acetoxynitrosamines.[7] In this case, intramolecular nucleophilic displacement of the chloro by the hydroxyl group gives the cyclic nitrosamine.

N-Nitroso 2,2-disubstituted oxazolidines can now be prepared cleanly and in good yields with nitrosyl chloride and anhydrous potassium carbonate. it is not known at this time whether symmetrical 2,2-disubstitutions have any effect on the regioselectivity of alkylation or if it prevents multiple alkylations. However, the nuclear magnetic resonance data indicates that these nitrosamines exist as the *E* rotamers. *N*-nitroso-2,2,4-trimethyloxazolidine (**5**) is an exception, with the *Z* rotamer representing 3% of the mixture.

Experimental Section

Proton and NMR spectra were recorded on a Nicolet NT-300 spectrometer with $CDCl_3$ as the solvent containing 0.5% tetramethylsilane. The IR spectra were obtained on a Perkin-Elmer 467 spectrometer. Low-resolution mass spectra were taken on a Finnigan 330 mass spectrometer equipped with a Finnigan 6000 MS data system. Gas chromatographic analyses were carried out on a Shimdazu Model 4BM gas chromatograph equipped with a Hewlett-Packard 18652A A/D converter coupled to the recorder of a flame ionization detector. A 2.5-m Tenax 80/100 GC column (Applied Science Division) was used.

***N*-Nitroso-2,2-dimethyloxazolidine (3).** To a solution of 10 g (0.16 mol) of ethanolamine in 100 mL of methylene chloride were added 15 g of anydrous potassium carbonate and 18 mL (0.24 mol) of acetone. The mixture was stirred at 25 °C under nitrogen for 6 h. Since GLC analysis of the reaction mixture at this time indicated that no ethanolamine remained, an aliquot was removed, and the solvent evaporated. NMR analysis of the crude mixture showed a 5.7:1 ratio of oxazolidine **2a** ($R_1 = R_2 = H$, $R_3 = R_4 =$ Me):Schiff base **2b** ($R_1 = R_2 = H$, $R_3 = R_4 =$ Me). This was based on the area of *gem*-dimethyls, δ 1.38 for the oxazolidine and δ 2.28 for the Schiff base. The reaction mixture was cooled to 0 °C, and nitrosyl chloride was slowly bubbled in. After being stirred for 30 min at 5 °C, the solution was filtered, and the solvent was removed on a rotary evaporator. The residue was vacuum distilled to give 15 g (72%) of **3**: bp 60–61 °C (1.9 mmHg); IR (film) 2985, 2935, 2885, 1414, 1370, 1300, 1235, 1162, 1045, 818 cm^{-1}; NMR ($CDCl_3$, ^1H) δ 1.73 (s, 6 H), 3.73 (t, 2 H), 4.15 (t, 2 H); NMR ($CDCl_3$, ^{13}C) 94.14 ppm (C-2), 43.05 (C-3), 62.18 (C-4), 26.36 (CH_3 on C-2); MS, *m/z* (relative intensity) 130 (4.5 M^+), 115 (1.1), 91 (3.8), 86 (10.1), 84 (5.5), 59 (12.3), 58 (39), 56 (3.6), 50 (9), 43 (100), 42 (11).

Anal. Calcd for $C_5H_{10}N_2O_2$: C, 46.15; H, 7.69; N, 21.54. Found: C, 46.18; H, 7.72; N, 21.70.

***N*-Nitroso-2,2,5-trimethyloxazolidine (4).** A solution of 20 g (0.266 mol) of 1-amino-2-propanol in 250 mL of methylene chloride was condensed with acetone as described above. NMR analysis of the reaction mixture indicated a 6.1:1 ratio of the oxazolidine **2a** ($R_1 = H$, $R_2 = R_3 = R_4 =$ Me):Schiff base **2b** ($R_1 = H$, $R_2 = R_3 = R_4 =$ Me). The reaction mixture was cooled to 0 °C, treated with nitrosyl chloride, and worked up as described above. Distillation of the crude product gave 28.4 g (75%) of **4**: bp 61 °C (1.3 mmHg) (lit.[3] bp 64 °C (0.2 mmHg)); NMR ($CDCl_3$, ^{13}C), 18.64 ppm (CH_3 on C-5), 25.98 and 27.69 (CH_3 on C-2), 49.32 (C-4), 69.63 (C-5), 95.00 (C-2).

***N*-Nitroso-2,2,4-trimethyloxazolidine (5).** Condensation of 2 g (0.027 mol) of 2-amino-1-propanol with acetone was carried out as described above; 12 h were required to complete the reaction. The mixture was nitrosated and worked up as described above to give 2.2 g (58%) of **5**: bp 45–46 °C (1.5 mmHg); IR (film) 2985, 2935, 2880, 1450, 1410, 1368, 1275, 1228, 1000, 828 cm^{-1}; NMR ($CDCl_3$, ^1H) 1.27 (d, 3 H), 1.69 (s, 3 H), 1.76 (s, 3 H), 3.78 (q, 1 H), 4.12 (q, 1 H), 4.45 (m, 1 H); the *Z* isomer represented 3% of the total as calculated from the area of Me on C-4, δ 1.59 (d), and *gem*-dimethyls, δ 1.50 and δ 1.55; MS, *m/z* (relative intensity) 144 (20, M^+), 115 (2.3), 100 (12), 98 (28), 84 (24), 71 (14), 70 (5), 69 (11), 68 (30), 67 (13), 58 (58), 42 (100), 41 (63).

Anal. Calcd for $C_6H_{12}N_2O_2$: C, 49.98; H, 8.39; N, 19.43. Found: C, 49.98; H, 8.34; N, 19.35.

***N*-Nitroso-2,2-dimethyl-5-phenyloxazolidine (6).** A 0.5 M solution of 6.7 g (0.048 mol) of 2-amino-1-phenylethanol in methylene chloride was condensed with acetone over a 12-h period as described above. The ratio of the oxazolidine **2a** ($R_1 = H$, $R_2 =$ Ph, $R_3 = R_4 =$ Me):Schiff base **2b** ($R_1 = H$, $R_2 =$ Ph, $R_3 = R_4 =$ Me) was 27:1. Nitrosation and workup was carried out as described above. The crude product was purified through dry-packed silica gel (activity III), eluted with 6:1 hexane/tetrahydrofuran, to give 7.21 g (73%) of **6** as a yellow oil: bp 148–150 °C (1.2 mmHg) (purification by distillation of large quantities of this material is not recommended); IR (film) 3060, 3010, 2985, 2935, 2880, 1950, 1882, 1810, 1755, 1605, 1595, 1453, 1414, 1370, 1287, 1168, 1030, 842, 760, 700 cm^{-1}; NMR ($CDCl_3$, ^1H) δ 1.78 (s, 3 H), 1.91 (s, 3 H), 3.35 (q, 1 H), 4.30 (q, 1 H), 5.21 (q, 1 H), 7.34 (s, 5 H); MS, *m/z* (relative intensity) 206 (M^+, 0.1), 105 (17.6), 104 (100), 103 (9.3), 78 (13.8), 77 (9.3), 71 (5), 70 (27), 55 (20), 43 (17).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.20; H, 6.90; N, 13.48.

***erythro*-*N*-Nitroso-2,2,4-trimethyl-5-phenyloxazolidine (7).** A solution of 552 mg (3.5 mmol) of norephedrine in 8 mL of methylene chloride was stirred with 2 equiv of acetone for 6 h in the presence of anydrous potassium carbonate. The NMR spectrum indicates a ratio of 32:1 oxazolidine **2a** ($R_2 =$ Ph, $R_1 = R_3 = R_4 =$ Me):Schiff base **2b** ($R_2 =$ Ph, $R_1 = R_3 = R_4 =$ Me). The reaction mixture was nitrosated with nitrosyl chloride and worked up as described above. The product was purified on dry-packed silica gel (activity III), eluted with 6:1 hexane/THF to give 555 mg (72%) of **7**: bp (oil bath temperature) 108 °C (0.1 mmHg); IR (film) 3060, 3025, 2990, 1950, 1885, 1810, 1755, 1605, 1455, 1420, 1380, 1280, 1008, 860 cm^{-1}; NMR ($CDCl_3$, ^1H) δ 0.67 (d, 3 H), 1.84 (s, 3 H), 1.96 (s, 3 H), 4.80 (m, 1 H, $j = 5.3$ Hz), 5.26 (d, 1 H, $J = 5.3$ Hz); NMR ($CDCl_3$, ^{13}C) 134.63 ppm, 128.32, 128.07, 125.97, 94.84, 77.70, 54.71, 29.38, 26.51, 12.48; MS, *m/z* (relative intensity) 119 (10), 118 (100), 117 (47.7), 115 (5.9), 91 (14), 84 (26.4), 77 (12.3), 63 (14.5).

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.45; H, 7.27; N, 12.72. Found: C, 65.60; H, 7.12; N, 12.86.

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Registry No. 1 (R^1, $R^2 =$ H), 141-43-5; 1 ($R_1 =$ H; $R_2 =$ Me), 78-96-6; 1 ($R_1 =$ Me; $R_2 =$ H), 78-91-1; 1 ($R_1 =$ H, $R_2 =$ Ph), 7568-93-6; **2a** (R_1, $R_2 =$ Hi R_3, $R_4 =$ Me), 20515-62-2; **2a** ($R_1 =$ H; R_2, R_3, $R_4 =$ Me), 52837-54-4; **2a** ($R_1 =$ H; $R_2 =$ Ph; R_3, $R_4 =$ Me), 87601-24-9; **2a** ($R_2 =$ Ph; R_1, R_3, $R_4 =$ Me), 60980-85-0; **2b** (R_1, $R_2 =$ H; R_3, $R_4 =$ Me), 44604-24-2; **2b** ($R_1 =$ H; R_2, R_3, $R_4 =$ Me), 96228-11-4; **2b** ($R_1 =$ H; $R_2 =$ Ph; R_3, $R_4 =$ Me), 96228-12-5; **2b** ($R_2 =$ Ph; R_1, R_3, $R_4 =$ Me), 96228-13-6; **3**, 96228-14-7; (*E*)-**4**, 77400-46-5; **5**, 96228-15-8; **6**, 96228-16-9; *cis*-**7**, 96228-17-0; Me_2CO, 67-64-1; norephedrine, 48115-38-4.

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The Role of Hydration and Stereoelectronic Effects in the Hydrolysis of cAMP

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It is well-known that the coenzyme cyclic adenosine 3′,5′-monophosphate[1] is enzymatically hydrolyzed to adenosine 5′-monophosphate[1] with a large exothermic

(1) The abbreviations used are cAMP, cyclic adenosine 3′,5′-monophosphate; 5′-AMP, adenosine 5′-monophosphate.

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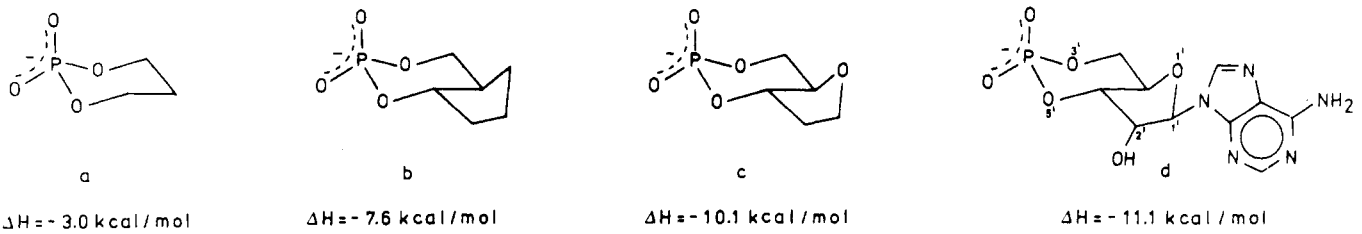
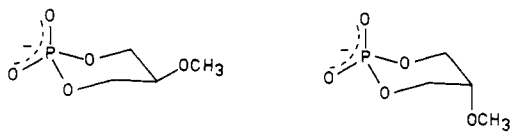


Figure 1. Enthalpies of hydrolysis or trimethylene phosphate (a), *trans*-2-hydroxycyclopentanemethanol cyclic phosphate (b), *trans*-2-hydroxytetrahydrofuranmethanol cyclic phosphate (c), and cAMP[1] (d).

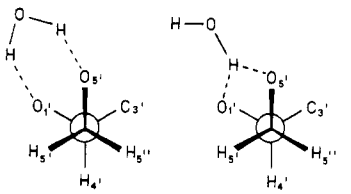
enthalpy (−11.1 kcal/mol), in contrast to trimethylene phosphate (−3.0 kcal/mol). Experimental and theoretical work has demonstrated that the large exothermic enthalpy of cAMP is caused by strain, stereoelectronic effects, and solvation effects. The various contributions to the enthalpy difference between cAMP and trimethylene phosphate, i.e., 8.1 kcal/mol (vide supra), can be derived from experimental work carried out by Gerlt et al.[2-4] Their calorimetric measurements showed that 4.6 kcal/mol is involved for strain, caused by the trans fusion of a cyclopentane ring to trimethylene phosphate (Figure 1). Introduction of an endocyclic oxygen results in a difference of 2.5 kcal/mol, due to stereoelectronic and solvation effects. The presence of the 2′-hydroxyl group and the adenine base on the 1′ location in cAMP is responsible for the remaining 1.0 kcal/mol. The aforementioned stereoelectronic effect disfavors the antiperiplanar arrangement of the phosphate oxygens $O_{5'}$ and $O_{3'}$ and the ribose oxygen $O_{1'}$ (gauche effect[5,6]). The magnitude of this gauche effect was assessed with NMR measurements of the equilibrium between axial and equatorial methoxy in 3-methoxytrimethylene phosphate.[4]



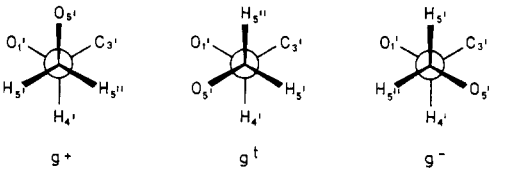
From these measurements it followed that the axial methoxy location (oxygens gauche) is 1.0 kcal/mol lower in energy than the equatorial methoxy location (oxygens trans). Therefore Gerlt divided the enthalpy difference of 3.5 kcal/mol between the hydrolysis of *trans*-2-hydroxycyclopentanemethanol cyclic phosphate and cAMP in 1.0 kcal/mol due to the gauche effect and 2.5 kcal/mol due to solvation effects. The experimental results are in fairly good agreement with quantum chemical calculations carried out by Scheffers-Sap and Buck.[7] They found that strain relief in the ribose ring is responsible for 2.2 kcal/mol (strain in the phosphate ring was not taken into account) of the overall 4.6 kcal/mol (vide supra). According to Scheffers-Sap and Buck the solvation effect suggested by Gerlt is a specific hydration between $O_{5'}$ and $O_{1'}$ which is absent in cAMP, since the distance between $O_{5'}$ and $O_{1'}$ is too large. They obtained for this effect a value of 2–3 kcal/mol, which is in good agreement with the experimental result of 2.5 kcal/mol (vide supra). For the hydration between $O_{5'}$ and $O_{1'}$ two structures were proposed, viz., a five-membered ring structure and a seven-membered ring structure.

Table I. Measured Population Densities of the Three Rotamers around the $C_{4'}$–$C_{5'}$ Bond of 2 in Various Solvents

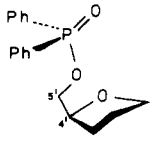
solvent	E_T	$x(g^+)$	$x(g^t)$	$x(g^-)$
C_6D_6	34.5	0.25	0.41	0.34
$CDCl_3$	39.1	0.33	0.38	0.29
$(CD_3)_2CO$	42.2	0.21	0.45	0.34
$(CD_3)_2SO$	45.0	0.17	0.53	0.30
CD_3CN	46.0	0.26	0.47	0.27
CD_3OD	55.5	0.27	0.46	0.26
D_2O	63.1	0.50	0.41	0.09



These structures were calculated to differ only 0.3 kcal/mol in favor of the five-membered ring,[7] a difference too small to select one of the structures. Presently we report new experimental work concerning the magnitude of the gauche effect and the solvation structure, based on a conformational analysis of the model systems 1 and 2. In particular we focused on the conformation around the $C_{4'}$–$C_{5'}$ linkage, which determines the position of $O_{5'}$ with respect to $O_{1'}$. The $C_{4'}$–$C_{5'}$ conformation can be described as an equilibrium between the three staggered rotamers gauche (+), (g^+), gauche (trans), (g^t), and gauche (−), (g^-).



The population densities $x(g^+)$, $x(g^t)$, and $x(g^-)$ of these rotamers were calculated from the NMR spin–spin coupling constants $J_{H_{4'}H_{5'}}$ and $J_{H_{4'}H_{5''}}$ as described by Koole et al.[8] Using this method, we were able to obtain an independent value for the magnitude of the gauche effect of 1.0 kcal/mol (vide supra). In order to isolate the gauche effect from other factors, we used the simplified model system 1. The thermodynamic parameters of the con-



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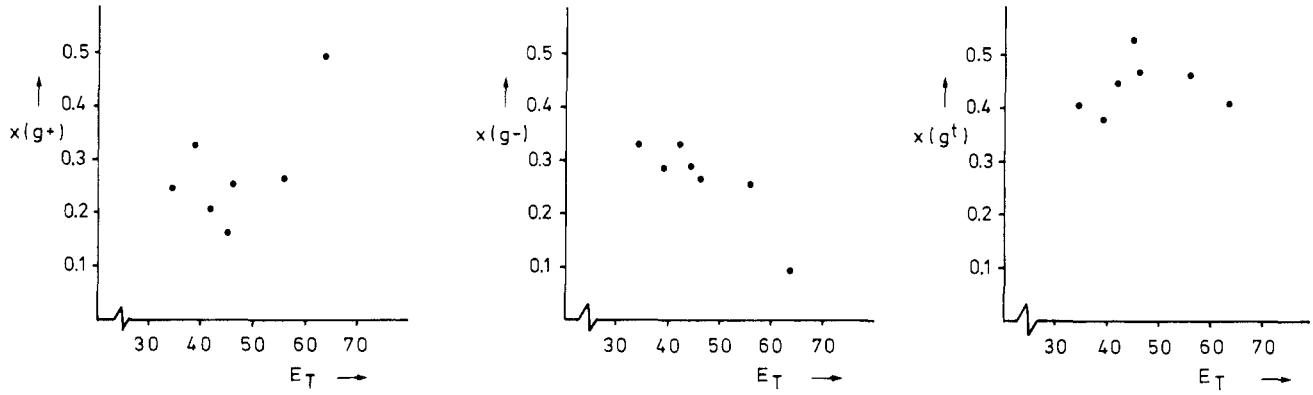
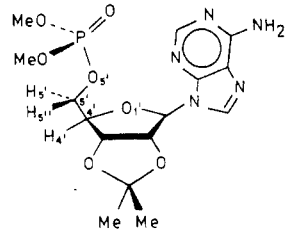


Figure 2. Population densities of the rotamers in solvents of varying polarity.[10]

formational equilibrium around $C_{4'}$–$C_{5'}$ were determined with variable-temperature NMR spectroscopy. Compilation of the conformational data at various temperatures in a van't Hoff plot yielded $\Delta H°(g^-, g^+) = -0.9$ kcal/mol, $\Delta S°(g^-, g^+) = -1.3$ cal/mol·K, $\Delta H°(g^-, g^t) = -1.2$ kcal/mol, and $\Delta S°(g^-, g^t) = -2.0$ cal/mol·K.[9] Since in cAMP the $C_{4'}$–$C_{5'}$ bond is locked in the g^- conformation, while in 5′-AMP the g^+ rotamer is dominant, our value of 0.9 kcal/mol for the gauche effect is in excellent agreement with Gerlt's observation. The solvation structure in 5′-AMP was elucidated by determination of the $C_{4'}$–$C_{5'}$ conformation of **2** in various solvents. In Figure 2, the rotamer



2

populations of g^+, g^t, and g^- are represented as functions of the solvent polarity E_T.[10] It appears that the population of the g^- rotamer, in which $O_{5'}$ is trans to $O_{1'}$, increases as the solvent polarity is lowered. This can be attributed to a charge repulsion between $O_{5'}$ and $O_{1'}$, which becomes more effective at lower polarities. No particular trends are observed for the variations of the g^+ and g^t rotamer populations with E_T. However, it can be seen directly that g^+ is the dominant $C_{4'}$–$C_{5'}$ rotamer in water, whereas g^t is clearly preferred in all other solvents including methanol. This change in preference must be due to a specific solvation between $O_{5'}$ and $O_{1'}$ in water that favors the g^+ rotamer. It seems reasonable to assume that this solvation has a seven-membered ring structure that can exist in water only.

Experimental Section

Spectroscopy. ^{1}H NMR spectra were run in the FT mode at 300 MHz on a Bruker CXP-300 spectrometer and at 500 MHz on a Bruker WM-500 spectrometer. Both instruments are interfaced with an ASPECT 2000 computer. A standard computer simulation–iteration procedure[11] was employed to obtain accurate values for spin–spin coupling constants. ^{31}P NMR spectra were run in the FT mode at 36.4 MHz on a Bruker HX-90 spectrometer with a Digilab FT-NMR-3 pulsing accessory. ^{31}P chemical shifts are related to 85% H_3PO_4 as an external standard.

Synthesis. [(Tetrahydrofurfuryl)oxy]diphenylphosphine Oxide (1). This compound was prepared as described in ref 8.

Dimethoxy(dimethylamino)phosphine. Phosphorus trichloride (0.5 mol, 69 g) was added over 30 min to trimethyl phosphite (1 mol, 124 g) that was kept at 60 °C. After completion of the addition the reaction mixture was cooled to 0 °C and diluted with 500 mL of sodium-dried diethyl ether. Dimethylamine (3 mol, 135 g) was bubbled through the reaction mixture. After filtration of the dimethylamine hydrochloride, evaporation of the diethyl ether yielded a yellowish oil that was distilled twice at 45 mm through a 20-cm Vigreux to afford 46 g (22%) of the desired product: bp 51–52 °C; ^{1}H NMR (C_6D_6) δ 2.63 (6 H, d, $N(CH_3)_2$, $J_{PNCH_3} = 8.8$ Hz), 3.42 (6 H, d, OCH_3, $J_{POCH_3} = 12.0$ Hz); ^{31}P NMR (C_6D_6) δ 147.6.

2′,3′-*O*-Isopropylideneadenosin-5′-yl Dimethyl Phosphite. A magnetically stirred solution of 2′,3′-*O*-isopropylideneadenosine[12] (6.51 mmol, 2.00 g) in 30 mL of dry 1,4-dioxane was kept at 85 °C. A solution of dimethoxy(dimethylamino)phosphine (11.20 mmol, 1.53 g) in 10 mL of dry 1,4-dioxane was added over 3 h. After stirring for 15 h at 85 °C, thin-layer chromatography (TLC) with methyl ethyl ketone (MEK) as eluent showed the 2′,3′-*O*-isopropylideneadenosine (R_f 0.21) to be completely converted in the product (R_f 0.52). Evaporation of the solvent afforded a viscous, yellowish oil that was separated on a Woelm silica gel column using dry MEK as eluent. Pure 2′,3′-*O*-isopropylideneadenosine-5′-yl dimethyl phosphite was obtained as a white crystalline material in 79% yield: mp 164–165 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (3 H, s, CH_3 isopropylidene), 1.64 (3 H, s, CH_3 isopropylidene), 3.47 (6 H, d, OCH_3, $J_{POCH_3} = 10.8$ Hz), 4.00 (2 H, m, $H_{5'}/H_{5''}$), 4.48 (1 H, m, $H_{4'}$), 5.05 (1 H, dd, $H_{3'}$), 5.39 (1 H, dd, $H_{2'}$), 6.19 (3 H, m, $H_{1'}/NH_2$), 8.04 (1 H, s, H_8), 8.36 (1 H, s, H_2); ^{31}P NMR ($CDCl_3$) δ 141.1. Anal. Calcd for $C_{15}H_{22}N_5O_6P$: C, 45.11; H, 5.55; N, 17.54. Found: C, 44.95; H, 5.68; N, 18.06.

2′,3′-*O*-Isopropylideneadenosin-5′-yl Dimethyl Phosphate (2). 2′,3′-*O*-Isopropylideneadenosin-5′-yl dimethyl phosphite (1.13 mmol, 450 mg) was dissolved in 25 mL of dry dichloromethane and an ozone–oxygen (15:85) stream was bubbled through. After 35 min, TLC with MEK as eluent showed the reaction to be complete (R_f 0.27). Evaporation of the dichloromethane yielded the product as a hygroscopic white solid in 96% yield: ^{1}H NMR ($CDCl_3$) δ 11.40 (3 H, s, CH_3 isopropylidene), 1.62 (3 H, s, CH_3 isopropylidene), 3.72 (6 H, d, OCH_3, $J_{POCH_3} = 11.0$ Hz), 4.28 (2 H, m, $H_{5'}/H_{5''}$), 4.51 (1 H, m, $H_{4'}$), 5.13 (1 H, dd, $H_{3'}$), 5.46 (1 H, dd, $H_{2'}$), 6.19 (1 H, d, $H_{1'}$), 6.42 (2 H, br s, NH_2), 8.08 (1 H, s, H_8), 8.48 (1 H, s, H_2); ^{31}P NMR ($CDCl_3$) δ 1.4. Anal. Calcd for $C_{15}H_{22}N_5O_7P$: C, 43.37; H, 5.34; N, 16.87. Found: C, 43.41; H, 5.44; N, 17.09.

Acknowledgment. This investigation has been supported by the Netherlands Foundation for Chemical Re-

(9) $\Delta H°(g^-, g^+)$ and $\Delta H°(g^-, g^t)$ denote the enthalpy differences $H°(g^-) - H°(g^+)$ and $H°(g^-) - H°(g^t)$, respectively, while $\Delta S°(g^-, g^+)$ and $\Delta S°(g^-, g^t)$ denote the entropy differences $S°(g^-) - S°(g^+)$ and $S°(g^-) - S°(g^t)$, respectively. The van't Hoff plots showed little scatter (straight lines with $r^2 = 0.997$),[8] indicating the reliability of the numerical values.

(10) The solvent polarity is not expressed as the bulk dielectric constant but as the empirically determined micropolarity E_T. See: March, J. "Advanced Organic Chemistry", McGraw-Hill: New York, 1977; p 335 and references cited there.

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search (SON) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO). The 500-MHz ^1H NMR spectra were run at the Dutch National 300/500 high field NMR facility at Nijmegen. We thank Dr. J. W. de Haan for valuable discussions and L. J. M. van de Ven and P. van Dael (Nijmegen) for the technical assistance in recording the NMR spectra.

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Two-Dimensional NMR Studies of Marine Natural Products. 2.[1] Utilization of Two-Dimensional Proton Double Quantum Coherence NMR Spectroscopy in Natural Products Structure Elucidation—Determination of Long-Range Couplings in Plumericin

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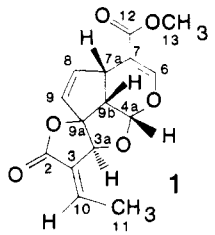
Two-dimensional NMR experiments have provided a convenient means of access to multiple quantum information,[2,3] this work leading to the development of the proton double quantum experiment recently described by Mareci and Freeman.[4] Although the proton double quantum technique has been applied to large molecule,[5-9] there have been no reported applications of the technique in natural products structure elucidation. We would therefore like to report the isolation of plumericin (1) from



1

Cliona caribboea and the utilization of the proton double quantum experiment to uncover spin coupling pathways where $J \sim 0$ Hz[3,6,9] which were not observed in the much more commonly utilized COSY experiment.[10-12] The assignment of the ^{13}C NMR spectrum of 1 is also reported through the use of two-dimensional proton–carbon heteronuclear chemical shift correlation techniques.[13-15]

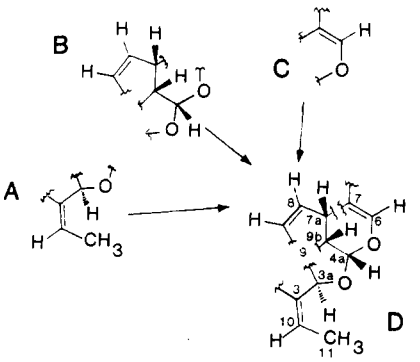


Figure 1. Structural fragments of plumericin assembled (A–C) from COSY data and from the two-dimensional proton double quantum spectrum (D) shown in Figure 2.

Results and Discussion

On the basis of the 300-MHz ^1H NMR spectrum and mass spectral data, 1 was tentatively identified as plumericin (3-ethylidine-3,3a,7a,9b-tetrahydro-2-oxo-2*H*,4*H*-1,4,5-trioxa-1*H*-dicyclopent[*a*,*hi*]indene-7-carboxylic acid methyl ester). The unprecedented occurrence of plumericin (1) in a marine invertebrate prompted us to initiate a carefully detailed study of the molecule. We were especially interested in the examination of the molecule for long-range spin-coupling pathways which would link together the several discrete proton spin systems contained in the structure despite the fact that no long-range coupling information was contained in the previous reports on the structure determination[16] or in the COSY spectrum. Rather than utilizing variants of the COSY experiment intended to emphasize long-range couplings,[11,17,18] we instead employed the proton double quantum experiment[4] which should also be suitable for this purpose.[3,6,9]

Structural fragments of plumericin (1) which are shown in Figure 1 were assembled from a COSY spectrum (not shown). Initial attempts at linking these components via homonuclear decoupling were unsuccessful because of the digitization employed during the survey decoupling experiments, thus representing a potential source of ambiguity in either the case of molecules of unknown structure or in those cases where the molecule is somewhat larger and the possibilities of selecting a permuted connectivity consequently are greater.

The proton double quantum coherence spectrum,[4] shown in Figure 2, did successfully link the structural components derived from the COSY experiment to afford the single large structural fragment shown in Figure 1. The final structure of the molecule follows directly from the large structural fragment. The utility of the proton double quantum experiment derives from several of its features which are worthy of further comment. First, responses in the double quantum frequency domain (ω_1 or F_1) are observed at the algebraic sum of the offsets of the coupled spins from the carrier frequency (0 Hz on the axis above

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