129064-86-4; (±)-**3a** mesylate, 129064-88-6; (±)-**3b**, 129064-91-1; (±)-**3b** ketal mesylate, 129064-87-5; (±)-**3b** mesylate, 129064-89-7; (+)-**4**, 129170-66-7; (−)-**4**, 102735-38-6; (±)-**4**, 129170-63-4; (+)-**5**, 103664-42-2; (−)-**5**, 103664-41-1; (±)-**5**, 85316-65-0; (+)-**6**, 102735-37-5; (−)-**6**, 129170-70-3; (±)-**6**, 129170-64-5; (+)-**7**, 129170-69-0; (−)-**7**, 129170-68-9; (±)-**7**, 129170-65-6; (+)-**8**, 93226-49-4; (−)-**8**, 35119-44-9; (±)-**8**, 14400-75-0; (+)-nor-**8**, 501-37-1; (−)-nor-**8**, 34429-56-6; (+)-**9**, 5487-32-1; (−)-**9**, 129170-73-6; (±)-**9**, 104048-27-3; (+)-nor-**9**, 588-39-6; (−)-nor-**9**, 129170-72-5; (+)-**10**, 79827-61-5; (−)-**10**, 35119-38-1; (±)-**10**, 2209-03-2; (+)-nor-**10**, 129170-71-4; (−)-nor-**10**, 645-38-5; (−)-**11**, 129064-92-2; (+)-**12**, 129064-93-3; (−)-**13**, 129064-94-4.

The E1cB Mechanism in the Alkaline Hydrolysis of *N,N*-Diethyl-*P*-(3,5-dimethyl-4-hydroxyphenyl)phosphonamidic Chloride

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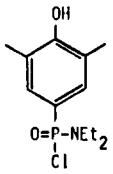
The alkaline hydrolysis of the title compound **1** proceeds via an E1cB mechanism. A tricoordinate phosphorus species intermediate **3**, or a metaphosphate-like transition state, constitutes the best hypothesis accounting for the observed kinetic results. The apparent bimolecular rate constant for the attack of hydroxide ion on the neutral 4-hydroxy-substituted chloride (k_aK_a/K_w) is more than 5 orders of magnitude larger than the true bimolecular rate constant for the attack of HO^- on the corresponding *methoxy* chloride **2** which possesses the $S_N2(P)$ mechanism. Support of the E1cB mechanism proposed for **1** comes also from activation entropy studies and by the effect of added nitrogen nucleophiles on reaction rates.

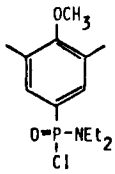
Recent work from this laboratory on acyl and sulfonyl transfer reactions has shown that aryl 4-hydroxybenzoates[1] and 4-hydroxyarenesulfonates[2] hydrolyze in moderately alkaline solutions via an E1cB mechanism involving *p*-oxoketene and sulfoquinone intermediates respectively.

In the light of the considerable biochemical significance of phosphate esters and related compounds,[3] we extended our investigations to the phosphoryl transfer reactions. Indeed, it is well known[4] that a number of such processes takes place through dissociative mechanisms, although the question of the occurrence of the monomeric metaphosphate ion (or its analogues) as an intermediate is still open.[5]

Now we report our preliminary results on the alkaline hydrolysis of *N,N*-diethyl-*P*-(3,5-dimethyl-4-hydroxyphenyl)phosphonamidic chloride (**1**) and *N,N*-diethyl-*P*-(3,5-dimethyl-4-methoxyphenyl)phosphonamidic chloride (**2**).[6]



(1)



(2)

Results and Discussion

The chloride **1** was prepared by reacting the dilithium compound obtained from 2,6-dimethyl-4-bromophenol and butyllithium with *N,N*-diethylphosphoramidic dichloride in anhydrous ether at room temperature. The reaction mixture, after the usual workup, was repeatedly chromatographed on silica gel, affording the pure product as a clear liquid. Reaction of **1** with diazomethane gave **2** as a pale yellow liquid. The identity of both **1** and **2** was assessed by ^1H NMR spectroscopy and by conversion into the corresponding 2′,4′-dinitrophenyl esters, which gave excellent elemental and spectroscopic analyses.

Results are summarized in the pH–rate profiles shown in Figure 1 (individual rate constants are given in the supplementary material). The reactions were followed spectrophotometrically by monitoring the decrease in absorbance due to the disappearance of the substrate. As it is known that in the acidic hydrolysis of phosphoroamidochloridates and phosphorodiamidic chlorides P–N bond fission may follow P–Cl bond cleavage,[7] we have checked the identity of the reaction taking place by ^1H NMR spectroscopy. We have observed that the multiplicity due to the P–N–C–H coupling of the nonequivalent methylenic hydrogen atoms of **1** disappeared upon acid hydrolysis (see the Experimental Section) whereas it was retained after alkaline hydrolysis: this fact clearly demonstrates that the P–N bond is not involved in the latter reaction.

In the pH range (7.3–14) employed, rates of hydrolysis were accurately pseudo-first-order over at least 90% of the total reaction (at pH <7 the reaction did not follow first-order kinetics any more, probably owing to the merging P–N bond fission) and depended on pH according to the rate laws 1 and 2 for compounds **1** and **2**, respectively, where K_a is the ionization costant of the phenolic group of **1**. The spectrophotometric K_a value [$K_a = (4.56 \pm 0.08) \times 10^{-9}$ M] was in good agreement with the kinetic

$$k_{obs} = [(k_o a_H/K_a) + k_a]/(1 + a_H/K_a) \quad (1)$$

$$k_{obs} = k'_o + k_b[OH^-] \quad (2)$$

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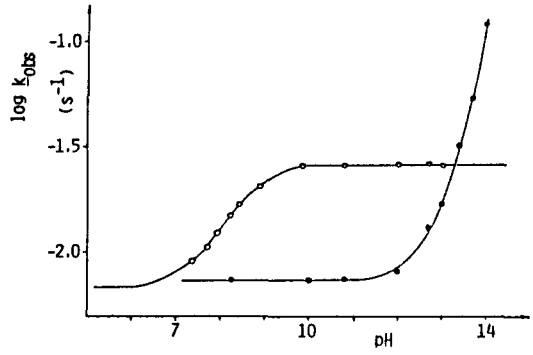

Figure 1. Plots of log k_{obs} (aqueous solutions, 25 °C, ionic strength made up to 1 M with potassium chloride) for the hydrolysis of compounds 1 and 2 (open and closed circles, respectively) versus pH. Curves are theoretical from eqs 1 and 2, and the values of the parameters are reported in the text.

one. Usual mathematical treatment of data gave the following rate costant values:

$$k_o = (7.3 \pm 0.1) \times 10^{-3}\ s^{-1}$$

$$k_a = (2.53 \pm 0.02) \times 10^{-2}\ s^{-1}$$

$$k'_o = (7.1 \pm 0.2) \times 10^{-3}\ s^{-1}$$

$$k_b = (9.54 \pm 0.08) \times 10^{-2}\ M^{-1}\ s^{-1}$$

Mechanistic studies on the hydrolysis of phosphinyl chlorides[8] and phosphorodiamidic chlorides,[7,9] and on the aminolysis of phosphonamidic chlorides in aprotic media,[10] have shown that these reactions occur through associative, $S_N2(P)$ mechanisms when no labile hydrogens are α to phosphorus. Accordingly, we infer that k'_o and k_b refer to nucleophilic attack of water and hydroxide ion respectively onto the phosphorus atom of **2**.[9]

The hydrolysis of **1** exhibits different features: as shown in Figure 1, k_{obs} at first increases as the pH increases and then becomes constant after ionization of the phenolic group has occurred. It is quite likely that also the rate constant k_o refers to nucleophilic attack of water on **1** itself, since it is almost identical in value to k'_o. In contrast, the apparent bimolecular rate constant (k_aK_a/K_w = 11 540 M^{-1} s^{-1}) for attack of hydroxide ion on the neutral substrate is 5 orders of magnitude larger than the k_b constant related to the chloride **2**. Such a high reactivity ratio cannot be accounted for by simple substituent effects, and we believe it represents good evidence in favor of the intervention of a different mechanism operating in the case of the chloride **1**. The most reasonable hypothesis is that an E1cB process occurs, involving either the tricoordinate intermediate **3** or a "borderline", metaphosphate-like transition state.[5] In this mechanism (Scheme I), the ionization of the hydroxy group of the substrate (K_a) is a prerequisite for the unimolecular elimination of chloride ion from the conjugate base (k_a) in the rate-determining step, the driving force for this pathway being the presence of a very good leaving group coupled with a suitably high "internal" nucleophilicity of the substrate.

As expected for a $S_N2(P)$ process,[8,9] we have found that at pH 12 addition of ammonia (in the concentration range 6.6 × 10^{-3} to 6.6 × 10^{-2} M) markedly speeds up the decomposition of **2** according to the rate law:

$$k_{obs} = (7.71 \pm 0.07) \times 10^{-3} + (0.135 \pm 0.02)\ [NH_3]$$

Scheme I

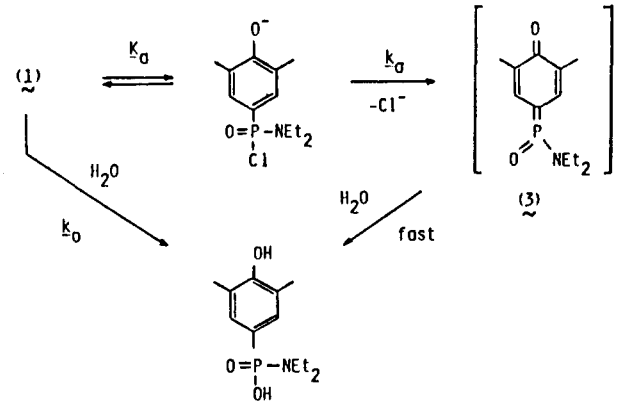

Table I. Activation Parameters for the Hydrolysis of the Chlorides 1 at pH 12.7 and 2 at pH 10.8

chloride	$\Delta H^{\ddagger}$, Kcal/mol	$\Delta S^{\ddagger}$,[a] cal/mol K	temp range, °C
1	16.6 ± 0.1	−10.1 ± 0.2	18.6–37.3
2	14.4 ± 0.1	−20.0 ± 0.3	15.5–36.6

[a] Calculated at 25 °C.

On the contrary, neither ammonia nor benzylamine accelerate the decomposition of **1** at the same pH, consistent with an elimination–addition mechanism. TLC experiments were unable to provide clear-cut evidence in favor of the formation of an amide product in the runs carried out in the presence of benzylamine. This fact can be reasonable explained on the basis of the very low selectivity toward nucleophiles of an intermediate like **3**, which is expected to be quite reactive.

The activation parameters for the reactions of hydrolysis of the chlorides are reported in Table I.

The value of the entropy of activation for the hydrolysis of **2** at pH 10.8 is well within the range expected for a $S_N2(P)$ mechanism. In the case of the chloride **1** the activation entropy for the hydrolysis at pH 12.7 is considerably less negative and, therefore, it seems more consistent with a unimolecular mechanism than with a bimolecular one. This $\Delta S^{\ddagger}$ value, moreover, could be only a lower limit to the actual one, possibly because of the contribution to the observed rate of a hydrolytic pathway consisting in the nucleophilic attack of a water molecule on the ionized substrate. Indeed, perusal of k_o and k'_o values indicates that the rate of the associative route is hardly affected by the substituents in the aromatic ring; this observation and literature data on related systems[11] suggest that reaction flux through this hydrolytic way could be as high as 30% of the whole.

In conclusion, we infer that the hydrolysis of **2** follows the expected $S_N2(P)$ mechanism, whereas in the case of **1** a different mechanism is operating. As above proposed, this mechanism could involve either the tricoordinate phosphorus species **3** as an intermediate or a metaphosphate-like transition state. On the basis of the present results no definitive conclusion on the existence along the reaction pathway of the intermediate **3** can be drawn, further kinetic as well as stereochemical information being required to shed more light on this question. Nevertheless, our results strongly suggest for the first time, at the best of our knowledge, the incursion of a dissociative mecha-

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nism in the hydrolysis of a phosphacyl[8] derivative devoid of α-protons.

Experimental Section

General. All starting reagents and solvents were purified and/or distilled before use. Buffer materials were analytical reagent grade. Water was double distilled and preboiled to free it from dissolved gases. Dioxan was purified by passage of the analytical grade material through an activated alumina column.

***N,N*-Diethyl-*P*-(3,5-dimethyl-4-hydroxyphenyl)-phosphonamidic Chloride (1).** A solution of 2,6-dimethyl-4-bromophenol[12] (4.2 g, 20 mmol) in dry ether (25 mL) was treated with *n*-butyllithium (25 mL, 1.6 M solution in hexane, 40 mmol) at 0 °C under nitrogen. The resultant cloudy solution was stirred at room temperature for 18 h, again cooled at 0 °C, and treated with *N,N*-diethylphosphoramidic dichloride[13] (3.8 g, 20 mmol) dissolved in dry ether (5 mL). The reaction mixture was allowed to warm to room temperature; after 24 h aqueous ammonium chloride (50 mL, saturated) was added, and the separated organic layer was washed sequentially with aqueous HCl (4%, 25 mL) and water (25 mL). The organic layer was dried over sodium sulfate and filtered, and the solvent was removed under reduced pressure. Column chromatography (E. Merck silica gel 60, 1:1 methylene chloride–ethyl acetate) of the resulting yellow oil allowed isolation of 1.5 g (28% yield) of the chloride as a pale yellow liquid. A small portion of this liquid was further chromatographed on a preparative TLC plate (E. Merck silica gel 60), affording the pure product: ^{1}H NMR ($CDCl_3$, TMS) δ 7.44 (d, J_{HP} = 14.9 Hz, 2 h, ArH), 3.15 (m, 4 H, NCH_2CH_3), 2.25 (s, 6 H, $ArCH_3$), 1.12 (t, J = 7.1 Hz, 6 H, NCH_2CH_3). The identity of the product was also confirmed by converting it, through standard methods, into **2',4'-dinitrophenyl *N,N*-diethyl-*P*-(3,5-dimethyl-4-hydroxyphenyl)phosphonamidate,** which had mp 133–4 °C (petroleum ether). Anal. Calcd for $C_{18}H_{22}N_3O_7P$: C, 51.1; H, 5.2; N, 9.9. Found: C, 51.5; H, 5.3; N, 9.8.

***N,N*-Diethyl-*P*-(3,5-dimethyl-4-methoxyphenyl)-phosphonamidic Chloride (2).** This compound was obtained by allowing the chloride **1** to react, for 48 h at room temperature in dry ether, with diazomethane (generated with the aid of the Aldrich Diazald Kit). The resultant yellow solution was evaporated under reduced pressure, affording a light yellow liquid. Preparative TLC (E. Merck silica gel 60, 1:1 methylene chloride–ethyl acetate) provided the pure product: ^{1}H NMR ($CDCl_3$, TMS) δ 7.53 (d, J_{HP} = 15 Hz, 2 H, Ar*H*), 3.75 (s, 3 H, OCH_3), 3.16 (m, 4 H, NCH_2CH_3), 2.32 (s, 6 H, $ArCH_3$), 1.13 (t, J = 7.1 Hz, 6 H, NCH_2CH_3). Again, the identity of the product was assessed by conversion into **2',4'-dinitrophenyl *N,N*-diethyl-*P*-(3,5-dimethyl-4-methoxyphenyl)phosphonamidate,** mp 124–5 °C (petroleum ether). Anal. Calcd for $C_{19}H_{24}N_3O_7P$: C, 52.2; H, 5.5; N, 9.6. Found: C, 52.0; H, 5.6; N, 9.5.

Products Analysis. (a) Alkaline Hydrolysis. The NMR spectra of both the chlorides **1** and **2** (15 mg) in a 1:1 acetone-d_6/deuterium oxide mixture (0.5 mL) were recorded, and then these solutions were made alkaline by adding few microliters of NaOD ca. 14 M in D_2O, and several spectra of the resulting solutions were taken at different times. **(b) Acidic Hydrolysis.** To fresh solutions of the chlorides in the deuterated mixture was added a few microliters of DCl 37% in D_2O, and again several NMR spectra were recorded at different times.

Kinetics. All kinetic measurements were done spectrophotometrically by recording the decrease in absorbance at either 277 or 236 nm due to the disappearance, respectively, of the chlorides **1** and **2**. In a typical run, the buffered solution (2.5 mL) was allowed to equilibrate to the required temperature in a 1-cm path length quartz cell placed in the thermostatted cell holder of the spectrophotometer. The reaction was initiated by adding an aliquot (10 μL) of the stock solution of the chloride (ca. 10^{-2} M) in dioxane. Reactions were usually followed over about 7 half-lives. The pH of the reactant buffers were measured before and after the reaction at the appropriate temperature. No buffer concentration effects were observed on the rates of hydrolysis of chloride **1** in the range of buffer concentrations employed (0.01–0.1 M). In the case of chloride **2** small effects were observed, and the rate constants at zero buffer concentration were obtained by extrapolation. The ionic strength was maintained at 1 M with potassium chloride. The pseudo-first-order rate constants were calculated on an Apple IIe PC with a program written by one of us (S.T.). The activation parameters were determined measuring the rates of hydrolysis at three temperatures (see Table I).

Registry No. 1, 129835-85-4; 2, 129835-86-5; 2,6-dimethyl-4-bromophenol, 2374-05-2; *N,N*-diethylphosphonamidic acid, 1498-54-0; 2',4'-dinitrophenyl *N,N*-diethyl-*p*-(3,5-dimethyl-4-hydroxyphenyl)phosphonamidate, 129835-87-6; 2',4'-dinitrophenyl *N,N*-diethyl-*p*-(3,5-dimethyl-4-methoxyphenyl)phosphonamidate, 129835-87-6.

Supplementary Material Available: Two tables reporting observed rate constants for the hydrolysis of the substrates (2 pages). Ordering information is given on any current masthead page.

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Ring Contraction of 1,2,4-Triazepino[2,3-*a*]benzimidazol-4-ones. New Fused β-Lactams

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Isolation of uncommon fused tetracyclic β-lactams **2** strongly supports a previously unconfirmed ionic mechanism for the ring contraction of nitrogen-bridged azolo-1,2,4-triazepin-3-ones in acetic anhydride. Procedures for the synthesis in good yields of substituted-pyrazolo[1,5-*a*]benzimidazoles from the corresponding [1,2,4]triazepino[2,3-*a*]benzimidazoles are reported.

Introduction

Gehlen and Drohla reported for the first time in 1970 the reaction between nitrogen-bridged triazepinones derived from 1,2-diamino-1,3,4-triazoles and ethyl acetoacetate in acetic anhydride solution. Two alternative structures, imidazo[2,1-*c*]-*s*-triazole or imidazo[1,2-*b*]-*s*-triazole, were proposed for the reaction products.[1] Four years later, Claramunt et al. firmly established that those ring-contraction products were pyrazolo[3,2-*c*]-*s*-triazoles and were, consequently, able to give the correct structure

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