structures[22,23] as well as enzymatic and nonenzymatic codon–anticodon recognition.[24] The odd tautomers of cytosine and guanine, for example, may well provide a molecular rationale for the widespread occurrence of A–C and G–U base pairs thought to be present in tRNA structures.[25]

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Studies on Transfer Ribonucleic Acids and Related Compounds. V.[1] Synthesis of Ribonucleotides with Phosphomonoester End Groups on a Polymer Support

Eiko Ohtsuka, Shigeo Morioka, and Morio Ikehara*

Contribution from the Faculty of Pharmaceutical Sciences, Osaka University, Toyonaka, Osaka, Japan. *Received August 20, 1971*

Abstract: Protected ribooligonucleotides with 3′-phosphate end groups have been synthesized on a 4′-aminophenoxymethylpolystyrene support. The dinucleotide, Bz-C^{Bz}-(OBz)-*p*-U(OBz)-*p*, which was prepared by condensation of Bz-C^{Bz}(OBz)-*p* with the amidate resin of U(OBz)-*p* and liberated with isoamyl nitrite, was isolated by gel filtration on Sephadex LH-20 in 38% yield. The synthesis of four dinucleotides containing monomethoxytrityl groups and the trinucleotide ApUpGp is described.

The concept of polymer support synthesis developed in the polypeptide field[2,3] has been introduced by Letsinger into polynucleotide synthesis.[4] Several approaches have been devised for the synthesis of deoxyribopolynucleotides without phosphate end groups.[5–7] Blackburn has synthesized pTpTpT[8] on an insoluble resin containing aminophenoxymethylstyrene and released the product with acid treatment.[10] The acid treatment is not applicable to purine deoxyribonucleotides. The glycosidic linkage of N-acylated deoxyadenosine is especially labile to acid. The 2-(α-pyridyl)-ethanol function which was used to link phosphomonoesters to polystyrene required alkali to liberate thymidine oligonucleotides.[11] Recently Yip and Tsou reported a synthesis of uridine trinucleotide without a phosphomonoester end group using succinylated polystyrene which was cleaved with ammonia from the product.[12] Neither the acidic nor the alkaline condition is compatible with the oligonucleotides bearing specific protecting groups suitable for the fragment condensation. Polymer support synthesis of protected oligonucleotides has yet to be achieved.

The present paper reports the synthesis of protected ribooligonucleotides bearing 3′-phosphate end groups using an insoluble polymer of 4′-aminophenoxymethylstyrene and isoamyl nitrite treatment to release the protected oligonucleotides. Previously we described that aromatic phosphoramidates of protected ribonucleotides were key intermediates for ribooligonucleotide synthesis and could be selectively converted to the corresponding phosphate by the treatment with isoamyl nitrite.[9] The aromatic amidate group of protected deoxyribooligonucleotides also has been removed by this method without damage to glycosidic linkages or N protecting groups.[13] In this paper charging and release of protected deoxyribo- and ribomononucleotides are described first. Detritylation of ribonucleotides linked to the polymer allows condensation with protected ribonucleoside 3′-phosphates to yield protected ribooligonucleotides.

Kinetics of Charging and Release of the Mononucleotide

The formation of the phosphoramidate linkage and the recovery of nucleotides were studied first using 3′-*O*-acetylthymidine 5′-phosphate (I) and 4′-aminophenoxy-

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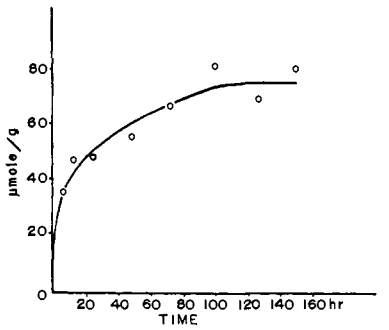
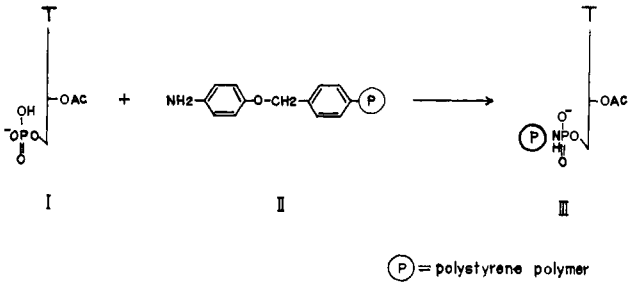


Figure 1. Pyridinium 3′-*O*-acetylthymidine 5′-phosphate (0.72 mmol) was allowed to react with resin (302 mg, 0.36 mmol of amino function) using DCC (7.1 mmol) in pyridine (1.4 ml) at 27–28° rotating the flask. At different time intervals, aliquots (*ca.* 15–20 mg) of the resin were taken and washed successively with pyridine, 1-butanol, and 1:1 pyridine–acetic acid. The washed resin was treated with isoamyl nitrite (0.07 ml) in 1:1 pyridine–acetic acid (0.24 ml) for 24 hr and centrifuged. An aliquot of the supernatant was subjected to paper chromatography in solvent B. The amount of the nucleotide was estimated by measuring the absorbance of the spots after elution from the paper chromatogram.

methylpolystyrene[10] (II). The resin contained 2% divinylbenzene and 1.19 mmol/g of amino functions as determined by elemental analysis. The nucleotide I and the resin II were condensed with dicyclohexylcarbodiimide (DCC) in pyridine (Chart I). Aliquots

Chart I



of the resin III were taken at different time intervals and the amount of nucleotide was measured to determine the extent of the charging. The reaction conditions and the results are shown in Figure 1 and Table I.

Table I. Charging of the Mononucleotide to the Aminophenoxy Resin

Time, hr	Aliquot taken, mg	Released nucleotide in supernatant/aliquot, A_{260} unit	Released nucleotide[a] in supernatant/g, μmol	Total nucleotide/g.[b] μmol
6	15.4	4.95	36	
12	30.3	12.6	47	
24	29.7	12.6	48	
48	23.0	11.2	55	
72	9.7	5.6	66	
100	12.8	9.1	81	94
125	9.1	5.5	68	94
148	8.4	5.9	80	95

[a] Measured as described in the legend to Figure 1. [b] Total nucleotide recovered by an extensive washing of the resin with 1:1 pyridine–acetic acid.

After 100 hr the reaction leveled off. As seen in the last column of Table I, extensive washing with pyridine–acetic acid liberated an additional amount of the nucleotide. This may mean that a certain amount of the nucleotide was bound rather firmly to guanidine residues which were formed from amino groups of the resin and DCC. About 8% of the amino groups of the resin was charged in this experiment. To test the recovery of the mononucleotide, the phosphorus content of the amidate resin III was determined and compared with the amount of liberated mononucleotide. The kinetic curve of the liberation of the mononucleotide with isoamyl nitrite in pyridine–acetic acid is shown in Figure 2. The reaction shown was performed by shaking the flask. Rotation of the flask, however, gave a faster reaction rate. Using conditions similar to Figure 2, 96% of the mononucleotide was released after 4 hr by rotating the reaction vessel.

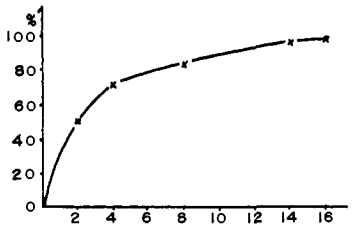


Figure 2. The phosphoramidate resin charged with 3′-*O*-acetylthymidine 5′-phosphate (59 mg, 0.15 mmol/g, as determined by phosphorus analysis) was treated with isoamyl nitrite (0.35 ml) in 1:1 pyridine–acetic acid (0.7 ml). Aliquots (40 μl) of the supernatant were taken and subjected to paper chromatography in solvent B. The amount released from the resin was expressed by percentage of the phosphorus content of the phosphoramidate resin. The reaction was performed by shaking the flask.

From these experiments it may be concluded that charging of the mononucleotide to the resin is not quantitative but the release of the mononucleotide from the resin is essentially quantitative.

Chart II

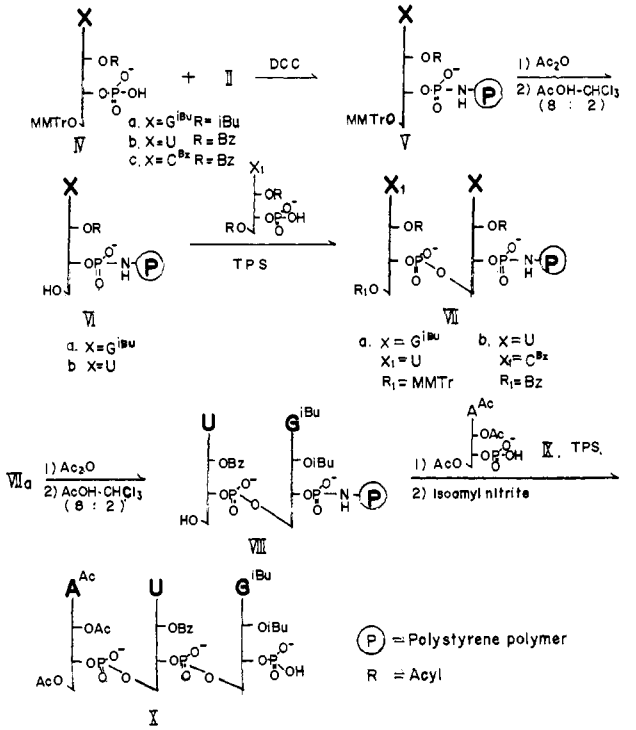


Table II. Reaction Conditions and Yields in the Synthesis of Dinucleotides

Product	Nucleotide attached to the polymer, μmol	Resin	Condensed nucleotide, μmol	Pyridine, ml	TPS, μmol	Reaction time, hr	Yield, %
MMTr-G$^{i\text{-}Bu}$(O-*i*-Bu)-*p*-U(OBz)-*p*	U(OBz)-*p*, 25	0.5	MMTr-G$^{i\text{-}Bu}$(O-*i*-Bu)-*p*, 125	1.5	250	46	40
MMTr-U(OBz)-*p*-G$^{i\text{-}Bu}$(O-*i*-Bu)-*p*	G$^{i\text{-}Bu}$(O-*i*-Bu)-*p*, 50	1.0	MMTr-U(OBz)-*p*, 250	1.5	550	49	36
MMTr-G$^{i\text{-}Bu}$(O-*i*-Bu)-*p*-G$^{i\text{-}Bu}$(O-*i*-Bu)-*p*	G$^{i\text{-}Bu}$(O-*i*-Bu)-*p*, 6.0	0.12	MMTr-G$^{i\text{-}Bu}$(O-*i*-Bu)-*p*, 90	0.5	480	49	5
MMTr-G$^{i\text{-}Bu}$(O-*i*-Bu)-*p*-C^{Bz}(OBz)-*p*	C^{Bz}(OBz)-*p*, 4.5	0.03	MMTr-G$^{i\text{-}Bu}$(O-*i*-Bu)-*p*, 50	0.5	110	36	20
Bz-C^{Bz}(OBz)-*p*-U(OBz)-*p*	U(OBz)-*p*, 73	0.25	Bz-C^{Bz}(OBz)-*p*, 52	0.5	295	8	38

Table III. Paper Chromatography, Electrophoresis, and Spectral Properties of Nucleotides

Compounds	Paper chromatography, R_f in solvent A[a]	B	C[a]	D	Paper electrophoresis, rel mobilities to Gp	Spectral properties, λ_{max}, nm H_2O	H^+	OH^-	$\epsilon_{280/260}$ H_2O
Cp	1.52	0.23	1.57						
Up	1.64	0.33	1.10	0.66	1.06				
G3′-*p*	1.00		1.00	0.38	1.00				
A3′-*p*	2.12		1.06	0.13					
UpGp	0.58		0.65		1.06	257	258	259	0.53
GpUp	0.43		0.61		1.06	257	259	260	0.55
GpGp	0.22		0.48		1.08	254	257	257–266	0.67
GpCp	0.45		0.80		1.03	258, 266	263, 276	267	0.74
CpUp	0.61		0.97			266	269	265.5	0.64
ApUpGp	0.22					257	258	259	0.46
Bz-C^{Bz}(OBz)-*p*		0.77							
U(OBz)-*p*		0.45							
Bz-C^{Bz}(OBz)-*p*-U(OBz)-*p*		0.70							

[a] R_f relative to G3′-*p*

Similarly, the resin II was condensed with MMTr-G$^{i\text{-}Bu}$(O-*i*-Bu)-*p* (IVa), MMTr-U(OBz)-*p* (IVb), and MMTr-C^{Bz}(OBz)-*p* (IVc) to the extent of 9, 40, and 18% of the amino function, respectively. The treatment of the amidate resins V with isoamyl nitrite in 1:1 pyridine–acetic acid released the protected nucleotides without damage to the protecting groups.

Synthesis of Protected Ribooligonucleotides

For the synthesis of ribooligonucleotides on the polymer, the unchanged amino functions on the resin were blocked by acetylation to prevent their further reaction. Detritylation of the amidate polymers V under various conditions was studied. The extent of detritylation was assayed by treating VI with isoamyl nitrite to release mononucleotides. A mixture of acetic acid–chloroform (8:2) at 30° cleaved the trityl group of V almost quantitatively within 24 hr. Substitution of chloroform with methylene chloride gave a complete reaction under the same conditions. If water was present in this reaction the phosphoramidate linkage was cleaved to a small extent. The detritylated resins VI were then used for the chain elongation. Protected mononucleotides were allowed to react with VI using triisopropylbenzenesulfonyl chloride (TPS) as the condensing reagent. The reaction conditions and yields are summarized in Table II. Dinucleotides were obtained in 20–40% yield except in the case of MMTr-G$^{i\text{-}Bu}$(O-*i*-Bu)-*p*-G$^{i\text{-}Bu}$(O-*i*-Bu)-*p*. The protected dinucleotides liberated from VII were characterized by paper chromatography and paper electrophoresis after removal of the protecting groups. R_f values and spectral properties are given in Table III.

For the synthesis of the trinucleotide ApUpGp, the resin VIIa was treated with acetic anhydride in pyridine and the trityl group of VIIa was removed as described for V. The resin VIII obtained was condensed with *N*,2′,5′-triacetyladenosine 3′-phosphate (IX) using TPS. The protected trinucleotide X was released by treatment of the amidate resin with isoamyl nitrite and deprotected with methanolic ammonia. The unprotected trinucleotide ApUpGp was purified by paper chromatography. The isolated yield from VIIa was 10%. An aliquot of ApUpGp was hydrolyzed with RNase M[14] to give Ap, Up, and Gp in the correct ratio.

Isolation of the Dinucleotide, Bz-C^{Bz}(OBz)-*p*-U(OBz)-*p*, by Gel Filtration

Isolation and purification of protected oligonucleotides can be performed by ion-exchange chromatography on TEAE–cellulose.[9] Gel filtration in organic solvents using Sephadex LH-20 has also been used for the isolation of a hexanucleotide.[15] This method should be useful for the separation of dinucleotides

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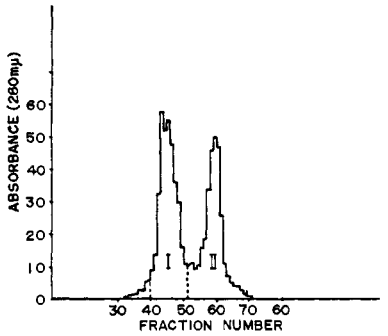

Figure 3. Gel filtration of the dinucleotide Bz-C^{Bz}(OBz)-p-U(OBz)-p. The concentrated solution (0.5 ml) of the reaction mixture was applied to a column (1.2 × 108 cm) of Sephadex LH-20 preequilibrated with 90% ethanol. Fractions of 1.1 ml were collected. Peak I contained the dinucleotide (760 A_{260} units, 468 A_{280} units) and peak II contained the mononucleotides (331 A_{280} units).

from polymer support synthesis, because dinucleotides released from the resin are free from the pyrophosphate of the incoming nucleotide, which has almost the same size as the dinucleotide. The reaction conditions for the synthesis of protected dinucleotide Bz-C^{Bz}(OBz)-*p*-U(OBz)-*p* are summarized in Table II. The release of the dinucleotide from VIIb was as described for V. The isolated yield, 38%, was comparable to the liquid-phase synthesis using Bz-C^{Bz}(OBz)-*p* and U(OBz)-pNHPhOCH$_3$.[16] The elution pattern and the condition of gel filtration on a column of Sephadex LH-20 are shown in Figure 3. Peak I contained the essentially pure dinucleotide which was characterized by paper chromatography and paper electrophoresis before and after removal of the protecting groups.

General Comments

The present study shows that the suitably protected ribooligonucleotides with 3′-phosphate which are key intermediates in the preparation of larger ribooligonucleotides by the fragment condensation method are synthesized on the phosphoramidate resin and released by isoamyl nitrite treatment in pyridine and acetic acid. It has also been shown that the ribodinucleotide products in polymer support synthesis are a less complex mixture than the ones obtained by liquid phase synthesis. The dinucleotide could be isolated from the mononucleotides by gel filtration which requires less time for elution and lower concentration of the buffer. This may be the method of choice for rapid syntheses of protected ribodinucleotides. As has been described for the synthesis of ApUpGp, the unprotected oligonucleotide could be obtained without column chromatography, providing the final product was separated from shorter oligonucleotides by paper chromatography or electrophoresis.

The synthesis of protected deoxyribooligonucleotides on a polymer support has not yet been achieved. We have described previously that protected deoxyribotrinucleotides are stable during treatment with isoamyl nitrite in pyridine–acetic acid.[13a] A highly liophilic aromatic phosphoramidate of deoxyribonucleotides which was used as a protecting group of the 5′-phosphomonoester was also treated with isoamyl nitrite to convert to the corresponding phosphate.[13b] Polymer support synthesis of protected deoxyribooligonucleotides can probably also be performed using the present method.

Stepwise condensation of mono- and oligonucleotides on polymer support for the synthesis of longer oligonucleotides is under investigation.

Experimental Section

General Methods. Paper chromatography was performed by the descending technique. The solvent systems used were: A, isopropyl alcohol–concentrated ammonia–water (7:1:2, v/v); B, ethanol–1 *M* ammonium acetate, pH 7.5 (7:3: v/v); C, 1-propanol–concentrated ammonia–water (55:10:35, v/v); D, saturated ammonium sulfate–water–isopropyl alcohol (79:19:2, v/v). Paper electrophoresis was performed at pH 7.5 (0.05 *M* triethylammonium bicarbonate, 900 V/40 cm) and 3.5 (0.05 *M* ammonium formate, 700 V/40 cm). Other general methods including enzymatic hydrolysis are as described previously.[9]

Pyridinium 5′-*O*-monomethoxytrityl-*N*,2′-*O*-dibenzoylcytidine 3′-phosphate,[9] 5′-*O*-monomethoxytrityl-2′-*O*-benzoyluridine 3′-phosphate,[17] and *N*,2′,3′-*O*-triacetyladenosine 3′-phosphate[18] were prepared as described. Pyridinium 5′-*O*-monomethoxytrityl-*N*,2′-*O*-diisobutyrylguanosine 3′-phosphate was synthesized from 5′-*O*-monomethoxytritylguanosine 3′-phosphate[19] using isobutyric anhydride and tetraethylammonium isobutyrate. 4′-Aminophenoxymethylpolystyrene[10] was prepared from polystyrene (100–200 mesh) containing 2% divinylbenzene, which was donated by Mitsubishi Chemical Industries. All reactions involving the resin were carried out rotating the reaction flask at 27–28° unless otherwise mentioned. The resin and nucleotides were rendered anhydrous with repeated evaporation of pyridine. After each condensation the resin was washed successively with aqueous 50% pyridine, 1:1 pyridine–acetic acid, 1:1 pyridine–methylene chloride, and 1:1 methylene chloride–ether. General procedures for the charging of mononucleotides to the resin are given in the legend to Figure 1. Elemental analysis of polymers for phosphorus was performed by a modification of Allen's method as described in ref 10.

Phosphoramidate Polymer Va. 4′-Aminophenoxymethylpolystyrene (1.26 g, 1.0 mmol of amino function) was swelled in pyridine and allowed to react with pyridinium 5′-*O*-monomethoxytrityl-*N*,2′-*O*-diisobutyrylguanosine 3′-phosphate (1 mmol) using DCC (10 mmol) in pyridine (15 ml) for 100 hr. Water (15 ml) was added and the mixture was kept at 30° for 2 hr. The resin was washed successively with pyridine, 1-butanol, and 1:1 pyridine–acetic acid. An aliquot was taken for analysis. The amount of the charged nucleotide was determined as described in the legend to Figure 1. The mononucleotide was charged to the extent of 1210 A_{260} units (0.072 mmol)/g.

Phosphoramidate Polymer Vb. The amino polymer (0.5 g, 0.59 mmol of amino function) was swelled in pyridine and condensed with pyridinium 5′-*O*-monomethoxytrityl-2′-*O*-benzoyluridine 3′-phosphate (1 mmol) using DCC (10 mmol) in pyridine (3 ml) for 100 hr. Water (3 ml) was added and the mixture was kept for 2 hr. The resin was washed as described for Va. The resin contained the mononucleotide 3260 A_{260} units (0.25 mmol)/g.

Detritylated Amidate Polymer VIa. Va (1.0 g, 0.05 mmol of nucleotide residue) was treated with acetic anhydride (0.8 ml) and pyridine (2 ml) for 48 hr. The resin was then detritylated with 8:2 acetic acid–chloroform (40 ml) at 30° for 24 hr and washed with solvents as described in the section on general methods.

Dinucleotide Amidate Polymer VIIa. The resin VIa obtained above was condensed with 5′-*O*-monomethoxytrityl-2′-*O*-benzoyluridine 3′-phosphate (0.25 mmol) using TPS (0.55 mmol) in pyridine (1.5 ml) in the presence of triethylamine (0.5 mmol) and tri-*n*-butylamine (0.28 mmol). After 49 hr 50% aqueous pyridine was added and the mixture was kept at room temperature for 2 hr. The resin was washed as described in the section on general methods. The yield (0.018 mmol, 36%) was determined by treatment of an aliquot of the resin with isoamyl nitrite as mentioned in the legend to Figure 1 to release the dinucleotide MMTr-U(OBz)-*p*-G-$^{i\text{-Bu}}$-

(16) Unpublished experiments by E. Ohtsuka, K. Fujiyama, and M. Ikehara.

(17) R. Lohrmann, D. Söll, H. Hayatsu, E. Ohtsuka, and H. G. Khorana, *J. Amer. Chem. Soc.*, 88, 819 (1966).

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(O-*i*-Bu)-*p*. R_f values and spectral properties of the unprotected dinucleotide are shown in Table III. For analysis UpGp was degraded with pancreatic RNase to give Up (0.69 A_{260} unit) and Gp (0.76 A_{260} unit) which were separated by paper chromatography in solvent C and measured absorbance in water. The ratio found was 1.1:1.0. The undigested compound was not detected.

Adenylyl-(3′–5′)-uridylyl-(3′–5′)-guanosine 3′-Phosphate. The phosphoramidate resin VIIa (0.81 g, 14.6 μmol of dinucleotide) was treated with acetic anhydride (0.8 ml) in pyridine (2 ml) for 20 hr and detritylated with 8:2 acetic acid–chloroform (60 ml) at 30° for 24 hr. The resin VIII was washed and swelled in pyridine. Pyridinium *N*,2′,5′-*O*-triacetyladenosine 3′-phosphate (0.25 mmol) was added to the suspension of the resin and rendered anhydrous with added pyridine and triethylamine (0.55 mmol). The mixture was allowed to react with TPS (0.55 mmol) in pyridine (1.5 ml) and tri-*n*-butylamine (0.27 mmol) for 8 hr at room temperature. Aqueous pyridine (50%, 1.5 ml) was added and the resin was washed by the usual method. Liberation of the trinucleotide X from the resin was carried out with isoamyl nitrite (0.7 ml) in 1:1 pyridine–acetic acid (1.4 ml) for 10 hr at room temperature. The resin was removed by filtration and the filtrate and washings were combined and evaporated with aqueous pyridine. The trinucleotide X was precipitated from the pyridine solution with ether. The unprotected trinucleotide ApUpGp was isolated by paper chromatography in solvent C after treatment of X with 15 *N* methanolic ammonia for 20 hr. The yield was 49 A_{260} units, 1.49 μmol (10.2%) from VIIa. R_f values and spectral properties are given in Table III. ApUpGp was digested with RNase M to give Ap (0.741 A_{260} unit), Up (0.504 A_{260} unit), and Gp (0.62 A_{260} unit) as measured by corresponding spots on the paper chromatogram (solvent D). The ratio found was 0.94:0.97:1.00. Undigested compounds were not detected.

Synthesis and Isolation of the Dinucleotide Bz-C^{Bz}(OBz)-*p*-U(OBz)-*p*- by Gel Filtration. Phosphoramidate resin (Vb) (0.25 g, 0.08 mmol of nucleotide) was treated with acetic anhydride (5 ml) in pyridine (10 ml) for 48 hr. The resin was washed and treated with acetic acid–chloroform (8:2) at 30° for 24 hr. Pyridinium *N*,2′,5′-*O*-tribenzoylcytidine 3′-phosphate (1390 A_{260} units, 0.052 mmol) was allowed to react with the resin swelled with anydrous pyridine using TPS (0.295 mmol) in pyridine (0.5 ml) and tri-*n*-butylamine (0.29 mmol) for 8 hr. Tri-*n*-butylamine (0.07 ml) and 50% aqueous pyridine (10 ml) were added. After 1 hr the resin was washed and treated with isoamyl nitrite (0.67 ml, 5 mmol) in 1:1 pyridine–acetic acid (1.34 ml) at 25° for 24 hr. The resin was removed by filtration and the filtrate and washings were concentrated to 0.5 ml. The solution was applied to a column (1.2 × 108 cm) of Sephadex LH-20 preequilibrated with 90% ethanol. The elution pattern and conditions are shown in Figure 3. Fractions 40–50 (peak I) were combined and evaporated with pyridine. The protected dinucleotide was precipitated from the pyridine solution with ether. The spectral properties of Bz-C^{Bz}(OBz)-*p*-U(OBz)-*p* were $\lambda_{max}^{H_2O}$ 235.5, 262, 306 nm; $\lambda_{max}^{H^+}$ 235.5, 262, 314 nm; $\lambda_{max}^{OH^-}$ 234, 272, 318 nm; $\epsilon_{235}/\epsilon_{260} = 1.45$ and $\epsilon_{260}/\epsilon_{305} = 3.37$. The spectral properties of CpUp are shown in Table III. CpUp (*ca.* 2 A_{260} units) was degraded with pancreatic RNase. The mixture was applied to paper electrophoresis (0.05 *M* ammonium formate, pH 3.5, 700 V/40 cm) to separate Cp (0.98 A_{260} unit at pH 2, 0.14 μmol) and Up (1.27 A_{260} units at pH 2, 0.13 μmol). The ratio found was 1.1:1.0. The undigested material was not detected.

Acknowledgment. We are indebted to Dr. M. Irie for the gift of RNase M and to Mitsubishi Chemical Industries for the polystyrene. We also thank Dr. D. Söll for reading the manuscript.

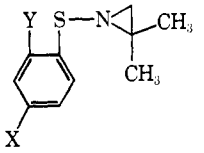
Communications to the Editor

Stereochemistry in Trivalent Nitrogen Compounds. XIX. Absence of a Rate Acceleration to Nitrogen Inversion in Sulfenylaziridines Due to d-Orbital Conjugation

Sir:

The possible effect of (p–d) π conjugation on barriers to nitrogen inversion has been a topic of some interest recently.[1] The early suggestion that (p–d) π conjugation lowers barriers in haloaziridines has been shown to be in error,[1e] and molecular orbital calculations have implied that planarity at nitrogen in silylamines is due to the low electronegativity of the silicon atom rather than d-orbital conjugation.[1a,1b] On the other hand, (p–d) π bonding has been suggested as a contributor to torsional barriers about sulfur–nitrogen bonds,[2] and a number of compounds with S–N bonds have been shown to be planar or nearly planar at nitrogen.[3] The low barriers to nitrogen inversion in sulfenyl-, sulfinyl-, and sulfonylaziridines[4] might have been due to d-orbital resonance since (p–p) π conjugation is known to lower aziridine nitrogen inversion barriers.[1]

Hammett analysis has demonstrated a substantial effect from polar substituents on torsional barriers in sulfenylsulfonamides and has indicated that the dependence observed was related to (p–d) π bonding between nitrogen and sulfur.[2b] A similar study of nitrogen inversion barriers would allow a determination of the importance of (p–d) π bonding in lowering nitrogen inversion barriers in sulfenylaziridines. We have examined nitrogen inversion barriers in a series of para-substituted benzenesulfenylaziridines, **1**. The free



1a, X = OCH_3; Y = H
b, X = CH_3; Y = H
c, X = Y = H
d, X = Cl; Y = H
e, X = Br; Y = H
f, X = NO_2; Y = H
g, X = Y = NO_2

energies of activation can be determined accurately[5] at

(1) For review articles which discuss this point see: (a) J. M. Lehn, *Fortsch. Chem. Forsch.*, **15**, 311 (1970); (b) A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem., Int. Ed. Engl.*, **9**, 400 (1970); (c) H. Kessler, *ibid.*, **9**, 219 (1970); (d) J. B. Lambert, *Top. Stereochem.*, **6**, 19 (1971); (e) S. J. Brois, *Trans. N. Y. Acad. Sci.*, **31**, 931 (1969).

(2) (a) W. B. Jennings and R. Spratt, *J. Chem. Soc. D*, 1418 (1970); (b) M. Raban and F. B. Jones, Jr., *J. Amer. Chem. Soc.*, **93**, 2692 (1971).

(3) (a) T. Jordan, H. W. Smith, L. L. Lohr, and W. N. Libscomb, *ibid.*, **85**, 846 (1963); (b) R. E. Cook, M. D. Glick, J. J. Rigau, and C. R. Johnson, *ibid.*, **93**, 924 (1971); (c) J. Kay, M. D. Glick, and M. Raban, *ibid.*, **93**, 5224 (1971).

(4) (a) F. A. L. Anet, R. D. Trepka, and D. J. Cram, *ibid.*, **89**, 359 (1967); (b) F. A. L. Anet and J. M. Osyany, *ibid.*, **89**, 352 (1967); (c) J. M. Lehn and J. Wagner, *Chem. Commun.*, 1298 (1968).

(5) D. Kost, E. H. Carlson, and M. Raban, *J. Chem. Soc. D*, 656 (1971).