Organoiron-Mediated Alkylation of Phosphite Esters: Synthesis of (Dicarbonyl)(η^5-cyclopentadienyl)iron-Derived Nucleoside Phosphonate Esters

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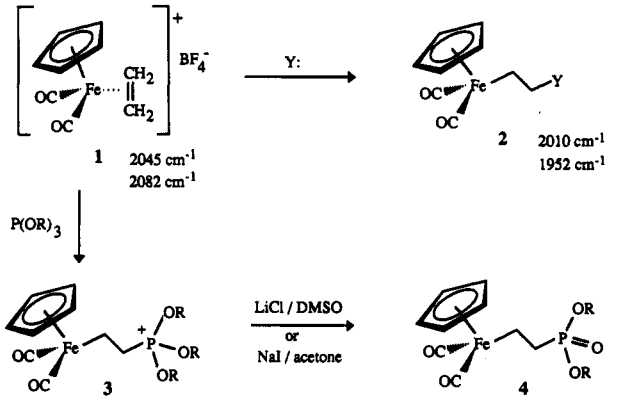
The phosphito triester group, which occurs as an intermediate in phosphoramidite-mediated oligonucleotide synthesis, was investigated as a site for reaction with transition metal reagents. A model study was initiated in which (dicarbonyl)(η^5-cyclopentadienyl)(η^2-ethylene)iron (Fp ethylene) was found to react with 5'-*O*-dimethoxytritylnucleoside 3'-phosphite esters to yield [2-[(dicarbonyl)(η^5-cyclopentadienyl)iron]ethyl]phosphonates. A phosphorus-modified T monomer 7 and a modified dApT dimer 11 were synthesized. The reaction was selective for phosphorus; Fp ethylene did not react either with completely protected dA or T. Although the (dicarbonyl)(η^5-cyclopentadienyl)iron-derived nucleoside phosphonates are stable to the conditions commonly used to construct oligonucleotides by phosphoramidite methodology, attempts to apply the reaction to the synthesis of an oligothymidine analogue failed because Fp ethylene apparently reacts with phosphotriester groups.

Introduction

Oligonucleotides based on methylphosphonate or other nonionic linkages between nucleoside units are of interest as antisense molecules for inhibiting mRNA or viral RNA function.[1-6] There is continuing interest in constructing oligonucleotide analogues, possessing structural modifications at phosphorus, that would (1) retain hybridization specificity, (2) show resistance to degradation by nucleases, (3) exhibit enhanced uptake by cells, and (4) have sites for the attachment of linker arms to moieties which would be capable of enhancing binding or facilitating the cleavage of nucleic acids.

If oligonucleotide analogues are to be broadly used in biological studies, they will have to be obtainable by routine automated synthesis. Modification at phosphorus can be achieved in conventional phosphoramidite or H-phosphonate synthesis protocols by (1) utilizing modified mononucleoside building blocks or (2) replacing the oxidation cycle with a reaction that yields the modified phosphorus linkage. The first approach works well for the construction of methylphosphonate-linked oligonucleotides,[7] while the second approach is appropriate for phosphoramidate-linked oligonucleotides.[8] Attempts to derivatize the phosphite triester linkage during oligonucleotide construction by Arbuzov-type reactions using alkyl halides have generally proven ineffective.[9]

Scheme I



One goal of our research is the development of new construction techniques for oligonucleotide analogues substituted at phosphorus by transition metal complexes. We have been investigating new methods for generating metal-derived phosphonate linkages in oligonucleotides during the course of automated synthesis by standard phosphoramidite or H-phosphonate chemistry. Our studies have encompassed three types of reactions between transition metal complexes and phosphite triesters, which lead to three distinct products, including the following: (1) metal-phosphite complexes, (2) metal-phosphonate complexes, and (3) metal-alkylphosphonate complexes. Preliminary results of this work have been reported.[10,11] This current paper reports the final results in our attempts to prepare nucleoside-derived metal-alkylphosphonate complexes.

Carbonyl or cyclopentadienyl transition metal complexes conjugated to oligonucleotides would be of potential interest for metalloimmunoassay,[12-15] as sequence-specific

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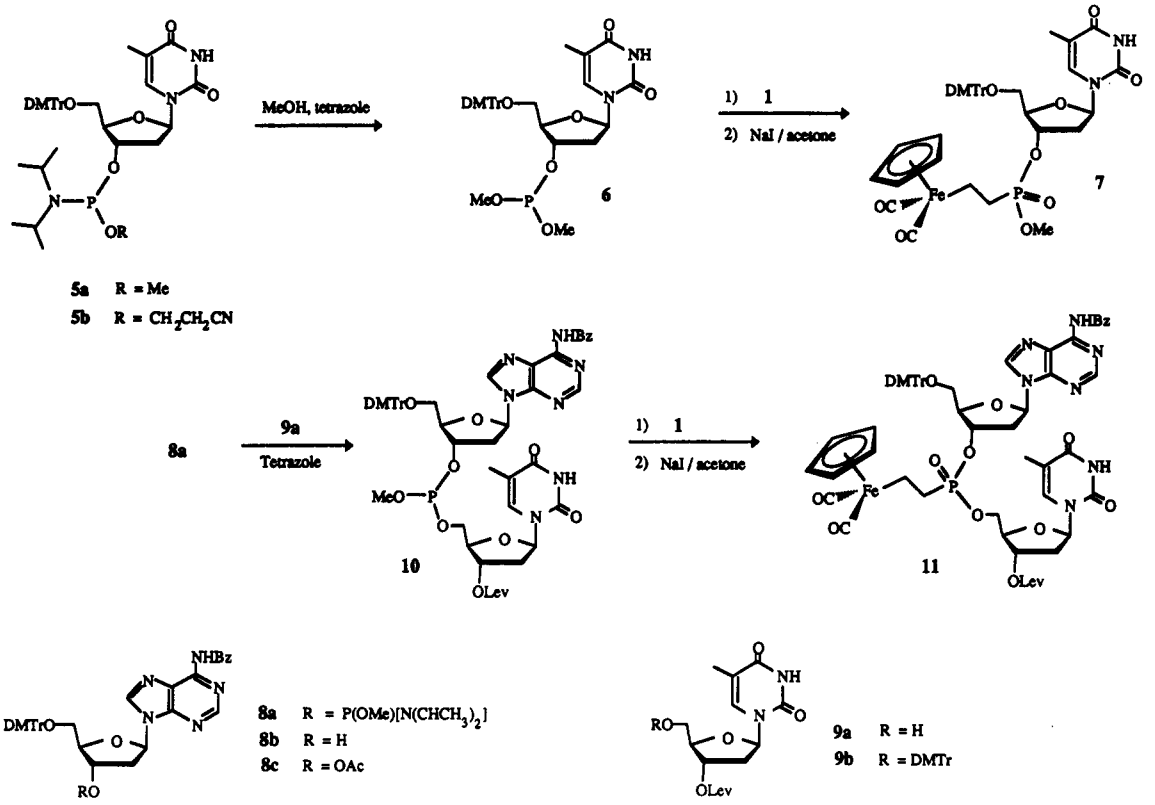
Scheme II



crosslinking reagents,[16] or in therapeutic applications.[17]

Discussion

Rosenblum et al.[18] have described the reaction of nucleophiles with (dicarbonyl)(η^5-cyclopentadienyl)(η^2-ethylene)iron cation (1) (abbreviated as Fp ethylene) (Scheme I) to yield products with structure 2. According to these studies, trialkyl phosphites are particularly avid nucleophiles for Fp ethylene. The initial product is the phosphonium salt 3, which can subsequently be transformed to a stable phosphonate 4 by reaction with LiCl in DMSO (60 °C, 1 h) or NaI in acetone (rt, 1 h). Since ultimately the goal was to introduce [2-[(dicarbonyl)(cyclopentadienyl)iron]ethyl]phosphonate linkages into oligonucleotides, it was necessary to establish whether this group would be sufficiently stable to survive the conditions of oligonucleotide synthesis. Diethyl [2-[(dicarbonyl)(cyclopentadienyl)iron]ethyl]phosphonate (4, R = Et), originally described by Rosenblum, was subjected to dichloroacetic acid in methylene chloride; ammonia in methanol at 60 °C for 8 h; (dimethylamino)pyridine, acetic anhydride, and lutidine in THF; and I_2 and lutidine in aqueous pyridine. None of the reagents caused decomposition as judged by ^{1}H NMR and IR.

With many types of alkylating reagents, there exists the potential for reaction at N-3 or O-4 of thymidine, N-7 or N-3 of deoxyadenosine, N-7, N-1, or O-6 of deoxyguanosine, and N-3 of deoxycytidine. Before investigating the reaction of Fp ethylene with nucleoside-derived phosphites, the reactivity of this reagent toward thymidine and deoxyadenosine was checked. The progress of Fp ethylene reactions is relatively easy to monitor through changes in the IR spectrum. The two carbonyl bands at 2082 and 2045 cm^{-1} (in acetonitrile or nitromethane) shift to 2010 and 1952 cm^{-1} when the [(dicarbonyl)(cyclopentadienyl)ethylene]iron cation is transformed to a [(dicarbonyl)(cyclopentadienyl)iron]ethyl derivative.

Variation in the frequencies of the carbonyl stretches in the IR are solvent dependent, but these changes are small compared to the relatively large shifts which occur during the reaction shown in Scheme I. At room temperature, neither 5′-*O*-(dimethoxytrityl)-3′-*O*-levulinylthymidine (**9b**) nor 5′-*O*-(dimethoxytrityl)-3′-*O*-acetyl-*N*^{6}-benzoyl-2′-deoxyadenosine (**8c**) reacted with Fp ethylene in either CH_3CN or CH_3NO_2 in the presence or absence of tetrazole. On the other hand, 5′-*O*-(dimethoxytrityl)-*N*^{6}-benzoyl-2′-deoxyadenosine (**8b**) (3′-OH unprotected) did react with Fp ethylene in both CH_3CN and CH_3NO_2 as ascertained by the appearance of bands at 2010 and 1952 cm^{-1} in the IR spectrum. The products were neither characterized nor isolated, but the results indicated the necessity of complete hydroxyl group protection in reactions of nucleoside-derived phosphites with Fp ethylene.

With these results in hand, we proceeded to investigate the reaction of Fp ethylene (1), first with a mononucleoside phosphite ester, then a dinucleoside phosphite ester, and finally with an oligonucleotide phosphite ester located at the 5′-terminus of an oligonucleotide under construction on a solid support. The first Fp-derived nucleoside

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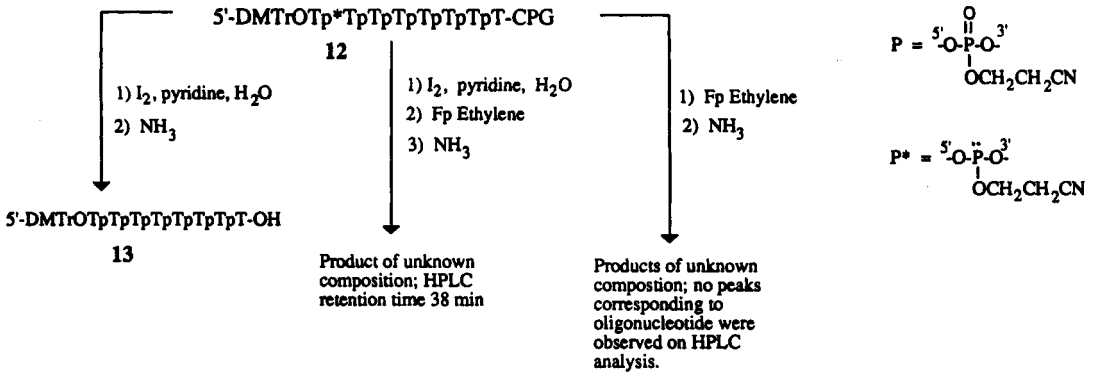
Scheme III



phosphite ester synthesized was 3′-[5′-*O*-(4,4′-dimethoxytrityl)deoxythymidinyl] methyl [2-[(dicarbonyl)(η^5-cyclopentadienyl)iron]ethyl]phosphonate (**7**). This was accomplished by reaction of phosphoramidite **5a** with methanol and tetrazole to yield an intermediate phosphite ester **6**, which was not isolated, but treated immediately with Fp ethylene (**1**) and, subsequently, with sodium iodide in acetone for 1 h at room temperature to yield **7**. It was also possible to use a β-cyanoethyl-derived phosphoramidite. The β-cyanoethyl group was then selectively removed from the intermediate phosphonium salt with concentrated methanolic ammonia. The phosphite ester dimer **10** generated in situ from phosphoramidite **8a** and 3′-*O*-levulinylthymidine (**9a**) also coupled satisfactory with Fp ethylene (**1**) followed by NaI to yield dinucleoside **11**.

The final hurdle was the reaction of Fp ethylene (**1**) with an oligomer on a solid support (CPG). Using standard phosphoramidite chemistry and the monomeric building block 5′-*O*-(dimethoxytrityl)thymidin-3′-yl-*O*-(cyanoethyl *N*,*N*-diisopropylphosphoramidite) (**5b**), octamer **12** (Scheme III) was prepared on an automated synthesizer. Initially this was transformed to the octamer T_8 (**13**) in order to obtain a standard for HPLC comparison and to establish that the automated synthesizer was working properly. Then, in place of the final oxidation step, which would have transformed the phosphite triester linkage between T_7 and T_8 to a phosphate triester linkage, we substituted the Fp ethylene reagent in CH_3CN. In each case, the oligomer was released from the solid support by treatment with concentrated ammonia for 2 h. A number of attempts to react Fp ethylene with the final phosphite ester linkage in an T_8 octamer synthesis were unsuccessful. Particularly mystifying was the failure to observe any peaks in the HPLC typical of dimethoxytrityl derived oligonucleotides. An acetonitrile–aqueous buffer gradient which reproducibly resulted in elution of 5′-DMTr T_8 at 25 min and 5′-DMTrT-3′-Lev (**9b**) at 54 min gave no peaks of any consequence throughout this region. Since 5′-DMTrT-3′-Lev (**9b**) does not react with Fp ethylene, it appeared possible that the problem lie in the phosphotriester linkages, a functional group for which we had not anticipated competing reactions. Two experiments appear to confirm this hypothesis.

First, as shown in Scheme III, when **12** was converted to the phosphotriester-linked oligomer and then treated with Fp ethylene, the expected product, following cleavage from the controlled pure glass support, was not 5′-DMTr T_8 but a new product of unknown structure which showed a longer retention time on HPLC (38 min) and a λ_{max} in the UV spectrum at 275 nm (in contrast to 5′-DMTr T_8 which absorbs at 265 nm).

A far simpler experiment also appeared to confirm the reactivity of phospho triesters. Reaction of triethyl phosphate with an excess of Fp ethylene (**1**) gave a new product of unknown structure, but with a shorter retention time (40 min) than Fp ethylene (52 min) and, like the product obtained from the reaction between Fp ethylene and CPG bound DMTrT_8, had a λ_{max} at 275 nm. The product was unstable and was not identified. Until the nature of the reaction between Fp ethylene and phosphate triesters can be elucidated, further study on oligonucleotide derivatization by Fp ethylene is not likely to be fruitful.

Experimental Section

General Procedures. All glassware was washed with acid ($^1/_3$ HCl–$^2/_3$ HNO_3 (v/v)), soaked in a base bath (KOH/iPrOH), rinsed with acetone, washed with soap, then rinsed with distilled water. Glassware was oven dried at 120 °C overnight before use. All chemicals used in this investigation were reagent grade unless otherwise stated. Phosphoramidites were purchased from Glenn Research. Tetrahydrofuran, methylene chloride, acetonitrile, pyridine, and 1,2-dichloroethane were purchased from Aldrich (<0.0005% H_2O), stored under nitrogen, and sealed with a rubber septum. All other reagents were purchased either from Aldrich, Strem, or Sigma. All solvents removed in vacuo were removed at ambient temperature unless otherwise stated.

Fp(ethylene)BF_4 was synthesized by the procedure outlined by Schmidt et al.[19] $FpCH_2CH_2P(O)(OEt)_2$ was synthesized by the procedure outlined by Lennon et al. (19).

Melting points were determined on a Buchi 510 apparatus. All readings are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on either a Varian XL-200, VXR-300, or VXR-500 spectrometer. All data is presented as ppm downfield from either tetramethylsilane or 85% H_3PO_4. UV–vis spectra were recorded on a Shimadzu UV260 spectrophotometer. IR spectra were recorded on a Digilab FTS-40 IR spectrophotometer. The mass spectrometry of all compounds run were done by the Mass Spectrometry Facilities at the Purdue University Department of Medicinal Chemistry and Pharmacognosy. All compounds were analyzed by fast atom bombardment. Silica gel used for column chromatography was Merck Silica Gel 60 (70–230 mesh). Whatman PE SilG/UV silica gel plates with polyester of glass backing were used. All TLC plates were pre-eluted with appropriate eluant and observed under UV radiation (254 nm).

DNA Synthesis Methods. The Milligen Biosearch automated DNA synthesizer (8750) with a thymidine CPG disposable reaction column (15 μmol or 1 μmol) packed with large pore CPG (Biosearch Cat. no. 6173-01) was used for studies of solid support synthesis. HPLC grade acetonitrile (Fischer, <0.005% H_2O), deblock solution (Biosearch cat. no. NU-6183) diluted from 25 mL to 1000 mL in CH_2Cl_2, tetrazole (Biosearch cat. no. NU6288) in acetonitrile, **5b** (R=CH_2CH_2CN) (500 mg in 20 mL of acetonitrile), and Fp ethylene (**1**) (150 mg in 15 mL of acetonitrile) were used in the appropriate reservoirs on the synthesizer. Standard Milligen amidite synthesis conditions were used except when the oligomer was modified with Fp ethylene; in these instances the oxidation step was replaced with six Fp ethylene cycles

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totaling 100 min. Concentrated methanolic ammonia (2 h at 25 °C) was used to cleave the dimer from the support and to deprotect the phosphorus.

HPLC Methods. A Beckman high-performance liquid chromatography system equipped with System Gold software, a 126 solvent module, and a 168 diode array detector was used with an Ultrasphere reversed-phase 5 μm spherical 80-Å pore C-18 guard (4.6 × 45 mm) and analytical (4.6 × 250 mm) column. A gradient elution was carried out with an aqueous triethyl ammonium acetate (TEAA, 0.1 M, pH 7) vs CH_3CN with a flow rate of 1 mL/min. The gradient used was as follows: 100% TEAA to 22% CH_3CN over 5 min, 22–30% CH_3CN over 15 min, 30–50% CH_3CN over 25 min, and 50–100% CH_3CN over 15 min.

Synthetic Procedures. Preparation of 3′-[5′-*O*-(4,4′-Dimethoxytrityl)deoxythymidinyl] Methyl [2-[(Dicarbonyl)(η^5-cyclopentadienyl)iron]ethyl]phosphonate (7). Compound **5a** (99 mg, 0.14 mmol), tetrazole (43 mg, 0.61 mmol), methanol (24 μL, 0.56 mmol), and CH_3CN (10 mL) were combined in a 50-mL schlenck tube under an atmosphere of argon. After 30 minutes **1** (90 mg, 0.3 mmol) was added; an IR assay showed complete conversion after an additional hour. IR (ν CO, CH_3CN): 2011 and 1953 cm^{-1}. The solvent was removed in vacuo and coevaporated with acetone (3 × 5 mL). The resulting oil was dissolved in acetone (5 mL) and combined with NaI (300 mg, 2 mmol). This reaction mixture was allowed to stir at ambient temperature for 1 h under an atmosphere of argon, at which time the reaction mixture was diluted with CH_2Cl_2 (10 mL) and extracted with water (4 × 15 mL). The organic layer was dried ($MgSO_4$), filtered, and dried in vacuo. The resulting oil was dissolved in a minimal amount of CH_2Cl_2 and loaded onto an activated (Brockmann III) aluminum oxide (neutral) column (10 g), which was eluted with CH_2Cl_2/NEt_3 (99/1). The yellow fractions were combined and concentrated to yield a thick gold oil which was triturated with hexane to yield **7**, a beige powder (77 mg, 67%). IR (ν CO, CH_2Cl_2): 2011 and 1953 cm^{-1}. ^{31}P NMR (δ, acetone-d_6): 32 ppm (d, RP=O). ^1H NMR (δ, acetone-d_6) 7.59 (m, H-6), 7.48–6.92 (m, aromatic), 6.38 (m, H-1′), 4.99 (s, Cp), 4.27 (m, H-3′), 3.91 (m, H-4′), 3.79 (s, OCH_3), 3.65 (d, $POCH_3$), 3.44 (m, H-5′), 2.55 (m, H-2′), 1.83 (m, PCH_2), and 1.46 (m, CH_3 and $FeCH_2$) ppm. MS: low-resolution *m/e* calcd ($M + Na^+$) 849, obsd 849; high-resolution *m/e* calcd for daughter ion $C_8H_7O_2Fe$ 190.9795, obsd 190.9790; *m/e* calcd for $C_{33}H_{36}O_9N_2PNa$ 658.2056, obsd 658.2061.

In an alternate procedure, compound **5b** (R = CH_2CH_2CN) was used in place of **5a** in order to determine if a β-cyano ethyl group could be selectively removed by concentrated methanolic ammonia (5 mL). The remainder of the work up was identical, yielding a similar product. IR (ν CO, acetone): 2009 and 1953 cm^{-1}. ^{31}P NMR (δ, acetone-d_6): 32 ppm (d, RP=O).

Preparation of 5′-[(3′-*O*-Levulinyl)deoxythymidinyl] 3′-[N^6-Benzoyl-5′-*O*-(4,4′-dimethoxytrityl)deoxyadenosyl] [2-[(Dicarbonyl)(η^5-cyclopentadienyl)iron]ethyl]-phosphonate (11). Compound **8a** (100 mg, 0.12 mmol), tetrazole (43 mg, 0.61 mmol), compound **9a** (41 mg, 0.12 mmol), and CH_3CN (10 mL) were combined in a 50-mL schlenk tube under an atmosphere of argon. After 30 min **1** (36 mg, 0.12 mmol) was added to the reaction mixture and stirred under an atmosphere of argon for 1 h. The solvent was removed in vacuo and coevaporated with acetone (3 × 5 mL) and then dissolved in acetone (5 mL). NaI (300 mg, 2 mmol) was added and the solution allowed to stir for 1 h at ambient temperature. The reaction mixture was dissolved in CH_2Cl_2 (10 mL) and washed with water (4 × 15 mL). The organic layer was dried ($MgSO_4$), filtered, and dried in vacuo to yield an amber oil. The oil was triturated with hexane to yield **11** as a beige solid (101 mg, 53%). IR (ν CO, acetone): 2009 and 1953 cm^{-1}. ^{31}P NMR (δ, acetone-d_6): 32 ppm (d, RP=O). ^1H NMR (δ, acetone-d_6): 8.60 (s, H-8 A), 8.30 (s, H-2 A), 7.59 (m, H-6 T), 8.04 (m, aromatic), 7.65–6.85 (m, aromatic), 6.55 (m, H-1′ A), 6.28 (m, H-1′ T), 5.31 (m, H-3′ T), 5.03 (s, Cp), 4.68 (m, H-3′ A), 4.46 (m, H-4′ A), 4.15 (m, H-4′ T), 3.78 (s, OCH_3), 3.59 (m, H-5′ T), 3.48 (m, H-5′ A), 2.81–2.57 (m, H-2″ and H-3″ T), 2.36 (m, H-2′ T), 2.13 (s, H-5″ T), 1.84 (s, CH_3 T), and 1.83–1.66 (m, $FeCH_2$ and PCH_2) ppm (A = deoxyadenosine and T = thymidine). MS: low-resolution *m/e* calcd ($M + Na^+$) 1270, obsd 1270; high-resolution *m/e* calcd for daughter ion $C_8H_7O_2Fe$ 190.9795, obsd 190.9792; *m/e* calcd for $C_{54}H_{55}O_{14}N_7PNa$ 1079.3442, obsd 1079.3445.

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Supplementary Material Available: ^1H NMR spectra of **7** and **11** and ^{31}P NMR spectrum of **11** (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Inversion of the Ground-State Spin Multiplicity by Electron-Withdrawing Groups in Trimethylenemethane Derivatives Generated Photochemically from Methylenequadricyclane Derivatives

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An inversion of the ground-state spin multiplicity of trimethylenemethane (TMM) by electron-withdrawing groups was investigated by EPR spectroscopy, for a series of TMMs **2b–g** generated photochemically from methylenequadricyclanes **1b–g**. Curie law analyses between 4 and 50 K proved the triplet ground states of the monophenyl derivative **2b** and the monocyano derivatives **2c–d** as well as that of the diphenyl derivative **2a**. The dicarbomethoxy derivative **2e** also exhibited the EPR signal, but the Curie plot was nonlinear and the signal disappeared irreversibly above 10K. The triplet ground state was inverted to the singlet by the carbomethoxy-cyano and dicyano substitutions, and **2f** and **2g** were EPR silent species similar to the singlet oxyallyl (OA) derivative **2h**. The singlet ground state of **2g** was demonstrated by its chemical behaviors which resemble those of **2h**.

We previously reported that photoreactions of benzhydrylidenequadricyclane (**1a**) and quadricyclanone (**1h**) formed the triplet trimethylenemethane (TMM) derivative **2a** and the singlet OA derivative **2h**, respectively.[1] These

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