Association Phenomena. 7. Mixed Chelate and Comicellar Catalysis of Acetyl Phosphate "Olysis" Reactions

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Abstract: The decomposition of acetyl phosphate has been studied under conditions designed to catalyze the process via a combination of mixed chelate and comicelle formation. In the presence of *n*-dodecylamine under micelle-forming conditions, the rate of decomposition is increased by a factor of 275, the optimum pH for the catalysis being 8.5. In the presence of the polyamide 1-undecyl-*N,N'*-bis[2-(hydroxyimino)propanoyl]ethylenediamine (**7**) and the metal ions Zn^{2+}, Cu^{2+}, and Ni^{2+}, the rate of decomposition is increased by factors of 60–140 at pH 11.5 where compound **7** exists in the hydroxamate form. The kinetics of the latter process have been measured and found to be first-order throughout the reaction, indicating that compound **7** acts as a catalyst for the *overall* process of hydrolysis. The inclusion of *n*-hexanol or *n*-octylamine in the system, in the hope that comicellization would induce transfer of the acetyl group from the phosphate to the alcohol or amine, failed to yield positive results.

The catalysis of the decomposition of acetyl phosphate by amine–ammonium micelles, chelate micelles, and metal-chelated polyamines and polyamides containing nucleophilic moieties was the subject of a pair of earlier papers in this series.[1,2] The purpose of the present paper is (a) to expand on this earlier work by carrying out a more careful investigation of the amine–ammonium micelle catalysis to determine the optimum pH for the process and (b) to synthesize a polyamide containing a nucleophilic moiety and a long hydrocarbon chain which will imbue the compound with micelle-forming properties, the capacity for forming mixed chelates with metals and acetyl phosphate, and the possibility for effecting polyfunctional catalysis.

Amine–Ammonium Micelle Catalysis. Melhado and Gutsche[1] discovered that the rate of acetyl phosphate decomposition is greatly enhanced by *n*-dodecylamine, which forms micelles, and is unaffected by *n*-butylamine, which does not form micelles. They observed a considerably greater enhancement by *n*-decylamine at pH 8 than at pH 7 or 9, indicating that the optimum falls somewhere in this region. To determine more precisely where it occurs, these experiments were repeated and measurements have been taken at 0.5 pH intervals. The results, recorded in Table I,[3] show that at pH 8.5, the rate is appreciably greater than at pH 8.0 or 9.0. The data also show that the ionic strength has a considerable effect on the rate of micelle-induced catalysis, higher ionic strengths resulting in lower rates of acetyl phosphate decomposition.

Attempts to demonstrate comparable catalysis with tertiary amines were unsuccessful. *N,N*-Dimethyldodecylamine had essentially no effect on the rate of decomposition of acetyl phosphate over the pH range 6–8, the rates varying from 2.9×10^{-3} to 4.0×10^{-3} min^{-1}. Similarly, 4-undecylpyridine exerted no significant catalysis over the pH range 4.3–9, showing a rate of 13.0×10^{-3} min^{-1} at pH 4.3, falling off to a rate of 6.2×10^{-3} min^{-1} at pH 5.0 and 3.0×10^{-3} min^{-1} at pH 9.0. The slight rate enhancement at pH 4 is not due to micellar catalysis but to the fact that at this pH, the concentration of acetyl phosphate monoanion is increased.

In the thought that the low solubility of the unprotonated forms of *N,N*-dimethyldodecylamine and 4-undecylpyridine might be responsible for their failure to show any significant catalysis of acetyl phosphate decomposition, a series of experiments in mixed micellar systems was carried out by using cetyltrimethylammonium bromide (CTAB) as a comicellar reagent. Although *N,N*-dimethyldodecylamine and 4-undecylpyridine remained soluble in 0.025 M CTAB over the pH ranges studied, no catalysis of acetyl phosphate decomposition was observed. In fact, with *N,N*-dimethyldodecylamine and CTAB, the rate was slightly lower than in the absence of CTAB. Two other comicellar experiments using CTAB were also investigated, one involving dodecanethiol and the other dodecanal oxime. Neither of these compounds showed any influence on the rate until pH levels above 10 were reached, where the concentration of the thiolate and oximate species becomes important and where catalysis by hydroxide also becomes significant. Attention was then refocused on the initial dodecylamine experiment, and the effect of CTAB on the catalysis of acetyl phosphate decomposition by this reagent was explored. Surprisingly, it was found that the rates are appreciably lower in the presence of CTAB, as indicated by the data in Table II. This decrease might be attributed to the more diffusely distributed charge of CTAB as compared with that of the dodecylammonium ion, with the result that acetyl phosphate binds less tightly in the

Table I. Rate of Acetyl Phosphate Decomposition in the Presence of *n*-Dodecylamine as a Function of pH and Ionic Strength

pH	ionic strength	rate const, 10^{-3} min^{-1}	relative rate[a]
7.0	0.035	32 ± 1	
	0.05	36 ± 1	9
	0.30	32 ± 1	
7.5	0.05	100 ± 1	25
8.0	0.035	760 ± 10	
	0.05	760 ± 10	190
	0.15	650 ± 25	
8.5	0.05	1100 ± 70	275
9.0	0.035	530 ± 20	
	0.05	530 ± 10	133
	0.15	180 ± 9	
9.5	0.05	218 ± 1	55

[a] The uncatalyzed rate of acetyl phosphate hydrolysis[3] was determined to be $4.0 \pm 0.2 \times 10^{-3}$ min^{-1}.

Table II. Effect of 0.025 M Cetyltrimethylammonium Bromide (CTAB) on the Catalytic Activity of 0.025 M Dodecylamine in the Decomposition of Acetyl Phosphate

	rate const, 10^{-3} min^{-1}		relative rate const	
pH	with CTAB	without CTAB	with CTAB	without CTAB
7.0	30 ± 1	36 ± 1	8	9
8.0	206 ± 26	760 ± 60	52	190
8.5		1100 ± 106		273
9.0	112 ± 0	530 ± 40	28	133
9.5		218 ± 10		55
10.0	62 ± 7		16	
11.0	31 ± 2		8	

(1) Melhado, L. L.; Gutsche, C. D. *J. Am. Chem. Soc.* **1978**, *100*, 1850.
(2) Lau, H.-p.; Gutsche, C. D. *J. Am. Chem. Soc.* **1978**, *100*, 1857.
(3) The reported values are 4.3×10^{-3} min^{-1} (DiSabato, G.; Jencks, W. P. *J. Am. Chem. Soc.* **1961**, *83*, 4393, 4400), 4.0×10^{-3} min^{-1} (Whitesides, G. M.; Siegel, M.; Garrett, P. *J. Org. Chem.* **1975**, *40*, 2516), and 3.8×10^{-3} min^{-1} (Koshland, D. E. *J. Am. Chem. Soc.* **1952**, *74*, 2286).

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Table III. Effect of 0.005 M Metal Ions on the Rate of Acetyl Phosphate Decomposition at 40 °C, pH 6

metal ion	rate const, 10^{-3} min^{-1}	relative rate
Cu^{2+}	4.4 ± 1	1
Zn^{2+}	4.4 ± 1	1
Ni^{2+}	5.1 ± 1	1.2

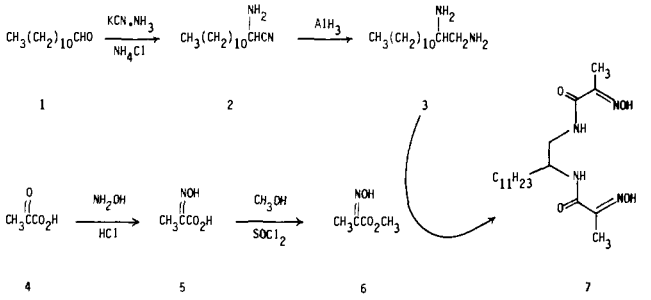
Table IV. Effect of 0.005 M **7**, 0.025 M CTAB, and 0.005 M Metal Ion on the Rate of Decomposition of Acetyl Phosphate at 40 °C and pH 11

metal ion	rate const, min^{-1}	relative rate
none	0.045 ± 0.002	11
Zn^{2+}	0.562 ± 0.049	140
Cu^{2+}	0.430 ± 0.025	108
Ni^{2+}	0.240 ± 0.025	60

dodecylamine–CTAB comicelle. It might also be attributed to a reduction of the concentration of the unprotonated form of dodecylamine in the comicelle as a result of the presence of CTAB.

Catalysis by 1-Undecyl-*N*,*N*′-bis[2-(hydroxyimino)propanol]-ethylenediamine (7). The earlier work of Melhado, Lau, and Gutsche[1,2] showed that (a) a modest degree of micellar catalysis of acetyl phosphate decomposition is observed with triethylenetetramine carrying a long hydrocarbon side chain and (b) a nucleophile attached to the polyamine or polyamide chelator is capable of intramolecular nucleophilic assistance. Both of these features are combined in compound **7**, which was synthesized in the following manner. Treatment of dodecanal with KCN, ammonium chloride, and HCl in an aqueous solution afforded 2-aminotridecanenitrile (**2**) which was reduced to 1,2-tridecanediamine (**3**) with aluminum hydride. The procedure of Lau and Gutsche[2] was use for the remaining steps and involved the interaction of the diamine **3** with methyl 2-oximinopropanoate (**6**), prepared by the action of MeOH and $SOCl_2$ on 2-oximinopropanoic acid (**5**). The white crystalline product showed a single TLC spot, possessed ^1H NMR and IR spectra compatible with the assigned structure, and had the correct elemental analysis.

Experiments with compound **7** in neutral aqueous solution are limited by its very low solubility. Even in the presence of 0.025 M CTAB, a 0.005 M solution remains cloudy. Upon adjusting the pH to 11.5, however, a clear solution is obtained as a result of the ionization of the hydroxyimino groups. When the concentration of **7** is doubled, the solution remains clear but it becomes viscous, possibly the result of a phase transition in which globular micelles change to cylindrical micelles. Addition of metal ions



to these solutions results in chelate formation in some instances, as indicated by color changes as well as the fact that no precipitates are formed. In the absence of compound **7**, the metal ions Zn^{2+}, Ni^{2+}, and Cu^{2+} form insoluble metal oxides at pH 11.5. Addition of Mn^{2+} to a solution of **7** at pH 11.5, however, results in a precipitate of MnO_2.

To study the combined effect of metals and **7** on the decomposition of acetyl phosphate, the effect of metals alone was first determined. The results, shown in Table III, indicate that Cu^{2+}, Zn^{2+}, and Ni^{2+} have essentially no effect on the rate of hydrolysis at pH 6, this pH being chosen because the metal hydroxides precipitate in more basic solution. Whether it is safe to extrapolate this result to pH 11.5 is unclear, because it is possible that OH groups coordinated to the metal at higher pH levels might play

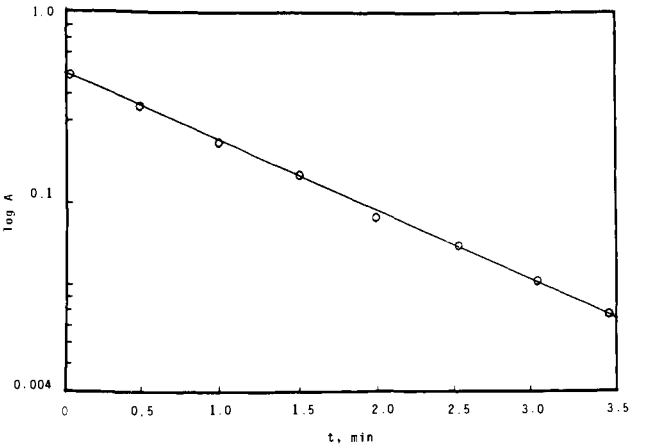


Figure 1. Rate of decomposition of acetyl phosphate in the presence of 0.0025 M **7**, 0.25 M CTAB, and 0.0025 M Zn^{2+} at 40 °C.

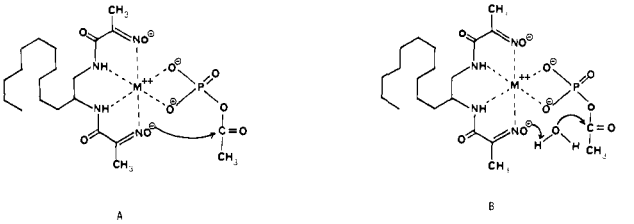


Figure 2. Catalysis of hydrolysis of acetyl phosphate by compound **7**.

Table V. Effect of 0.025 M *n*-Hexanol, *n*-Octylamine, or *n*-Butylamine on the Rate of Acetyl Phosphate Decomposition in the Presence of 0.005 M **7**, 0.025 M CTAB, and 0.005 M Metal Ions at 40 °C and pH 11.5

metal ion	added nucleophile	rate const, min^{-1}	relative rate
none	*n*-hexanol	0.046 ± 0.01	11.0
Zn^{2+}	*n*-hexanol	0.553 ± 0.051	138
Cu^{2+}	*n*-hexanol	0.420 ± 0.04	105
Ni^{2+}	*n*-hexanol	0.237 ± 0.01	59.3
Zn^{2+}	*n*-octylamine	0.130 ± 0.015	32.5
Cu^{2+}	*n*-octylamine	0.107 ± 0.009	26.8
Ni^{2+}	*n*-octylamine	0.063 ± 0.006	15.8
Zn^{2+}	*n*-butylamine	0.121 ± 0.008	30.3
Cu^{2+}	*n*-butylamine	0.110 ± 0.010	27.5
Ni^{2+}	*n*-butylamine	0.058 ± 0.004	14.5

a part in the hydrolysis process. With CTAB and compound **7** in the absence of metal ions, only a modest enhancement in the rate of decomposition was observed, while with CTAB and compound **7** in the presence of metals considerably more significantly rate enhancements occurred, as shown in Table IV.

In all cases, first-order kinetics were observed, as illustrated by Figure 1. Since the initial concentrations of acetyl phosphate and metal ion (which is assumed to form the metal–**7** complex) are the same, this kinetic result indicates that the catalyst is not consumed in the reaction. The mechanistic pathway that we have assumed for this system is that suggested by Breslow and Malmin[4] for the decomposition of acetyl phosphate in the presence of a chelated oxime. They postulated that an acyl transfer to the oxime oxygen occurs, followed by rapid hydrolysis of the oxime acetate, as illustrated in Figure 2A.

Compound **7**, acting as a catalyst under the conditions described above, can be considered to be a phosphatase mimic, catalyzing the transfer of the acetyl group from acetyl phosphate to water. The ultimate goal of this project, as stated in earlier papers,[1,2] is to devise an acyl-transfer mimic wherein the acetyl group becomes attached to a nucleophile other than water. Attempts to achieve this result with the present system, however, have been

(4) Malmin, J. E. Ph.D. Thesis, Columbia University, New York, 1969. Breslow, R. *Adv. Chem. Ser.* **1971**, *No. 100*, 21.

unsuccessful. A reaction mixture containing compound **7**, metal ions, CTAB, and *n*-hexanol showed little change in rate of decomposition as a result of the addition of alcohol, as shown in Table V; analysis of the product gave no evidence for the formation of hexyl acetate. Similarly, the addition of *n*-octylamine or *n*-butylamine to the system failed to yield any amide, and the rates of acetyl phosphate decomposition were actually somewhat reduced. It is postulated that the reduction in rate is the best of the competition between the amines and the phosphate for the coordination sites in the chelate. The failure to observe acetyl transfer to the added nucleophiles might be due to (a) a failure to form any of the mixed micelle, (b) formation of a mixed micelle in which the added nucleophile is not proximate to the acylated hydroxyimino function, or (c) a reaction pathway different from that depicted in Figure 2A, viz., the one depicted in Figure 2B in which the oxime abstracts a proton from an appropriately positioned water molecule, thereby generating hydroxide in the vicinity of the acetyl phosphate and liberating acetic acid directly without the formation of an acyl intermediate; such a pathway would appear to foreclose the possibility of the system operating as an acetyl-transfer mimic.

Experimental Section[5]

Dilithium acetyl phosphate was prepared by the general method of Stadtman and Lipmann[6] as modified by Kurz.[7] A 200-mL sample of isopropenyl acetate was cooled in an ice bath, and 25 mL of 85% phosphoric acid was added dropwise (2 drops/s) with stirring over a period of 20 min. Sulfuric acid (1 mL) was added as a catalyst, the temperature of the stirred mixture was kept at 23–28 °C, and after 40 min the orange reaction mixture was cooled in a dry ice–acetone bath and cautiously treated with 50 mL of ice-cold water (temperature maintained at ca. 0 °C). The pH was adjusted to ca. 5 by the addition of 100 mL of freshly prepared 4 N LiOH solution, this process being carried out as rapidly as possible (ca. 15 min) while maintaining the temperature close to 0 °C. Enough water was then added to bring the volume to 500 mL, and the mixture was extracted 3 times with ether to remove the excess isoprenyl acetate. The aqueous layer was separated, the pH was adjusted to 8 with 4 N LiOH, and the Li_3PO_4 was precipitated by centrifugation at 2000 rpm for 15 min. The clear supernatant was decanted, treated with five volumes of 95% EtOH, and the lithium acetyl phosphate was precipitated by centrifugation. The supernatant was discarded, and the white precipitate was suspended in absolute EtOH and again collected by centrifugation. The above process was repeated several times, and finally anhydrous ether was used in place of EtOH. The ether was removed by decantation, and the white precipitate was dried out under vacuum over P_2O_5 in a desiccator. This crude product was purified by fractional precipitation, as described by Stadtman and Lipmann,[6] to give a 50% recovery of material with a purity of 97–99%.

2-Aminotridecanenitrile (2). To a 2-L round-bottomed flask fitted with a magnetic stirrer and a pressure-compensated addition funnel was added 65.1 g of NH_4Cl, 71.6 g of KCN, 430 mL of water, and 1170 mL of 28% aqueous ammonia. To the stirred solution, 200 g of dodecanal (**1**) was added dropwise over a period of 30 min, during which time the temperature rose to 34 °C and then fell back to room temperature. The reaction mixture was treated with 200 mL of ether and stirred for 6 h to dissolve the white precipitate that had formed. The ether layer was separated, and the aqueous layer was extracted several times with ether. The combined ethereal extract was concentrated to ca. 500 mL and cooled to 10 °C, and the precipitate that formed was removed by filtration. This was washed with petroleum ether and dried overnight to yield 200 g (76%) of crude product which appeared to be a single material on TLC analysis. A 30-g sample of this material was pulverized and dissolved in 400 mL of water to which 50 mL of ether was added to aid the dissolution and prevent foaming. To the clear solution, 60 mL of 50% NaOH was added, with stirring, and the solution was then extracted 3 times with 300-mL portions of ether. The combined etheral extract was dried and evaporated to yield a solid showing a single spot on TLC: ^{1}H NMR (CCl_4) δ 0.8 (3, t), 1.25 (2, b, OH), 2.25 (2, s), 3.6 (1, m); IR (neat) 1475, 1370, 1140, 800–900, 725 cm^{-1}. Anal. Calcd for $C_{13}H_{27}N_2Cl$: C, 63.29; H, 10.95; N, 11.36. Found: C, 63.73; H, 11.19; N, 11.80.

1,2-Tridecanediamine (3). To a 1-L three-necked, round-bottomed flask equipped with reflux condenser, mechanical stirrer, and addition funnel 10.65 g of lithium aluminum hydride and 500 mL of THF were added. The stirred mixture was cooled to 0 °C and treated with 13.03 g of 100% sulfuric acid added dropwise over a period of 15 min. The solution was vigorously stirred for 1 h, and a solution of 23.3 g of 2-aminoundecanenitrile in 35 mL of THF was added over a period of 30 min. The excess hydride was destroyed by slow addition of 1:1 THF/H_2O to the cooled reaction mixture, and 150 mL of a 10% solution of NaOH was added to coagulate the fine precipitate. The clear THF solution was removed by decantation, and the remaining solid was extracted with several 200-mL portions of ether. The combined THF–ether extract was dried and evaporated to give 28.7 g of crude product which was purified by dissolving a 20 g sample in 250 mL of ether through which HCl gas was bubbled to form the amine hydrochloride. The solution was concentrated to ca. 100 mL and cooled to 10 °C and the precipitate collected by filtration. Two recrystallizations from acetonitrile gave a pure sample of the dihydrochloride of **3** from which the free amine was obtained by dissolving 10 g of the dihydrochloride in 150 mL of MeOH, adding a solution of 4.6 g of KOH in 50 mL of MeOH, removing the KCl precipitate by filtration, and evaporating the MeOH. The residue was redissolved in ether which was dried and evaporated to yield the free amine **3** as a colorless solid showing a single spot in TLC: ^{1}H NMR ($CDCl_3$) δ 0.9 (3, t), 1.35 (23, br s), 2.7 (2, m), 3.75 (2, m); IR (neat) 3300, 2920, 2830, 1600, 1470, 1380, 890, 820, 720 cm^{-1}. Anal. Calcd for $C_{13}H_{32}N_2Cl_2$: C, 54.36; H, 11.15; N, 9.76. Found: C, 54.87; H, 11.51; N, 10.06.

1-Undecyl-*N*,*N*′-bis[2-(hydroxyimino)propanol]ethylenediamine (7). A sample of 8.4 g of 1,2-diaminotridecane was dissolved in 40 mL of methanol and treated with 10.83 g of methyl 2-oximinopropanoate (**5**), prepared by the action of methanol and thionyl chloride on 2-oximinopropanoic acid, as previously described.[2] The mixture was stirred at 46 °C for 2 h, and 300 mL of water was added, causing the immediate precipitation of a white solid. The solution was acidified with 20 mL of 10% HCl and centrifuged and the centrifugate treated with 300 mL of water and 20 mL of 10% HCl and again centrifuged. The centrifugate was dissolved in 500 mL of ether, and the ether solution was dried and evaporated to give a very pale-yellow solid. Two recrystallizations from MeOH afforded a white crystalline product in 40% yield: ^{1}H NMR (Me_2SO-d_6) δ 0.9 (3, t), 1.6 (23, br s), 1.9 (6, s), 3.4 (5, s), 8.3 (2, s); IR (KBr) 3380, 3200, 3050, 2940, 2920, 1660, 1610, 1580, 1550 cm^{-1}. Anal. Calcd for $(C_{10}H_{36}N_4O_4)_2 \cdot 3CH_3OH$: C, 56.94; H, 9.72; N, 12.9. Found: C, 57.19; H, 10.17; N, 12.19.

Critical micelle determinations were carried out on dodecylamine hydrochloride and 4-undecylpyridine hydrochloride by the dye absorption method,[8] using methyl orange as the dye. A 25-mL solution of 0.25 surfactant and 5.34×10^{-4} M methyl orange was equilibrated at 40 °C in a water-jacketed beaker. The pH was adjusted to 2.00 with 4 M HCl, giving a solution with a λ_{max} at 506 nm. The concentration of this solution was then successively reduced by dilution by using an aqueous solution of 5.34×10^{-4} M methyl orange so that the concentration of the methyl orange was not affected by the dilution. For each dilution, the concentration of the surfactant was reduced by a factor of 5/9, the temperature was equilibrated at 40 °C, the pH of the solution was adjusted to 2.00, and the absorption was measured. As the surfactant concentration transited through the CMC, a change in color of the solution from orange to yellow took place and a shift of λ_{max} was observed. The CMC for dimethyldodecylamine hydrochloride was determined to be 0.016 M and that for 4-undecylpyridine hydrochloride to be 0.032 M. Because of the low solubility of the free amines, the CMC values at higher pH levels could not be measured.

Product Assay Procedures: (a) Converter Solution. One volume of hydroxylamine solution (prepared by dissolving 28 g of NH_2OH in 72 g of water), one volume of NaOH solution (prepared by dissolving 14 g of NaOH in 86 g of water), and two volumes of buffer solution (prepared by mixing four volumes of 0.1 M NaOAc and one volume of 0.1 M acetic acid) were mixed.

(b) Acetyl Phosphate Assay. To 2.0 mL of the converter solution a 1.0-mL aliquot from the reaction mixture was added. After 10 min, 1.0

(5) Boiling points are uncorrected. Melting points were determined on a Thomas-Hoover Uni-Melt apparatus. Infrared (IR) spectra were determined on a Perkin-Elmer 283B spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Hitachi-Perkin-Elmer R-24B spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ 0.0) as an internal standard. pH Measurements were made with an Orion Research Microprocessor Ionalyzer Model 901 using a Beckman 40498 glass electrode and a Corning 476002 calomel reference electrode. Thin-layer chromatographic (TLC) analyses were carried out on Analtech Uniplate silica gel (adsorbant thickness 250 μm) developed with iodine vapor.

(6) Stadtman, E. R.; Lipmann, F. *J. Biol. Chem.* **1950**, *185*, 549.

(7) Kurz, J. L. Ph.D. Thesis, Washington University, St Louis, MO, 1958.

(8) Shinoda, K.; Nakagawa, T.; Tamamuishi, B.; Isemura, T. "Colloidal Surfactants"; Academic Press: New York, 1963; pp 1–96. Wood, J. A. *J. Chem. Educ.* **1972**, *49*, 161. Corrin, M. L.; Harkins, W. D. *J. Am. Chem. Soc.* **1947**, *69*, 679.

mL of 4 M HCl was added, followed by 1.0 mL of 0.37 M $FeCl_3$ solution. The absorbance of the resulting solution was then measured.

(c) **Ester Assay.** A 1.0-mL volume of NaOH solution was placed in a 15-mL test tube to which 1.0 mL of 28% NH_2OH solution was also added. The absorbance of the resulting solution was then measured.

(d) **Amide Assay.** A 0.5-mL volume of NaOH solution was placed in a 15-mL test tube to which 1.0 mL of reaction mixture was added. After 20 min, 1.0 mL of 40% NH_2OH·HCl solution was added. This mixture was heated for 90 min at 90 °C and then allowed to cool to room temperature, after which 1.0 mL of 4 M HCl, 1.0 mL of 0.37 M $FeCl_3$, and 0.5 mL of water were added. The absorbance of the resulting solution was then measured.

Kinetic Measurements. Solutions for kinetic studies were prepared immediately before use. A 25-mL solution containing all the ingredients except acetyl phosphate was equilibrated at 40 °C in a water-jacketed beaker. The pH of the solution was monitored continuously with a pH meter standardized at 40 °C. The pH of the solution was adjusted to the desired level by adding a few drops of 1.0 N NaOH (for pH 9–11) or 0.1 N NaOH (for pH 7–9). An accurately weighed sample (ca. 2.3 mg) of dilithium acetyl phosphate was added to the solution, and aliquots were taken at 30-s to 3-min intervals, depending on the anticipated rate of the reaction. The course of the reaction was followed by means of the acetyl phosphate assay. Ester assays were performed whenever the possibility of ester formation existed, and amide assays were carried out when amines were present. The reactions were followed for a period of 10 min to 6 h. T_∞ aliquots were taken at 6–24 h, depending on the reaction rate. In all cases, the plot of the log values of the concentrations vs. time yielded a straight line. Rate constants were determined graphically and by a least-squares computer program. The rate constants for each reaction were determined 3 times from three separte runs, and a 5–7% range in the rate constant was generally observed.

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Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth–Emmons–Wittig Reaction†

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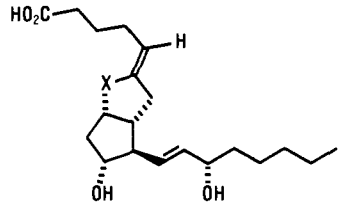
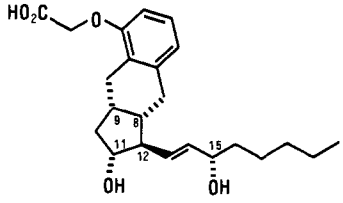
Contribution from The Upjohn Company, Kalamazoo, Michigan 49001. *Received May 8, 1985*

Abstract: A convergent synthesis of the novel, potent antiulcer agent U-68,215 (**3**), a benzindene prostacyclin analogue, is described. U-68,215 is prepared via a cyclopentane annulation sequence in optically pure form in 14 steps and 12% yield from 5-methoxy-2-tetralone (**8a**). The key step in the synthesis involves the coupling of the phosphonate reagent **6** (the chirality of which was derived from a Sharpless resolution of an allylic alcohol precursor) with the enol lactone **7a** (prepared in 50% overall yield from **8a**) to produce enone **5** via a modified intramolecular Wadsworth–Emmons–Wittig reaction. Hydrogenation of **5** followed by an unusual one-pot equilibration–reduction sequence generates the four centers around the cyclopentane ring with complete stereocontrol.

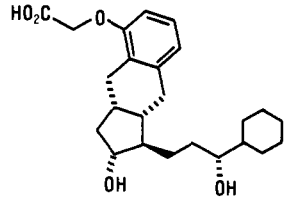
Several years ago, we first reported the synthesis and initial biological evaluation of the benzindene prostaglandins, chemically stable potent prostacyclin (PGI_2, **1a**) mimics.[1] The parent



1a X = O (PGI_2)
1b X = CH_2



2 (U-60,959)



3 (U-68,215)

compound U-60,959 (**2**), a carbacyclin (**1b**) type analogue containing a fused aromatic ring, was about one-fifth as active as PGI_2 at both inhibiting platelet aggregation and lowering blood pressure.[2] A less well-recognized property of prostacyclin is its ability to function as an antiulcer agent.[3] Further examination of U-60,959 indicated that it also was an effective gastric cytoprotective agent and weak inhibitor of gastric acid secretion.[4] More recent structural modification of the benzindene lower side chain has identified the cyclohexyl analogue **3** (U-68,215) as an exciting new antiulcer agent. While by the intravenous route of administration U-68,215 is equipotent with prostacyclin on platelets and blood pressure, given orally **3** is an extremely potent cytoprotective and gastric antisecretory agent.[5] Orally in rats, **3** is roughly 140 times as active as U-60,959 at inhibiting gastric acid secretion, being effective as an antiulcer agent at microgram/kilogram levels. Most importantly, U-68,215, which is a stable high melting crystalline solid, appears completely devoid of the typical side effects associated with prostaglandins of the E type; i.e., even at doses 100 times the antiulcer dose, it does not cause diarrhea, has no antifertility activity, and does not induce cellular proliferation of the gastrointestinal mucosa.[5]

† Dedicated to Prof. Albert Eschenmoser on the occasion of his 60th birthday.

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