An alternative mechanism which might be considered is initial cleavage of the C(9)–CO bond, resulting in the dipolar ion (7 → 8) and subsequent elimination of CO to form anthracene. Formation of an intermediate such as 8 having an anionic charge at the carbon α to the aromatic ring may be faciliated by introduction of the nitro group, which may be in accord with the data in Table I. Such a mechanism would also be favored by polar solvents. Inconsistently, the data in Table II show a rate depression with an increase of solvent polarity.

Experimental Section

Melting points were taken using a capillary and are corrected. Infrared spectra were determined with a 215 Hitachi grating infrared spectrophotometer and ^1H NMR spectra with a Varian T-60A.

2-Nitro-11-isopropylidenedibenzonorbornadiene (3). 11-Isopropylidenedibenzonorbornadiene (2, 939 mg) was dissolved in a mixture of 10 mL of dichloromethane and 50 mL of acetic anhydride. To the solution was added 758 mg of copper(II) nitrate, and the mixture was allowed to stand overnight at room temperature with stirring. The reaction mixture was filtered to remove the precipitate and concentrated under reduced pressure. The residue was extracted with ether, and the ether layer was washed with water, dried, and evaporated, leaving 2.4 g of an oil. When the oil was chromatographed over silica gel, 50% benzene–50% hexene eluant gave the starting material 2, and then 100% benzene eluant gave 3: mp 197–197.5 °C; NMR ($CDCl_3$) δ 1.60 (s, 6 H, isopropylidene), 4.85 (s, 2 H, bridgehead), 6.85–7.40 (m, 4 H, aromatic), 7.35 (d, 1 H, aromatic H at C_4), 7.90 (d of d, 1 H, aromatic H at C_3), 8.05 (d, 1 H, aromatic H at C_1); IR ($CHCl_3$) 1350, 1530 cm^{-1} (NO_2). Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.26; H, 5.52; N, 5.01.

Dibenzonorbornadien-11-one (1). Ozone gas was absorbed by a solution of 210 mg of 2 in 10 mL of dichloromethane at −30 °C with stirring. When 2 disappeared, nitrogen gas was introduced to remove excess ozone and then dimethyl sulfide was added. After being stirred for 15 min, the mixture was washed with ice water, dried, and evaporated, leaving 195 mg of a crystalline ketone: IR ($CHCl_3$) 1800 cm^{-1} (C=O).

2-Nitrodibenzonorbornadien-11-one (4). A solution of 97 mg of 3 in 10 mL of dichloromethane was treated as above. A crystalline ketone (61 mg) was obtained: IR ($CHCl_3$) 1350 and 1520 (NO_2), 1805 (C=O) cm^{-1}.

Dinitrodibenzonorbornadien-11-one (5). To a solution of 251 mg of 4 in 10 mL of dichloromethane was added 1.31 g of a nitric acid–sulfuric acid mixture (prepared by mixing 5 g of fuming nitric acid, 90 g of sulfuric acid, and 8 g of water) at 0 °C with stirring. The mixture was stirred for 2 h, poured into ice water, and extracted with dichloromethane. The dichloromethane solution was washed with ice water, dried, and evaporated under reduced pressure, leaving 290 mg of crystal: IR ($CHCl_3$) 1810 and 1830 (C=O), 1350 and 1530 (NO_2) cm^{-1}.

Kinetic Measurements. Rates were determined by measuring intensities at UV maxima of the anthracene or nitroanthracenes produced using a Hitachi recording spectrometer. The UV maxima used were the following: 340, 358, and 378 nm for anthracene in dioxane; 346, 364, and 415 nm for 2-nitroanthracene in dioxane; and 345 nm for dinitroanthracene. The UV maxima of 2-mononitroanthracene in other solvents used for kinetics were as follows: 346, 363, and 415 nm in ethanol; 348, 365, 417, and 440 nm in benzene; and 344, 362, 383, 403, and 426 nm in heptane. First-order plots were linear.

Registry No.—1, 30131-11-4; 2, 30131-12-5; 3, 68928-10-9; 4, 68936-71-0; 5 (isomer 1), 68928-11-0; 5 (isomer 2), 68928-12-1.

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Synthesis and pH Effects on the Hydrolysis of 5′-Adenosyl Phenylalaninate

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Received September 12, 1978

Considerable research on the mechanism of protein synthesis has resulted in the current view that two ribosomal bound aminoacyl-tRNA's undergo an intermolecular reaction that culminates in the formation of a dipeptidyl-tRNA bound to the A (acceptor) site on the ribosome. Subsequent reactions leading to the coded protein sequence are a repetitive sequence of steps involving ribosomal movement of the peptidyl-tRNA to the P site, codon–anticodon binding of the next specific aminoacyl-tRNA at the A site, and peptide bond formation.

Chemical models of coded peptide bond formation have been described by both Li and Zemlicka[1] and Ringer, Chladek, and Ofengand[2] using 2′(3′)-aminoacyladenosine derivatives.

The genetic coding mechanism defines peptide bond formation as occurring through 3′-aminoacyladenylates on the tRNA terminus. Although this process appears to be the successful survivor of evolution, it does not preclude other primative recognition patterns as progressive steps in development of ribosomal protein synthesis. One such mechanism of amino acid–nucleic acid recognition process that has the necessary chemical features for peptide synthesis is that involving 5′-aminoacyl nucleosides. Selectivity can be gained by application of the stacking and hydrogen-bonding properties that order nucleic acid structures. An entropic advantage that favors peptide bond formation can be gained by the use of polynucleotides as templates to order the interacting aminoacylnucleosides in juxtaposition. This report describes the initial phases of this research, the synthesis and pH stability of the 5′-adenosine ester of phenylalanine.

Formation of the intermediate 5′-(2′,3′-*O*-isopropylidene)-adenosyl *N*-(carbobenzyloxy)-DL-phenylalaninate (3) was found to proceed in excellent yield (94%) by acylation of 2′,3′-*O*-isopropylideneadenosine with the symmetrical anhydride of *N*-(carbobenzyloxy)-DL-phenylalanine (2) in pyridine solvent (Scheme I). Facile removal of the isopropylidene protecting group was accomplished in aqueous methanolic hydrochloric acid to yield 5′-adenosyl *N*-(carbobenzyloxy)-DL-phenylalaninate (4, 70%). Subsequent hydrogenolysis of 4 using 5% palladium on barium sulfate in methanol containing 5% hydrochloric acid produced 5′-adenosyl DL-

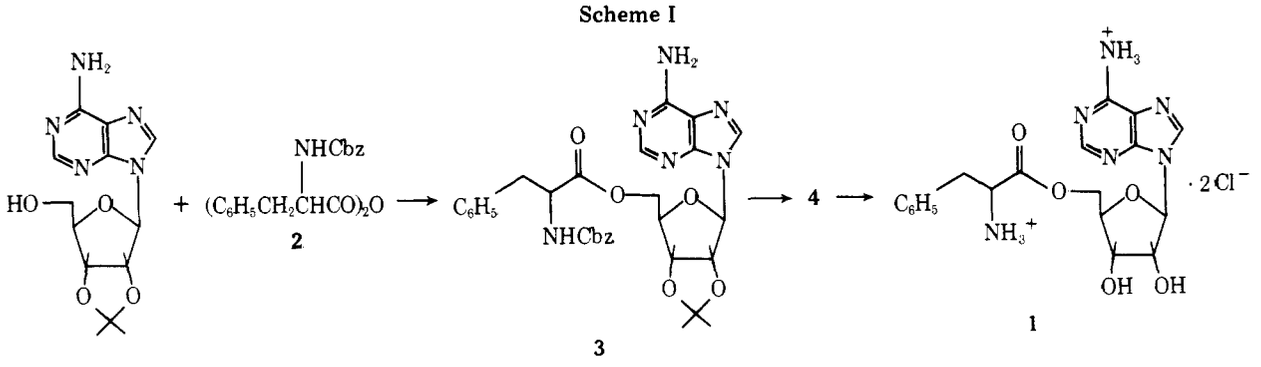
Table I. Observed Rate Constants for the Hydrolysis of 5′-Adenosyl Phenylalaninate at 37 °C[a]

pH	$t_{1/2}$, min	$k_{obsd} \times 10^3$, min^{-1}	log k_{obsd}
5.2	1700	0.41	−3.39
5.9	740	0.94	−3.03
7.0	260	2.64	−2.58
8.0	95	7.33	−2.13
8.7	88	7.9	−2.10
9.0	91	7.6	−2.12
10.0	20	34	−1.47
10.4	7.6	91	−1.04
10.8	3.3	207	−0.68

[a] These values were extrapolated to zero buffer concentration from experimental results using 0.1 and 0.05 M phosphate buffer adjusted to 0.30 ionic strength with potassium chloride.

0022-3263/79/1944-1003$01.00/0

Scheme I



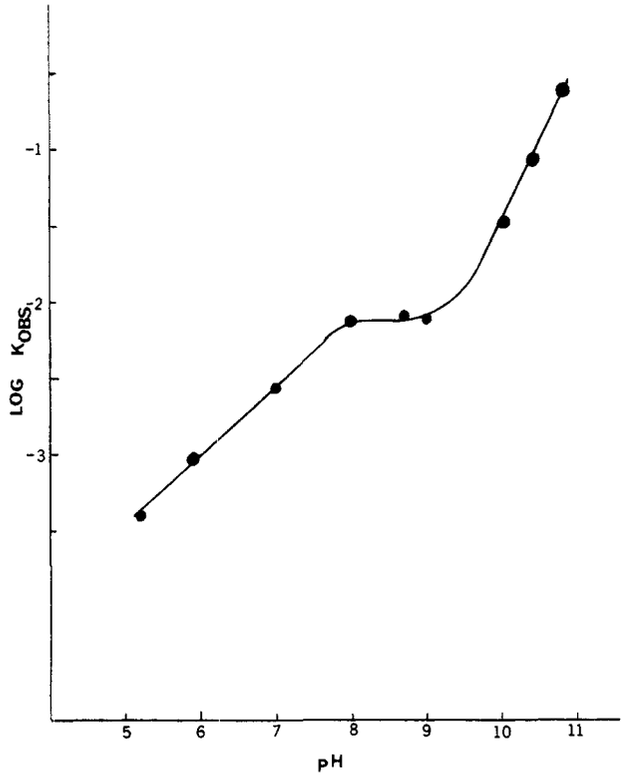


Figure 1. Plot of the log k_{obsd} vs. pH for the hydrolysis of 5′-adenosyl phenylalaninate at ionic strength 0.3 extrapolated to zero buffer concentration at 37 °C.

phenylalaninate dihydrochloride (1) in 76% yield. Removal of the carbobenzyloxy protecting group could be accomplished in shorter time and higher yield (83%) by using palladium oxide catalyst in 80% acetic acid solvent. Compound 1 is exceedingly hygroscopic.

The hydrolysis of 5′-adenosyl phenylalaninate at 37 °C and ionic strength 0.30 was extrapolated to zero buffer concentration to give the results shown in Table I. On first observation the pattern suggests that the course of the reaction is similar to that followed in the hydrolysis of the 2′- or 3′-aminoacyl esters of adenosine.[3] However a plot of the log of the k_{obsd} against pH shows in Figure 1 an unexpectedly enhanced rate at a pH below neutrality. The rate profile above pH 8 in Figure 1 confirms a mechanism of hydrolysis involving hydroxide ion attack on the two predominant species, the protonated and neutral forms of the ester. The rate constants for base-catalyzed hydrolysis of the two species in the reaction were determined from eq 1, where k_{OH}, the second-order rate constant, can be determined for hydrolysis of the molar fraction of protonated (EH^+) and neutral (E) esters. The pK_a's of the ester were determined by titration at 25 °C in a solution of ionic strength 0.30. The respective pK_a's are 4.36 and 7.26 for ionization of the diprotonated (EH^{2+}) and monoprotonated (EH^+) series.

$$k_{obsd}(E_t) = k_{OH}^{EH^+}[EH^+][OH^-] + k_{OH}^{E}[E][OH^-] \quad (1)$$

From the mole fractions of the respective protonated and neutral esters for the range pH 7.0 to 8.7, the reaction follows the rate law of eq 2.

$$k_{obsd}(E_{total}) = 20\,000[EH^+][OH^-] + 160[E][OH^-] \quad (2)$$

The buffer effect on the hydrolysis was determined at the various pH values. Increasing buffer concentrations increased the rate of hydrolysis below pH 8 and decreased the reaction rate above pH 8. At pH 5.2 a 15% rate increase was noted in going from 0.05 to 0.10 M buffer; a comparable change at pH 10 gave a 10% rate decrease.

A change in the mechanism of hydrolysis occurs in the pH range of 5.2 to 8. If the reaction throughout the entire pH range followed the equation $k_{obsd} = k_{OH}[OH^-]$, transformation to $\log k_{obsd} = \log k_{OH} + pH - pK_w$ should result in a slope of unity for the plot in Figure 1. The experimental results give a slope of 0.98 above pH 9; however, the pH 5.2 to 8 span shows a slope (0.44) of one-half the expected value.

The points that can be analyzed by this study are the differences in rate or mechanism in the hydrolysis of 5′-adenosyl phenylalaninate as compared to either the simple ester or the 2′(3′)-adenosyl ester, as it is found naturally in phenylalanyl-tRNA.

The hydrolysis of 5′-adenosyl phenylalaninate at pH values above 8 follows the expected rate law in eq 2. As with all similar hydrolytic studies of esters of amino acids, hydroxide ion attack of the protonated ester greatly exceeds the rate of attack of the neutral ester. Values ranging from 90 (valyl-tRNA)[4] to about 150 (leucyl-tRNA)[5] are reported for the enhancement of rate of protonated ester hydrolysis; similar values were observed for the hydrolysis of methyl histidinate[6] ($k_{OH}^{EH^+}$ is 100 × k_{OH}^{E}) and ethyl leucinate[5] ($k_{OH}^{EH^+}$ is 143 × k_{OH}^{E}). In the present study, $k_{OH}^{EH^+}$ for 5′-adenosyl phenylalaninate is 125 × k_{OH}^{E}.

The second point for comparison is the rate acceleration noted with aminoacyl esters of adenosine over that of the simple esters of amino acids. For example, Wolfenden[5] reported that hydroxide ion attacks leucyl-tRNA 30 times more rapidly than ethyl leucinate. Ethyl phenylalaninate at pH 10.7 has a $t_{1/2}$ at 25 °C of 71 min,[6] which under the experimental conditions calculates for a k_{OH}^{E} of 14 L mol^{-1} min^{-1}. At 37 °C the data of Gatica and co-workers[7] show a $t_{1/2}$ for phenylalanyl-tRNA of 3 min at pH 10, the most alkaline solution examined, which, allowing for the temperature effect and pH difference, is about a factor of 30 favoring hydrolysis of the tRNA ester over hydrolysis of ethyl phenylalaninate.

The 5′-adenosyl ester had an intermediate rate about one-seventh the reported rate of phenylalanyl-tRNA hydrolysis. The predominant factor to account for the rate enhancement observed with the 2′(3′)-adenosyl esters and the tRNA esters has been attributed to participation of the neighboring cis

hydroxyl group in the hydrolysis. Schuber and Pinck[4] analyzed this effect with the conclusion that the catalytic participation of the vicinal hydroxyl group cannot account fully for the acceleration. It is apparent from the fourfold rate difference between the 5′-adenosyl and ethyl esters of phenylalanine that either participation by the adenosine group is assisting the hydrolysis or the anion of the primary 5′-hydroxyl of adenosine is a considerably better leaving group than ethoxide anion. Participation by the 3′-hydroxyl group is one of several possibilities that could contribute to more rapid hydrolysis of the 5′-adenosyl ester of phenylalanine compared to ethyl phenylalanate.

In a report on the hydrolysis of aminoacyl-tRNA's by Gatica and co-workers,[7] an unusual pattern is seen below pH 8 in the plot of log k_{obsd} vs. pH. In their studies both the phenylalanyl and threonyl esters of tRNA showed rate enhancement below a pH of 8 that indicates a different mechanism of hydrolysis. We also observed this pattern.

The slope of the plot in Figure 1 at high pH is consistent with the equation $\log k_{obsd} = \log k_{OH} + pH - pK_w$, wherein a plot of log k_{obsd} vs. pH should have a slope of 1. At pH values below 8, the change in slope (0.44) suggests a change in mechanism. The enhanced rate in acid over that expected from the equation suggests participation in the hydrolysis by the diprotonated EH_2^{2+} species, presumably affecting the rate of solvolysis. The exceedingly slow rate of hydrolysis of 5-adenosyl phenylalaninate in acid precluded an extensive study of this mechanism.

Experimental Section

Melting points (uncorrected) were taken on a Thomas-Hoover apparatus. Infrared spectra (KBr) were obtained with either Beckman IR-33 or Perkin-Elmer 727 spectrophotometers. Nuclear magnetic resonance spectra were obtained from either a Varian EM-360 or a Varian T-60 spectrometer equipped with a Nicolet TT7 Fourier transformation system using tetramethylsilane as an internal standard and chloroform-*d* as solvent (for 1 the solvent was methanol-d_4). Microanalyses were performed on a Hewlett-Packard 185B CHN analyzer at the University of Kansas Analytical Laboratory or by Midwest Microlab, Ltd., Indianapolis, Indiana. "Dry column" chromatography was performed on Woelm activity grade III silica gel (ICN Pharmaceuticals, Inc.), containing 0.5% fluorescent indicator (254 nm). Thin-layer chromatography (TLC) was carried out with Brinkman EM reagent precoated plates (0.25 mm silica gel 60 F-254). Fluorescent zones were visualized under UV light (Mineralite USVL-13, Ultraviolet Products, Inc.). Anhydrous pyridine was obtained by stirring reagent grade pyridine over potassium hydroxide overnight, followed by distillation from calcium hydride. 2′,3′-*O*-Isopropylideneadenosine and *N*-(carbobenzyloxy)-DL-phenylalanine were obtained from Sigma Chemical Co.; 5% palladium on barium sulfate and palladium oxide (77.52%) were the products of Engelhard Industries. pH was measured with a Beckman Expandomatic SS-2 pH meter using a combination microelectrode (Beckman). High pressure liquid chromatography (LC) was performed on a Waters Associates Model 6000A equipped with a Waters Model 440 UV detector (254 nm), using prepacked columns (Partisil-10 SCX, 25 cm × 4.6 mm × 0.25 in.) obtained from Reeve Angel (Whatman).

***N*-(Carbobenzyloxy)-DL-phenylalanine Anhydride (2).** This was prepared by the procedure of Rammler and Khorana[8] using *N*-(carbobenzyloxy)-DL-phenylalanine (13.2 g, 44.1 mmol) and dicyclohexylcarbodiimide (5.0 g, 24.3 mmol) in ethyl acetate solvent. The product was obtained as white, feathery needles (11.05 g, 87%), mp 128.5–129.5 °C (lit.[8] mp 125–126 °C).

Anal. Calcd for $C_{34}H_{32}N_2O_7$ (M_r 580.6): C, 70.33; H, 5.56; N, 4.82. Found: C, 70.68; H, 5.68; N, 4.74.

5′-(2′,3′-*O*-Isopropylidene)adenosyl *N*-(Carbobenzyloxy)-DL-phenylalaninate (3). A modification of the general procedure of Gerzon and Kau[9] was used in which a solution of **2** (3.91 g, 6.7 mmol) in anhydrous pyridine (6 mL) was added to a cooled (0–5 °C), stirred solution of 2′,3′-*O*-isopropylideneadenosine (2.0 g, 6.5 mmol) in pyridine (20 mL). The solution was stirred for 12 h while being allowed to come to room temperature. Water (10 mL) was added, the solution stirred for 30 min, and the solvent removed in vacuo. The residue was partitioned between ethyl acetate (50 mL) and water (50 mL), and the organic layer separated and was washed with 10% sodium bicarbonate (2 × 50 mL), dried (sodium sulfate), filtered, and concentrated in vacuo to about 20 mL. This solution was applied to a dry silica gel column (200 g) which was developed with ethyl acetate (200 mL); the major band (R_f 0.5–0.7) was separated, washed with chloroform–methanol (4:1 v/v), and filtered, and the organic solution was evaporated in vacuo to produce **3** as a white foam. The crude product was dissolved in chloroform (10 mL) and added dropwise to cold, stirred pentane (100 mL) to produce **3** (3.6 g, 94%) as a white powder: mp 83–85 °C; IR 3350 (NH_2), 3200 (NH), 1740 (C=O of ester), 1700 (C=O of carbobenzyloxy), 1640 and 1600 (C=C and C=N), 1385 and 1370 (*gem*-dimethyl), 1200 (C–O of ester) cm^{-1}; NMR δ 8.3 (1, s, H_8), 7.9 (1, s, H_2), 7.2 (12, e, Ph and NH_2), 6.0 (1, s, $H_{1'}$), 5.6–5.3 (3, e, $H_{2',3',4'}$), 5.2 (2, s, benzylic of carbobenzyloxy), 4.5 (1, m, H–C_α of Phe), 3.0 (2, d, benzylic of Phe), 1.7 (3, s, CH_3), 1.4 (3, s, CH_3).

Anal. Calcd for $C_{30}H_{22}N_6O_7$ (M_r 588.6): C, 61.22; H, 5.48; N, 14.28. Found: C, 61.44; H, 5.31; N, 13.88.

5′-Adenosyl *N*-(Carbobenzyloxy)-DL-phenylalaninate (4). The general procedure of Gerzon and Kau[9] was used in which **3** (1.5 g, 2.5 mmol) was dissolved in methanol (150 mL), 0.5 N hydrochloric acid (30 mL) added, and the solution heated at reflux for 10 h. The solution was then neutralized with 0.5 N ammonium hydroxide and concentrated in vacuo to about 40 mL, and the resulting mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with saturated sodium chloride (2 × 60 mL), dried (sodium sulfate), filtered, and evaporated in vacuo to produce **4** as a white foam which was crystallized from chloroform–hexane to produce 0.97 g (70%) of **4** as colorless plates: mp 112 °C dec; IR spectrum was identical with **3**, with the exceptions that the 3150-cm^{-1} region is broader and the *gem*-dimethyl peaks at 1385 and 1370 cm^{-1} are absent; NMR spectrum was identical with **3**, with the modification that the singlets at δ 1.7 and 1.4 are absent and the envelope at δ 5.6–5.3 integrates for 5 H.

Anal. Calcd for $C_{27}H_{28}N_6O_7 \cdot 0.5H_2O$ (M_r 557.6): C, 58.27; H, 5.21; N, 15.10. Found: C, 58.00; H, 5.16; N, 15.10.

5′-Adenosyl DL-Phenylalaninate (1). Method A. To a solution of **4** (0.7 g, 1.3 mmol) in methanol (100 mL) was added 5% methanolic hydrochloric acid (5 mL) and 5% palladium on barium sulfate (50 mg). Hydrogen was bubbled through the stirred solution at 25 °C for 6 h. The catalyst was removed by filtration through Celite and the solution evaporated in vacuo. The white solid obtained was recrystallized from methanol–ethyl acetate to give **1** as the dihydrochloride salt (0.5 g, 76%): mp 166–170 °C dec; IR 3400 (NH_3^+), 3200 (O–H), 1750 (C=O of ester), 1640 and 1600 (C=C and C=N), 1200 (C–O of ester), 1090 (C–O of alcohol) cm^{-1}; NMR δ 8.45 (1, s, H_8), 8.4 (1, s, H_2), 7.2 (7, s, Ph and NH_2), 6.1 (1, d, $H_{1'}$), 4.7–4.2 (5, e, $H_{2',3',4',5'}$), 3.3 (3, e, benzylic and H_α of Phe).

Anal. Calcd as $C_{19}H_{22}N_6O_5 \cdot (HCl)_2 \cdot 0.5CH_3OH$: C, 46.53; H, 5.21; N, 16.70; Cl, 14.09. Found: C, 47.00; H, 5.22; N, 17.10; Cl, 13.73.

Method B. A solution of **4** (1.2 g, 2.19 mmol) in 80% acetic acid (50 mL) and 0.5 N HCl (5 mL) was cooled to 0 °C. Palladium oxide (77.52%, 200 mg) was added, and hydrogen was bubbled through the solution. The reaction was shown to be complete by TLC (chloroform–methanol, 4:1) after 3 h. The solution was gravity filtered to remove catalyst and then evaporated in vacuo to give a viscous yellow oil (2.71 g). This residue was dissolved in methanol (10 mL) and added dropwise to cold, stirred ethyl acetate (100 mL). The precipitated white powder was collected by suction filtration under nitrogen and dried in vacuo overnight to give 0.92 g (83%) of **1**, mp 151–153 °C dec.

Anal. Calcd as $C_{19}H_{22}N_6O_5 \cdot (HCl)_2 \cdot H_2O \cdot 0.5CH_3OH$: C, 44.92; H, 5.41; N, 16.12; Cl, 13.60. Found: C, 45.31; H, 5.25; N, 15.40; Cl, 13.76.

Dissociation Constants (pK_a) of 5′-Adenosyl DL-Phenylalaninate (1). A 3-mL solution of **1** (0.020–0.026 M) in water (pH 7.00, ionic strength 0.3 by addition of potassium chloride) was titrated with 0.0493 N sodium hydroxide (ionic strength 0.3 at 25 °C) and the pH monitored as described above. The results of two such experiments gave observed values which were corrected to give $pK_{a1} = 4.36 \pm 0.11$ (ionization of $C_6NH_3^+$ of the adenosine moiety) and $pK_{a2} = 7.26 \pm 0.08$ (ionization of the α-NH_3^+ group). Corresponding literature pK_a values for adenosine[10] and methyl phenylalaninate[11] are 3.45 and 7.05, respectively.

Correction values for the electrode system used were obtained by titration of potassium hydrogen phthalate (Fisher Certified Standard Reagent) and L-phenylalanine methyl ester hydrochloride (Vega-Fox Biochemicals, Inc.). Potassium hydrogen phthalate (0.85–0.093 M) or methyl L-phenylalaninate hydrochloride (0.090–0.100 M) dissolved in water (3 mL, pH 7.00) was titrated with 0.0493 N sodium hydroxide; observed pK_a ($N = 3$) values were 5.02 ± 0.07 (lit.[12] $pK_a = 5.51$) and 6.55 ± 0.03 (lit.[11] $pK_a = 7.05$), respectively.

Kinetics of the Hydrolysis of 1. Buffer solutions for the hydrolysis of 1 contained potassium phosphate (0.05 or 0.10 M); observed rate constants were extrapolated to zero buffer concentration to correct for buffer catalysis. Sufficient potassium chloride was added to achieve an ionic strength of 0.3. The pH of the reaction mixtures was maintained to within ±0.10 pH unit for at least 2 half-lives. Reactions were initiated by combining appropriate volumes of the buffer and an aqueous solution of 1 (final concentration, 0.56 mM). Aliquots (20 μL) of the reaction mixtures (maintained at 37 °C) were removed at timed intervals and injected onto a Partisil SCX column as described above. The column was eluted with 0.08 M ammonium phosphate buffer (pH 3.5), 2.0 mL/min (1500–1800 psi). Under these conditions, the retention times for DL-phenylalanine, adenosine, and 1 were 1.35, 2.25, and 6.90 min, respectively. The amount of unhydrolyzed 1 was measured by electronic integration of the resulting peak. All rate measurements were made in duplicate, and reactions were followed for 3 half-lives (N = 4–10). Apparent first-order rate constants were calculated by a linear least-squares analysis of the resulting data; in all experiments but one, the correlation coefficient was 0.96 or greater.

Acknowledgment. This work was supported by grants from the State of Kansas General Research Fund and Biomedical Research Support Grant RR 5606 from the National Institutes of Health; C.R.P. was supported by an NSF predoctoral fellowship.

Registry No.—1 dihydrochloride, 68867-06-1; 2, 68926-48-7; 3, 68867-07-2; 4, 68867-08-3; 2′,3′-*O*-isopropylideneadenosine, 362-75-4.

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3-(Dimethylamino)-1-propyne: Convenient Precursor for a Versatile Mixed Cuprate Reagent

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Received September 25, 1978

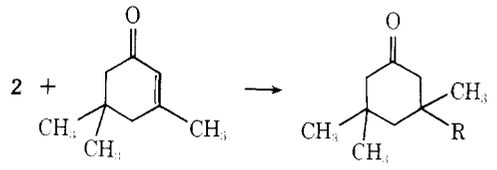
In recent years a number of publications have appeared concerning the use of mixed cuprate reagents in conjugate addition reactions.[1-4] We report here on the mixed cuprate **2** which is prepared as outlined in Scheme I. We believe that **2** has several advantages over the previously reported reagents: (1) the reagent's precursor **1** is commercially available at low cost; (2) any coupling products resulting from oxidation are readily removed via an acid extraction; and (3) one need not employ a complexing agent or a large excess of the mixed cuprate when R = CH_2=CH_2. Isophorone was chosen as the enone for our experiments as this ketone has been extensively studied in conjugate addition reactions with organocuprates.[1] The results of our experiments are contained in Table I.

Scheme I

$$(CH_3)_2NCH_2C{\equiv}CH \xrightarrow[(2)\ CuI\ (3)\ RLi]{(1)\ CH_3Li} R[(CH_3)_2NCH_2C{\equiv}C{-}]CuLi$$

1 **2a**, R = CH_3; **b**, R = $CH{=}CH_2$

Table I

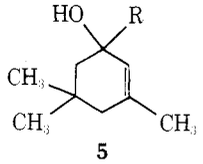


3 **4**

R	registry no.	solvent	temp, °C	yield of **4**[a] %	starting material recovered, %
CH_3	68843-13-0	THF	0	0	not determined
CH_3		THF	−40	0	96
CH_3		Et_2O	0	85–100[c]	0–15
CH_3		Et_2O	−20[b]	100	0
CH_3		Et_2O	−40[b]	84	12
CH_3		Et_2O	−80[b]	17	29
CH_2=CH	68843-14-1	Et_2O	−50	15[d]	60
CH_2=CH		Et_3N	−50	52–58	38–40

[a] All yields were determined via gas chromatography. Compound **3** was the limiting reagent. [b] The reaction which formed the mixed cuprate, i.e., reaction 3, Scheme I, was carried out at this temperature also. [c] Registry no., 14376-79-5. [d] Registry no., 27749-07-1.

Initial attempts at adding **2** to **3**, which employed THF as solvent, were unsuccessful; however, when ether was used as solvent, the yield of product was excellent. At very low temperatures (−80 °C) yields were low, but a substantial amount of starting material had been consumed. We assume that at this temperature the mixed cuprate did not form completely; thus, when enone was added, unreacted RLi probably added in a 1,2 fashion to form the alcohol **5**. We stress that this is only



5

conjecture as our means of analysis only allowed for the determination of **3** and **4**; we did not pursue the matter further. The fact that cuprate **2** will not form at low temperature precludes the application of our method to the formation of mixed cuprates from highly unstable lithium reagents. We had initially hoped that **2** could be formed at low temperature with relatively unstable α-halolithium intermediates.

A reliable procedure for effecting the conjugate addition of a vinyl group from a mixed cuprate to an enone in high yield without employing a large excess of the copper reagent or a complexing agent, which is oftentimes difficult to remove, has not been reported to date.[1-4] We have found that when triethylamine is employed as solvent, cuprate **2b** will add to isophorone in good yield (52–58%). If ether is used instead of triethylamine, the yields are reduced drastically. We attribute the success of the amine solvent to its ability to better solubilize the intermediate copper(I) acetylide and thus accelerate the reaction of acetylide with RLi at the low temperature required to keep the vinyl cuprate from decomposing.

Experimental Section[5]

Starting Materials and Reagents. Methyllithium in ether (Ventron Corp.) and vinyllithium in THF (Organometallics, Inc.) were standardized by the usual double titration method. Commercial samples of CuI were obtained from Fisher Scientific Co. and purified

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