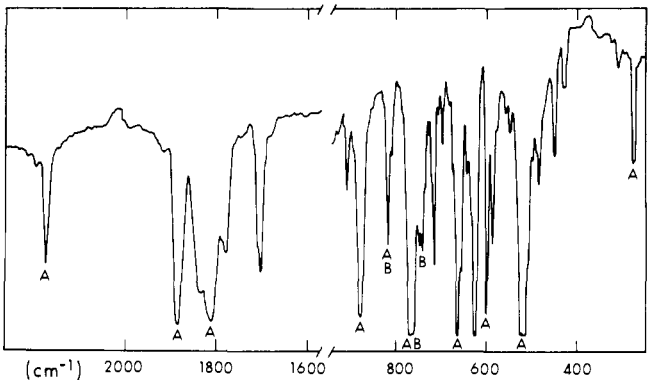

Figure 2. An IR spectrum of **8** in 3-methylpentane taken at 135 K. The absorptions due to **9** and the solvent are indicated by A and B, respectively.

finger print and above 1500 cm^{-1} the presence of a medium absorption at 1700 cm^{-1} deserves attention (*vide infra*).

Photochemical reactions of **5** at 4–10 K duplicate approximately those performed at 77 K, but the formation of an additional minor product is noticeable. Thus, the 4 K photolysate (designated as **11**), after being warmed to 135 K, exhibited an additional ^{19}F NMR signal at $\delta(CFCl_3)$ 60.2 ppm and its intensity was approximately one-tenth of that assigned to **8** (*vide supra*). This new signal disappeared at around 220 K, but the fate of this thermolysis is not yet clear. The IR spectrum of **11** in an argon matrix contained some minor absorptions in addition to those of **8**, and the overall intensity of its UV absorption was definitely less intense than what one expects with the 100% conversion of **5** into **8**, even when all possible errors in measurement are taken into account. While the formation of this new, minor product is definite and its identification is highly desirable, one can safely state at this stage that the main (90% or more) photoproduct at 4 K is **8**, and not the corresponding tetrahedrane derivative.

Tetrakis(trifluoromethyl)[4]annulene (**8**) is the first symmetrically substituted derivative of **1**, whose full spectral characterization has been completed. It has a singlet ground state. If the assignment of the IR band at 1700 cm^{-1} (*vide supra*) to the C=C stretching vibration proves to be correct,[17] then the geometry of **8** is not square, but rectangular. The present study has also demonstrated that the direct irradiation of **8** at low temperatures does not lead to the formation of the tetrahedrane system at least as a major course of reaction,[1b] but rather to that of a species which undergoes the 1,3 bond cleavage of the bicyclobutane system.[18]

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(9) Because of the presence of trifluoroacetic anhydride that forms as a result of photoinduced fragmentation of **5**, only two regions, one for double bonds and the other below 900 cm^{-1}, are useful for the identification of the product in question.
(10) Approximately 10 or 20 μL of **5** in 0.5 mL of the solvent for ^{19}F NMR (solvent lock) and 90 μL in 1.5 mL for ^{13}C NMR (^{19}F-decoupling at 69.0 ppm, acetone-d_6 in $CHFCl_2$ lock) were used.
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(12) ^{19}F NMR spectra of **5** are temperature dependent.
(13) For ^{19}F NMR spectral data of reference compounds (intensity in bracket): **6**, $\delta(CFCl_3)$ 55.8, 58.6, and 62.5 (1:1:1) in tetrahydrofuran-d_8; **7**, $\delta(CFCl_3)$ 64.7and66.8(1:1)inC_6F_6(δ166.5);hexakis(trifluoromethyl)bicyclo[2.2.0]-hexane (**10**), $\delta(CFCl_3)$ 66.0 and 66.5 (2:1) in pentane, 65.4 and 66.0 in tetrahydrofuran-d_8. See also ref 8a; (a) J. A. Ross, R. P. Seiders, and D. M. Lemal, *J. Am. Chem. Soc.*, **98**, 4325 (1976); (b) Y. Kobayashi, I. Kumadaki, A. Ohsawa, and Y. Sekine, *Tetrahedron Lett.*, 2841 (1974).
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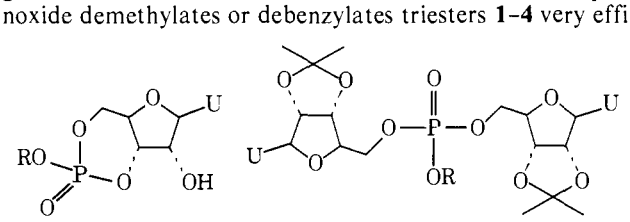
Synthesis of Oligoribonucleotides Based on the Facile Cleavage of Methyl Phosphotriester Intermediates

Sir:

One significant aspect of oligoribonucleotide synthesis is the development of new protecting groups[1,2] for the phosphate, hydroxyl, and amino moieties, for example the masking of phosphodiester intermediates as specifically designed triesters (β,β,β-trichloroethyl ester, β-cyanoethyl ester, phenoxy esters) from which the parent is obtained by the action of either a reducing[1,3] or a distinctly alkaline reagent.[1,4] We wish to report that the methyl group may serve as an alternate protecting group for phosphodiesters, offering the advantage of selective removal under very mild conditions, without phosphate isomerization.[5] This method represents the first directed chemical synthesis of oligoribonucleotides of defined sequence using an S_N2-based cleavage of a phosphate protecting group.

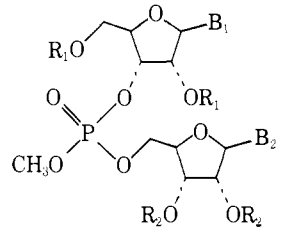
The ability of thiolate to cleave carboxylate esters[6] and in particular simple phosphate triesters[7] suggested that the method could be used synthetically in the production of oligoribonucleotides. Indeed, it was found that lithium thiophenoxide demethylates or debenzylates triesters **1**–**4** very effi-



1, R = CH_3
2, R = $CH_2C_6H_5$
3, R = CH_3
4, R = $CH_2C_6H_5$

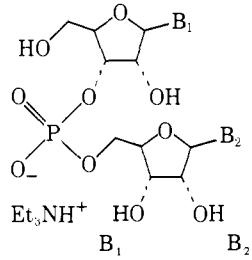
ciently (>95%) in THF/HMPA at ambient temperature within 30 min. It was later observed that the dealkylation proceeds under even milder conditions, where thiophenoxide

is generated in situ (C_6H_5SH in Et_3N/dioxane). In the application of this methodology to the synthesis of a dinucleoside phosphate with the natural 3′ → 5′ phosphodiester linkage, we prepared the intermediary triester according to Letsinger.[3] Methylphosphorodichloridite[9] was treated successively with 2′,5′-*O*-di(tetrahydropyranyl)uridine[10] (1 equiv) and 2′,3′-*O*-diacetyluridine[11] (0.5 equiv) in THF in the presence of pyridine (5 equiv) at −78 °C. Oxidation of the resulting phosphite triester with I_2/H_2O at 0 °C, followed by workup and preparative thin-layer chromatography produced a 40% yield of triester **5** along with a 25% yield of the symmetrical 3′ → 3′ triester. The triester **5**, characterized by NMR, ex-



	R_1	R_2	B_1	B_2
5	THP	$-COCH_3$	U	U
6	THP	$-COC_6H_5$	U	N,NBz_2A
7	THP	$>C(CH_3)_2$	U	N^2BzG

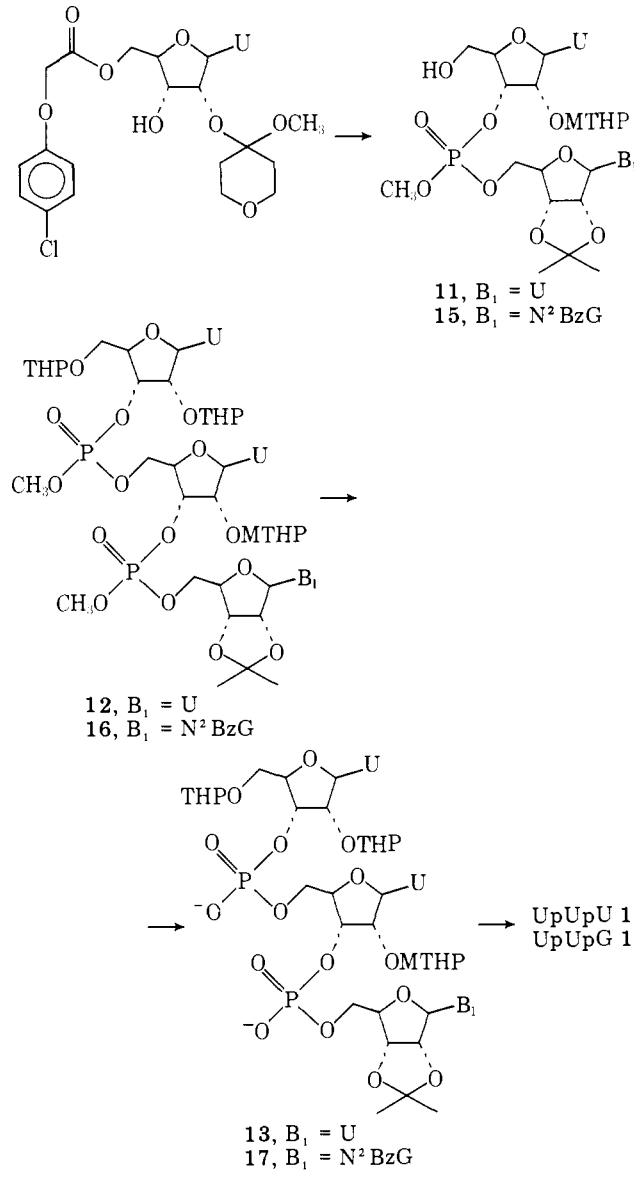
hibited a sharp doublet at δ 3.80 (J = 11.4 Hz) due to the methyl protons of the triester, a distinguishing feature in the spectra of all such triesters characterized in this work. Treatment of **5** (0.05 mmol) with a mixture of thiophenol (0.25 mL), triethylamine (0.5 mL), and dioxane (0.5 mL) for 1 h at 25 °C gave exclusively (by high-voltage electrophoresis) the deprotected diester. The reaction mixture was evaporated and partitioned (ethyl acetate/water) to give an aqueous solution of the triethylammonium salt of the desired phosphodiester (>90%). Routine deprotection using NH_3 saturated methanol and 80% acetic acid gave, after ion-exchange chromatography on Sephadex A-25, pure UpU (**8**) (50% from **5**). The product was completely hydrolyzed both by ribonuclease A to Up (1.0) and U (0.9), and by venom phosphodiesterase to U (1.0) and pU (1.0). The product was chromatographically and electrophoretically identical with UpU previously reported.[12]



	B_1	B_2
8	U	U
9	U	A
10	U	G

In an analogous manner UpA and UpG were synthesized. The triester intermediates **6** and **7** were obtained in 40 and 60% yields respectively from 2′,3′-*O*-*N*,*N*-tetrabenzoyladenosine[13] and N^2-benzoyl-2′,3′-*O*-isopropylideneguanosine.[14] Demethylation of **6** and **7** proceeded smoothly in both cases, producing the corresponding diesters in 85 and 75% yields, respectively. Debenzoylation and deacetalization followed by ion-exchange chromatography gave pure **9** and **10** in 50% yields from **6** and **7**. The dinucleoside phosphates were completely hydrolyzed by both ribonuclease and venom diesterase.

	RNase	Venom
UpA (**9**)	Up:A 1.0:0.9	U:pA 1.2:1.0
UpG (**10**)	Up:G 1.0:1.1	U:pG 1.1:1.0



To demonstrate the generality of this method, we elaborated the synthesis approach to include a trinucleoside diphosphate. The dinucleoside phosphotriester **11** was prepared from 5′-*O*-*p*-chlorophenoxyacetyl-2′-*O*-methoxytetrahydropyranyluridine[15] in a 43% yield after liberation of the 5′-hydroxyl group with methanolic ammonia. The trinucleoside diphosphate triester **12** was obtained in a similar fashion in 35% yield from **11**. Demethylation of **12** proceeded smoothly in 80% yield to give **13**. Complete deprotection and preparative paper chromatography afforded pure UpUpU (**14**) (35% from **12**), homogeneous by electrophoretic and paper chromatographic criteria.[12] Compound **14** was completely hydrolyzed by ribonuclease A to Up (2.1) and U (1.0), confirming the exclusive presence of the natural 3′ → 5′ phosphodiester linkages. The trinucleoside diphosphate UpUpG (**18**) was synthesized in analogous manner via the intermediates **15**, **16**, and **17**. Triester **16** (31% from **15**) was deprotected (89%) to give **17**. Final deprotection and purification gave UpUpG (33% from **16**) which exhibited appropriate chromatographic and electrophoretic properties.[12] The ribonuclease A digestion was complete, producing Up (2.0) and G (1.0).

The methyl phosphotriester linkages were stable for several days at 20 °C to nitrogen nucleophiles such as triethylamine, morpholine, and pyridine as well as to methanolic solutions of ammonia. In combination with thiophenol, pyridine proved ineffective as a base for the demethylation while both mor-

pholine and triethylamine were satisfactory. These observations are consistent with the view that thiolate acts as a nucleophilic agent in an S_N2 attack on carbon. All of the demethylation reactions gave only one nucleotidic product with no traces of material derived from S_N2 attack at $C_{5'}$.

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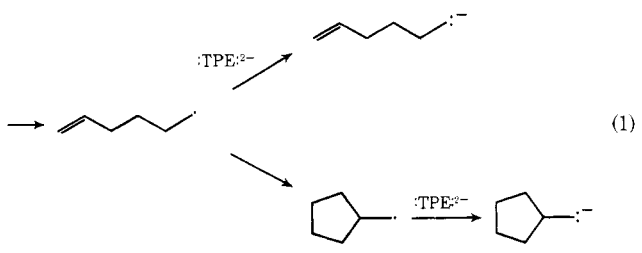
Halogen Effects in Electron-Transfer Reactions of Alkyl Halides with Disodium Tetraphenylethylene. Do Alkyl Halide Anion-Radicals Have Finite Lifetimes in Solution?

Sir:

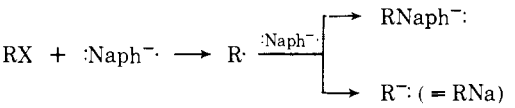
In 2-methyltetrahydrofuran at room temperature, disodium tetraphenylethylene (:TPE:$^{2-}$) at initial concentrations 1–3 $\times 10^{-2}$ M reacts with 5-hexenyl chloride, bromide, and iodide to give both 1-hexene and methylcyclopentane, with 1-hexene/methylcyclopentane = 0.2–0.6.[1,2] In the same solvent, sodium metal reacts with 5-hexenyl chloride to give both products with 1-hexene/methylcyclopentane = 10–13. Thus, the great majority of the cyclization found in the :TPE:$^{2-}$ reactions cannot be attributed to cyclization of intermediate 5-hexenylsodium. That it is due instead to cyclization of intermediate 5-hexenyl radicals is confirmed by the observation that the ratio 1-hexene/methylcyclopentane decreases from 0.6 to 0.02 as the initial concentration of :TPE:$^{2-}$ is varied from 3×10^{-2} M down to 1×10^{-3} M. This is consistent with the competition shown in eq 1, and the observations are in quantitative agreement with this scheme for 12 experiments spanning the concentration range given.[1] Further, *tert*-pentyl chloride reacts more rapidly with :TPE:$^{2-}$ than pentyl chloride, yet *tert*-pentyl chloride gives only 9% olefins; no traces of olefins are found from pentyl chloride. Thus, the initial steps of these reactions cannot have significant components of nucleophilic displacement and elimination. Electron transfer giving intermediate alkyl radicals R· from alkyl halides RX is occurring instead.



(1)

This is all parallel to previous findings for the related reactions of alkyl halides with sodium naphthalene (:Naph$^-$·).[4] The parallel ceases with the consideration of halogen effects on product yields. In reactions with sodium naphthalene, the yield of reduction products (those derived from intermediate alkylsodiums RNa, as opposed to "alkylation" products) is halogen independent (X = I, Br, Cl, F).[4,5] In reactions with disodium tetraphenylethylene in 2-methyltetrahydrofuran, primary alkyl iodides give 66 ± 3% reduction products, while bromides give 52 ± 3% and chlorides give 34 ± 5%.[6]

The important part of the mechanism for the alkyl halide–sodium naphthalene reaction is presented in eq 2.[4] There is no



(2)

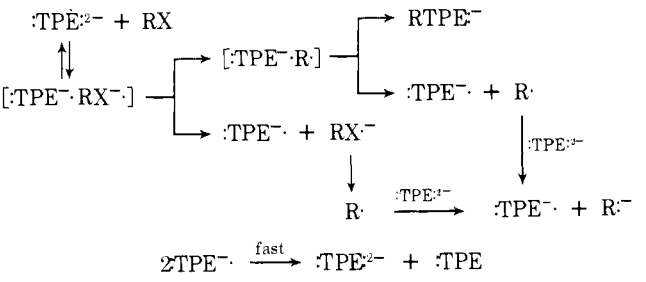
halogen effect because the C–X bond is broken before the product-partitioning steps. By similar reasoning, the analogous initial step for reactions of disodium tetraphenylethylene will also predict no halogen effect (eq 3).

$$RX + :TPE:^{2-} \rightarrow [:TPE^{-}\cdot\ R\cdot] \qquad (3)$$

Here the brackets indicate a geminate radical pair that has not suffered permanent separation by relative diffusion.[7-9] The finding of a distinct halogen effect requires a special explanation.

If the alkyl halide anion-radical RX^-· is introduced as an intermediate of finite lifetime in a scheme that is a simple extension of eq 2 to the case of a reactant dianion, Scheme I, then a prediction of a halogen effect can be made. Here the halogen dependence arises in the competition between the decomposition of RX^-· in the geminate radical pair [:TPE$^-$· RX^-·] and the diffusive separation of this pair. The longer the lifetime of RX^-·, the greater the fraction of radical pairs [:TPE$^-$· RX^-·] that suffer permanent separation and thereby give reduction product ultimately, rather than the alkylation product that results from cage reactions.[10] This explanation requires that RX^-· lifetimes be sufficient to permit a significant competition with permanent diffusive separation of the geminate radicals. If typical diffusion parameters apply, rate constants for RX^-· must be near 10^{10} s^{-1}.[7-9]

Scheme I



Counterions are omitted above, but aggregation must be at least to the ion pair and neutral triple ion stage. The disproportionation of sodium tetraphenylethylene in 2-methyltetrahydrofuran lies far to the right (:TPE:$^{2-}$) side at equilibrium. ESR measurements of [:TPE·$^-$] indicate that it is about 10^{-6} M during a typical reaction.