, and the UV spectrum gave peaks at 270 and 295 nm.

Synthesis of *N*-Chloroacetylphthalimide (V)—To a solution of 10 g. (0.059 mole) of chloroacetic acid was added 6.1 g. (0.059 mole) of dicyclohexylcarbodiimide in 120 ml. of tetrahydrofuran. After standing for 4 hr., the urea was filtered off, leaving a solution of the anhydride of approximately 10% (w/v). Two grams of potassium phthalimide was added to 20 ml. of the solution, and the suspension was refluxed for 5 hr. with stirring. The solution was filtered and evaporated to 10 ml., and the precipitate was collected. After three recrystallizations from tetrahydrofuran, a white compound was collected, m.p. 177–179° [lit. (13) m.p. 179–180°]. NMR showed a symmetrical A_2B_2 pattern at 7.92 and 7.98δ (four protons) and a singlet at 4.70δ (two protons), confirming *N*-acylation.

Synthesis of *N*-Bromoacetylphthalimide (VI)—The synthesis was identical to that of V, except that bromoacetic acid was used in the initial step. A product of m.p. 153–155° was obtained.

Anal.—Calc. for $C_9H_{10}BrNO_3$: C, 44.94; H, 2.27; N, 5.24. Found: C, 45.24; H, 2.49; N, 5.37.

NMR showed a symmetrical A_2B_2 pattern at 7.92 and 7.98δ (four protons) and a singlet at 4.60δ (two protons), confirming *N*-acylation.

Synthesis of *N*-(Morpholinocarbonyl)phthalimide (VII)—This compound was synthesized according to the method of Grigat (14), except that the starting material was *N*-(ethoxycarbonyl)phthalimide instead of *N*-(phenoxycarbonyl)phthalimide. The product showed m.p. 204–205° [lit. (14) m.p. 207–208°]. NMR showed a sym-

[1] Cary 14.
[2] Varian T60 or A-60A.
[3] Perkin-Elmer 700.
[4] Corning model 12.
[5] Silicar, TLC-7G1, Mallinckrodt Chemical Works, St. Louis, Mo.
[6] Aldrich Chemical Co., Milwaukee, Wis.

Table I—Delivery Volume as a Function of Pressure

Liquid	Rate, ml./p.s.i. (10^3)	Total Volume Delivered, ml. 1400 p.s.i.	2100 p.s.i.	2800 p.s.i.
Calcium carbonate, 5%	6.7	10	14.7	19
Syrup USP	7.1	10	15	20
Water	6.8	12	16.8	21.5
Alcohol USP	7.1	13	18	23

EXPERIMENTAL

Materials and Equipment—The liquids used in this study were: distilled water; syrup USP; shellac, 2.7 kg. (6 lb.) cut; 5, 15, and 35% (w/v) aqueous suspensions of calcium carbonate; and a 2% (w/v) solution of methylcellulose[1], 500 cps.

The equipment utilized to evaluate the factors involved in an automated tablet-coating system was a self-programming automated tablet-coating system with two automatic spray guns[2] as previously described (4).

Fluid Delivery Studies—Fluid delivery experiments were conducted to ascertain the influence of pressure, spray tip orifice size, and type of liquid on the volume of spray delivered.

The volume of fluid delivery in milliliters was determined from 1400 to 2800 p.s.i. nozzle pressure in 140 p.s.i. pressure increments. The tip orifice sizes varied from 0.023 cm. (0.009 in.) to 0.053 cm. (0.021 in.) in diameter. All experiments were conducted in an air conditioned room at approximately 25° and 30–40% relative humidity.

Three-second fluid spray delivery cycles were used, and five replicate samples of each liquid under study were collected, at each pressure and nozzle tip size, in a 100-ml. graduated cylinder; the resulting volumes were recorded.

Spray Pattern Characteristics—Spray patterns were determined for the liquids studied, each containing 1% (w/v) FD&C Red No. 2 dye for contrast. The spray from the activated gun of the automated tablet-coating system was directed at a specially designed target which consisted of a 61-cm. square pane of glass with five concentric circles painted 10 cm. apart. The tip of the spray gun was positioned 30 cm. from the glass surface and at the center point of the target. The spray cycle was set for a 0.25-sec. solution delivery. The patterns were subsequently observed at 1400-, 1960-, and 2800-p.s.i. nozzle pressure (the lower, middle, and upper pressure range, respectively) for all tip sizes ranging from 0.023 cm. (0.009 in.) to 0.053 cm. (0.021 in.) in orifice diameter. After each spray, the pattern dimensions were taken and pattern uniformity was noted.

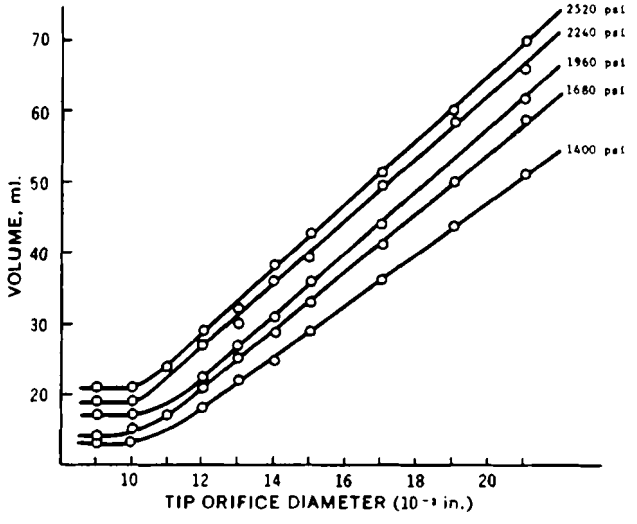


Figure 3—*Change in delivery with respect to change in tip orifice size using water.*

[1] Methocel MC, Dow Chemical Co., Midland, Mich.
[2] Graco Hydro-Spray Unit, Gray Co., Minneapolis, Minn.

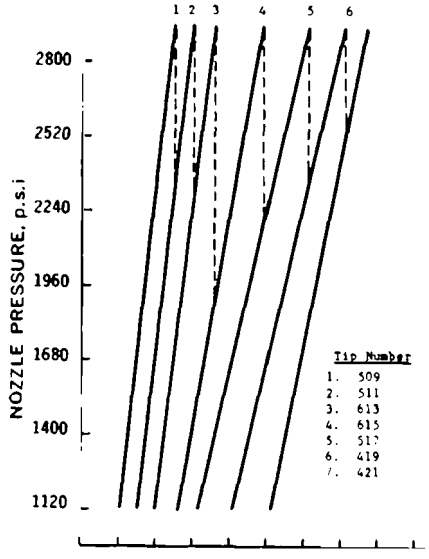


Figure 4—*Fluid delivery curves, 3-sec. cycle.*

RESULTS AND DISCUSSION

Fluid Delivery—The pressure–volume curves in Fig. 1, constructed from fluid delivery data obtained with a 0.023-cm. (0.009-in.) spray tip and a 3-sec. delivery, show that the change in fluid volume delivered as a function of pressure was constant. The curves are representative of some of the liquids studied, and each shows excellent linearity. The rate of change of delivery (Table I) for the liquids represented in Fig. 1 was essentially the same.

A 3–4-ml. difference in total volume delivered at each pressure increment was found between the four liquids studied. These small volume differences do not appear to be significant, but the data show a trend toward a decrease in volume delivered with an increase in fluid viscosity and solids content when comparing syrup and calcium carbonate with water and alcohol. A significant difference would be expected at a much lower or at atmospheric pressure. The data, therefore, indicate that fluid volume delivery is essentially independent of the physical properties of the fluid at very high pressures.

Fluid delivery curves for the three calcium carbonate suspensions, which varied from a "watery" to an "ointment-like" consistency (Fig. 2)[3], are in essence identical and confirm that the elevated pressures used in the study obliterated the effects of the physical properties of the fluids delivered.

In Fig. 3, the volume of water delivered in 3 sec. *versus* tip orifice diameter shows a good linear relationship within the range of 0.030 cm. (0.012 in.)–0.053 cm. (0.021 in.). This finding is unusual because one would expect an orifice–volume relationship based on

Figure 5—*Spray patterns with water. Left: 0.023-cm. (0.009-in.) tip size and 30 × 9-cm. pattern size. Right: 0.053-cm. (0.021-in.) tip size and 40 × 30-cm. pattern size.*

[3] Data points for Fig. 2 were omitted for the purpose of clarity.

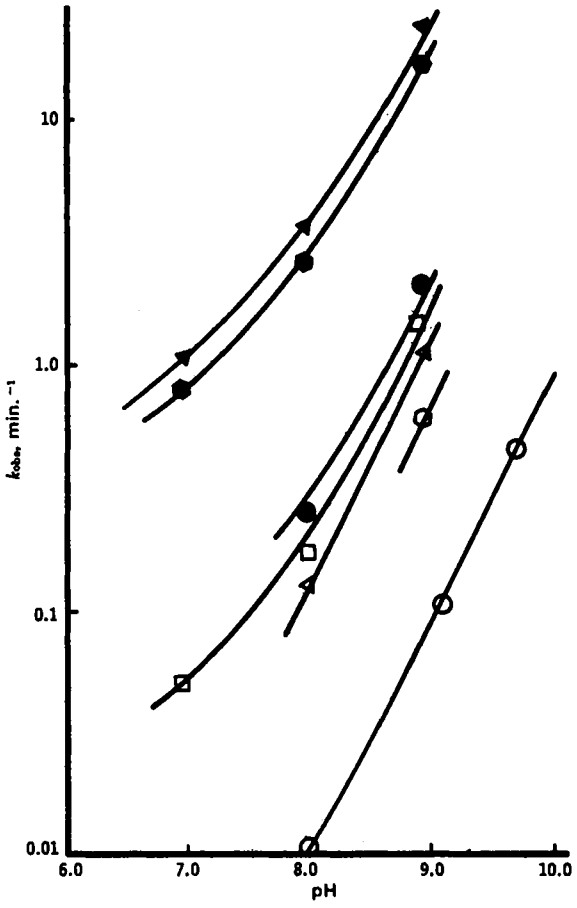


Figure 1—*Plot of log* k_{obs} versus *pH for hydrolysis of* N-*acyl phthalimides. Key:* ○, $R = N(CH_3)_2$[a]; ○, *R = morpholino;* △, $R = C_2H_5$; □, $R = C_2H_5O$; ●, $R = CH_3$; ●, $R = CH_2Br$; *and* ▲, $R = CH_2Cl$. *(For definition of R, see Scheme I.)* ([a]*Unpublished data, T. Higuchi and F. Kametani.*)

(*b*) help disperse any negative charge built up on the nitrogen in the transition state.

Similarly, for the reactions that took place at the *N*-acyl carbonyl, the rates were found to be proportional to the electron-withdrawing power of R, again referring to R in Scheme I.

Effects of R on Reaction Path—If the rates for the attack of base at the phthalimide carbonyls are to be compared to those at the *N*-acyl carbonyl, it is important to consider that there are two phthalimide carbonyls as compared to one *N*-acyl carbonyl. Statistical considerations, therefore, predict that more of the *N*-acyl phthalamic acid would be formed than phthalimide.

Which path (Path I or II) provides the better leaving group could be a matter for further discussion. However, for the task at hand, the route of reaction can be explained on the basis of the susceptibility of the various carbonyl groups to attack by a nucleophile. A close look at the compounds that hydrolyzed *via* Path I revealed a common property. The R group for each of the compounds was electron donating to the *N*-acyl carbonyl; *i.e.*, dimethylamino and morpholino can donate electrons to the *N*-acyl carbonyl by resonance because the amine group possesses a free pair of electrons. Where R is a methyl or an ethyl group, electrons are donated to the *N*-acyl carbonyl by induction. If R is an ethoxy group, a carbamate linkage results. The specific interactions of the R group with the *N*-acyl carbonyl actually change the character of the reaction centers, making the comparison of attack at the phthalimide carbonyls to the *N*-acyl carbonyl difficult. All these R groups deactivate the *N*-acyl carbonyl while, at the same time, as the *N*-acyl group (RCO), they activate the phthalimide carbonyls by being electron withdrawing at those carbonyls.

Phthalimide–acyl cleavage occurs only if the *N*-acyl carbonyl is sufficiently activated by electron-withdrawing R groups, such as $-CH_2Br$ and $-CH_2Cl$, so it can compete with attack at the phthalimide carbonyls. Thus, the product of reaction appears to be determined by susceptibility of the appropriate carbonyl to attack. The slightest activation of the *N*-acyl carbonyl, even by the phenoxymethylene R group (9), has been shown to lead to reaction at the *N*-acyl carbonyl. The idea that the carbonyl activation is the product-determining factor in the hydrolysis of *N*-acyl phthalimides may be best explained in terms of free energy of activation. Electron-withdrawing *N*-acyl groups lower the free energy of activation for Path I. Proportionally, however, there may be greater effect on the free energy of activation for Path II by the changes in R; *i.e.*, for VII, $\Delta G^{\ddagger}_{\text{Path II}} >>> \Delta G^{\ddagger}_{\text{Path I}}$, whereas for III, $\Delta G^{\ddagger}_{\text{Path II}} > \Delta G^{\ddagger}_{\text{Path I}}$. For V and VI, $\Delta G^{\ddagger}_{\text{Path I}} \gg \Delta G^{\ddagger}_{\text{Path II}}$, thus predicting that compounds like *N*-(phenylacetyl)phthalimide with a poor electron-withdrawing R group should degrade *via* Paths I and II, *i.e.*, both pathways being detectable.

In summary, chemical modification of imides through *N*-acylation requires a detailed study of the products of the *in vitro* hydrolysis because it cannot be assumed that the product will be the parent imide. This study has shown that *N*-acylated imides, when hydrolyzed, can regenerate the parent imide if the *N*-acyl carbonyl is sufficiently activated to compete with possible reaction at the imide carbonyls.

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