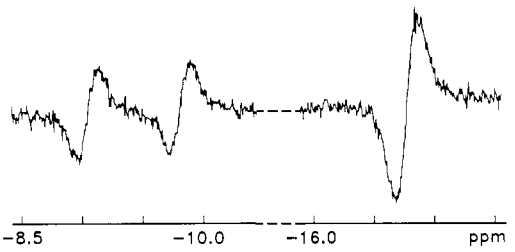
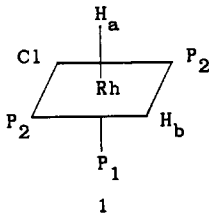


Figure 2. The enhanced transient NMR spectrum of the hydride region of $RhH_2(PPh_3)_3Cl$ (structure **1** of text) formed from parahydrogen in deuteriobenzene. Because of ligand exchange, the only resolved J splitting is for the coupling of the proton at -9.4 ppm to the trans ^{31}P (ref 2 and 3). The unique information is in the phase of the multiplets which shows that the unresolved scalar coupling between the hydride protons is negative.

confirmed qualitatively, and the agreement with experiment is excellent.

An experimental enhancement factor S_{obsd}/S_{eq}, arbitrarily based on the outer lines of the methyl triplet, is defined as the ratio of the transient signal after the H_2 burst to the signal from the equilibrium magnetization (at 300 K) of the molecules formed from that burst. To make this measurement accurately the sequence of H_2 burst, $\pi/4$ pulse, and data acquisition was delivered repeatedly. After each repetition and a delay of 45 s to allow full equilibration, the total propionitrile produced up to that point was measured by acquiring the response to a $\pi/2$ pulse. Enhancement factors of 100-200 were measured on several samples with either deuteriobenzene or deuteriochloroform as solvent. The variability between samples is greater than the 10% accuracy of measurement on each.

This enhancement in excess of 10^2 relative to the equilibrium magnetization per molecule is already very promising for applications. However, the calculations described above lead to a theoretical maximum enhancement of $fS_{max}/S_{eq} = fkT/3h\nu_o = 3.5 \times 10^3$ possible for this molecule and p-H_2 mole fraction. The catalytic intermediate is believed to have the structure **1** around the Rh center.[2,3,5-7] Since the two protons are already inequivalent, this intermediate is also expected to show antiphase transients when formed from para-enriched H_2. The experimental observation is shown in Figure 2 for a reaction mixture from which substrate was omitted in order to avoid depletion of **1**. Interestingly, the phase of these multiplets gives the *absolute* sign of this coupling as negative, information which is not normally available in spectra derived from a paramagnetic initial condition.



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The inverse of the disappearance rate for the J order of the catalyst dihydride during the period between the H_2 burst and the rf pulse is $T_{1J}^s = 0.28 \pm 0.03$ s. This relaxation time allows a simple explanation for the diminishment factor D defined as the ratio of measured to ideal propionitrile signal enhancement. The largest observed value of $D = S_{obsd}/fS_{max} = 2 \times 10^2/3.5 \times 10^3$ is explained if the rate of transfer of protons from catalyst to substrate is $\simeq 0.2$ s^{-1}. Values in this range have been reported for other alkenes.[7] Additional studies will allow an independent measurement of these rates and an assessment of whether the observed spin dynamics are consistent with the assumed reaction mechanism.[5-7] We have made preliminary observations on another catalytic system; the same phenomenon of large antiphase multiplets is observed on the dihydrido species $H_2Ir(CO)Cl(PPh_3)_2$ formed by addition of para-enriched H_2 to Vaska's compound.[8]

Finally, we note the possibility for a related method of high sensitivity NMR. In the present study ortho-para population differences are converted to nuclear magnetism, which is then measured. The inverse of this phenomenon would be to deduce the nuclear spin order of an ensemble of molecules by measuring the ortho-para population differences of the H_2 formed by their dehydrogenation. Since the spin state is modified by the dynamics under rf pulses and internal couplings, the branching ratio to ortho and para products would depend on the NMR of the dihydrogen precursor.

Acknowledgment. This work was supported in part by the Atlantic Richfield Foundation.

Note Added in Proof. The phenomenon reported here and predicted in ref 1 may have been observed elsewhere unwittingly and interpreted as spin sorting of a radical pair intermediate (chemically induced dynamic nuclear polarization or CIDNP). See Hommeltoft et al. (Hommeltoft, S. I.; Berry, D. H.; Eisenberg, R. *J. Am. Chem. Soc.* **1986**, *108*, 5346) for such an example and for further references. Professor Eisenberg has informed us that the storage of their samples in liquid nitrogen prior to reaction in the room temperature spectrometer likely created a high concentration of parahydrogen. We thank Professors J. Bargon and R. G. Lawler for bringing this work to our attention.

Registry No. $Rh(PPh_3)_3Cl$, 14694-95-2; acrylonitrile, 107-13-1.

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Methane- and Difluoromethanediphosphonate Analogues of Geranyl Diphosphate: Hydrolysis-Inert Alternate Substrates

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Several groups have conducted mechanistic and structural studies with diphosphate analogues where a bridging oxygen is replaced by carbon (methanediphosphonates) or nitrogen (imidodiphosphates) in situations where it is desirable to repress hydrolysis of P-O-P linkages.[1-3] The major concerns associated with using these analogues are differences between pK_a's and reactivities of the analogues and normal substrates and problems associated with synthesis, especially for imidodiphosphates. Blackburn and co-workers reported that replacement of bridging methylene by a difluoromethylene unit in diphosphonates restored the pK_a's of analogues to values almost identical with those of the natural substrates.[4-6] We recently developed synthetic procedures for introducing methanediphosphonate and difluoromethanediphosphonate moieties into a variety of molecules, including isoprenoids[7] and nucleotides,[8] and now report comparative studies

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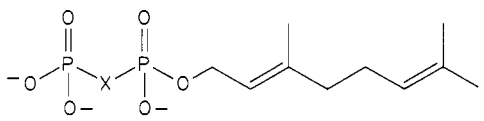
Table I. Kinetic Constants for 1′-4 Condensation Catalyzed by Avian Liver Farnesyl Diphosphate Synthetase[a] and Solvolysis[b]

substrates	V_{max}, μmol mg^{-1} min^{-1}	K_m (IPP), μM	K_m (GPXP), μM	k, s^{-1}
1, **4**[c]	0.72 ± 0.13	0.29 ± 0.10	0.25 ± 0.09	
1				3.0×10^{-4}
2, **4**[d]	0.01 ± 0.002	0.20 ± 0.11	0.35 ± 0.24	
2				1.1×10^{-6}
3, **4**[e]	0.09 ± 0.020	0.10 ± 0.13	1.79 ± 0.53	
3				3.9×10^{-4}

[a] Incubations were at 37 °C. Rates were measured by the acid lability assay (ref 6). Assay buffer contained 20 mM BHDA, 1 mM magnesium chloride, 10 mM 2-mercaptoethanol, 0.25 mM potassium azide, and 0.1% BSA, pH 7.00. [b] At 25 °C in 0.2 M potassium phthalate buffer, pH 2.50. [c] [**1**], 0.14–0.88 μM; [**4**], 0.17–0.67 μM. [d] [**2**], 0.49–1.39 μM; [**4**], 0.2–0.46 μM. [e] [**3**], 0.20–0.88 μM; [**4**], 0.38–1.02 μM.

with geranyl diphosphate (**1**), geranyl methanediphosphonate (**2**), and geranyl difluoromethanediphosphonate (**3**), where the methanediphosphonates serve as hydrolysis-resistant alternate substrates in prenyl transfer and cyclization reactions.



X = O (1); CH_2 (2); CF_2 (3)

Kinetic constants[9] for the 1′-4 condensation between allylic diphosphates **1**, **2**, and **3** and isopentenyl diphosphate (**4**) catalyzed by avian liver farnesyl diphosphate synthetase are shown in Table I. The relative reactivities of the diphosphate, methanediphosphonate, and difluoromethanediphosphonate moieties as leaving groups were determined in solvolysis experiments by measuring the rate of formation of radiolabeled products from [1-^{3}H]**1**, **-2**, and **-3**,[10] under conditions where heterolysis of the carbon–oxygen bond was rate-limiting.[11] The first-order rate constants (see Table I) showed a 250-fold decrease in reactivity when the central oxygen in the diphosphate moiety was replaced by carbon, which was restored when the methylene hydrogens were replaced by strongly electron-withdrawing fluorines. A similar pattern was seen in V_{max}'s for the enzyme-catalyzed reactions. Diphosphonate **2** was substantially less reactive than **1**, and replacement of the methylene hydrogens by fluorine increased V_{max} ninefold. If one compares catalytic efficiencies (V/K) at subsaturating concentrations, **3** is, however, only twice as efficient as **2** because of a fivefold larger K_m.

All three allylic substrates gave farnesyl diphosphate (**5**) as the exclusive product. Incubation of **1**, **2**, or **3** (6.0 μmol) with [1-^{14}C]**4** (1.5 μmol, 26 μCi/μmol) with the enzyme (100 μg, 1.1 U/mg) in 20 mM BHDA (*endo*-bicyclo[2.2.1]heptene dicarboxylate), 1 mM magnesium chloride buffer, pH 7.00, at 37 °C followed by treatment with *E. coli* alkaline phosphatase (28 μg, 57 U/mg), 200 mM lysine, pH 10.4, gave only (*E*,*E*)-farnesol (**6**).[12] In related experiments [1-^{3}H]**1**, **-2**, or **-3** were incubated with the *E. coli* enzyme in 50 mM lysine buffer, pH 10.4, at 37 °C. Under conditions where **1** (15 μg, 42 nM, 2.56 μCi/μmol) was completely hydrolyzed to [1-^{3}H]geraniol (**7**) in 4 min, a 10-fold increase in the concentration of phosphatase did not give detectable hydrolysis of [1-^{3}H]**2** (17 μg, 47 nM, 2.96 μCi/μmol) or [1-^{3}H]**3** (17 μg, 43 nM, 3.27 μCi/μmol) above a control sample without an enzyme in 90 min. We conservatively estimate the difference to be a factor of 10^4.

Table II. Distribution of Label upon Treatment of [1-^{3}H]**1** and **-3** with Cyclase Preparations from Lemon Peel[a]

substrates	time, h	% total ^{3}H	
		8, **9**, **10**[b]	**7**, **11**, **12**
1	1	0.17	16[c]
3	1	0.11	0.37[d]
1	48	0.03	25[c]
3	48	0.28	1.5[d]

[a] Incubations were in 100 mM TES–NH_3, 3 mM maganese sulfate, 20 mM 2-mercaptoethanol, pH 7.00, at 30 °C. [b] The major products were **9** and **10**; relative ratios for **8**, **9**, and **10** were similar. [c] Ratio **7**:**11** + **12** > 80. [d] Ratio **7**:**11** + **12** ~ 0.9.

In many studies with cell-free systems, the activities of isoprenoid enzymes are overwhelmed by high levels of nonspecific phosphatases which hydrolyze the diphosphate moiety before the isoprenoid enzymes can act.[13,14] Difluoro analogue **3** also was compared with **1** as a phosphatase-inert substrate for monoterpene cyclase activity in a cell-free homogenate from lemon peels, a system known to contain high levels of phosphatase activity.[15,16] [1-^{3}H]**1** (37 μg, 0.1 μM, 33 μCi/μmol) or [1-^{3}H]**3** (40 μg, 0.1 μM, 33 μCi/μmol) were incubated with 60 mg of protein. Samples were extracted with hexane, and a portion was counted to measure formation of products. The remainder was mixed with authentic samples of α-pinene (**8**), β-pinene (**9**), limonene (**10**), geraniol (**7**), linalool (**11**), and α-terpineol (**12**) and analyzed by TLC to determine the relative contributions to the product mixture from cyclase activity (**8**–**10**),[17] phosphatase activity (**7**), and solvolysis (**7**, **11**, and **12**).[15,18,19] The data are shown in Table II. In a 1-h incubation, where the ratio of cyclase/phosphatase activity was 0.01, as determined by the ratio of **8**–**10**:**7**, incorporation of radiolabel into cyclized products was comparable for **1** and **3**, although a much larger proportion of **1** had suffered hydrolysis, presumably catalyzed by nonspecific phosphatases. In a 48-h incubation with a different cell-free extract where the cyclase/phosphatase ratio was 3×10^{-4}, as determined by a 1-h incubation, the efficiency of incorporation of **3** into cyclase products was 10-fold higher than for **1**.

Our results clearly demonstrate that methanediphosphonate and difluoromethanediphosphonate derivatives of geraniol are alternate substrates for isoprenoid enzymes. When used at saturating levels, **3** is a particularly efficient replacement, with a V_{max} only eightfold lower than **1** for 1′-4 condensation. These observations are consistent with the proposal that the difluoromethylene unit more closely approximates the electronegativity of the normal bridging oxygen.[20] Moreover, the alternate substrates are not degraded by phosphatases. Although they, as well as the natural

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(11) Tidd, B. K. *J. Chem. Soc. B.* **1971**, 1168–1176.
(12) Radioactivity comigrated with authentic (*E*,*E*)-farnesol on silica TLC plates (R_f 0.36, 2:1 hexane/ethyl acetate). This observation was confirmed by GCMS analysis (30-m Durabond DB-5 column, 150–250 °C, 15 °C/min; VG Analytical Micromass 7070E mass spectrometer) and by GLPC analysis on a 30-m fused silica Carbowax-20M column (65–165 °C, 20 °C/min) that cleanly resolved authentic samples of *Z*,*Z* (18.9 min), *Z*,*E* (20.8 min), *E*,*Z* (21.7 min), and *E*,*E* (23.0 min) isomers. Cane, D. E.; Ha, H. J.; Pargellis, C.; Waldmeier, F.; Swanson, S.; Murthy, P. P. M. *Bioorg. Chem.* **1985**, *12*, 246–265.
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(16) Cori, O.; Rojas, M. C. *Methods Enzymol.* **1985**, *110*, 406–417.
(17) TLC experiments using argentated silica plates[16] (12.5% $AgNO_3$, developed in benzene) showed that the radioactivity in the hydrocarbon products comigrated with authentic samples (α-pinene R_f 0.71, β-pinene R_f 0.56, and limonene R_f 0.46).
(18) Chemical hydrolysis of **1**–**3** produced **11** (~60%) and **12** (~3%) in addition to **7** (~37%),[15] while enzymatic hydrolysis of **1** only gave **7**. TLC analysis of radioactive samples (2:1 hexanes/ethyl acetate on silica gel 60, geraniol R_f 0.29, α-terpineol R_f 0.36, and linalool R_f 0.45) with authentic samples showed that alcohols formed from **3** are primarily from chemical hydrolysis.
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(20) Blackburn, G. M. *Chem. Ind. (London)* **1981**, 184.

substrate, are susceptible to solvolytic degradation, this is not a significant problem when the pH of the buffer is maintained at 7 or above, even during prolonged incubations at 37 °C. We anticipate that methane- and difluoromethanediphosphonates will find increasing use as alternate substrates and inhibitors inert to hydrolytic activity and as mechanistic probes in cases where it is desirable to change the reactivity of the leaving group.

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Novel Phosphonylphosphinyl (P-C-P-C-) Analogues of Biochemically Interesting Diphosphates. Syntheses and Properties of P-C-P-C- Analogues of Isopentenyl Diphosphate and Dimethylallyl Diphosphate

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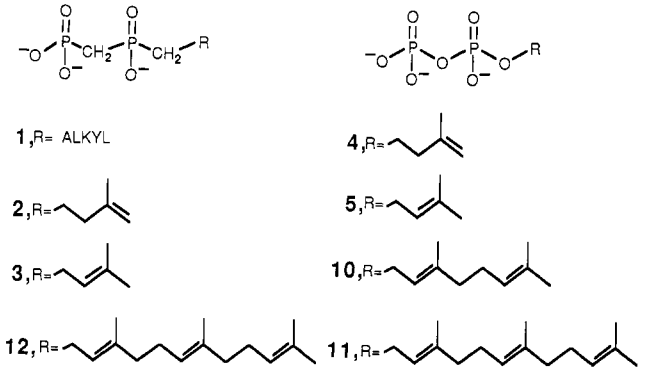
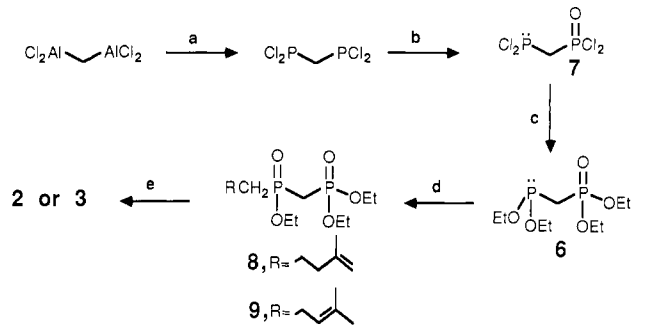
There are numerous reports of phosphonate analogues of biologically interesting compounds.[1] A related class of analogues whose biological properties have not been mentioned, except for an undocumented claim in the patent literature,[2] is the phosphonylphosphinyl system, a moiety in which the bridging oxygen between the two phosphorus atoms of the diphosphate unit and the bridging ester oxygen to the rest of the molecule are both replaced by methylene groups as shown below for **1**.[3,4] Attempts



by Gilmore and Huber[5] to prepare a vinyl derivative related to **1** by using the symmetric Horner-Emmons reagent ethyl bis-((diethoxyphosphinyl)methyl)phosphinate were unsuccessful. Some asymmetric derivatives related to **1** were recently reported by Novikova and co-workers,[6,7] but no derivatives of obvious biological relevance were prepared. We reasoned that application

Scheme I[a]



[a] (a) PCl_3, KCl, $P(O)Cl_3$;[7] (b) DMSO, 23 °C;[7] (c) 4 equiv EtOH + 4 equiv pyridine; (d) RCH_2Br, 100-200 °C; (e) TMSBr, 23 °C/MeOH, H_2O/NH_3.

of this chemistry could lead to a new class of diphosphate analogues and now report the syntheses of **2** and **3**, P-C-P-C-analogues of isopentenyl diphosphate (**4**) and dimethylallyl diphosphate (**5**), mandatory precursors of all isoprenoids.

Phosphonylphosphinyl analogues **2** and **3** were prepared from phosphonylphosphonite **6** and the appropriate alkyl halides via an Arbuzov reaction. Although **6** was previously reported by Novikova et al.,[6] we were unable to repeat their synthesis and instead used the route outlined in Scheme I to prepare the compound from **7** in 63% yield.[8] Phosphonite **6** was then allowed to react with 5-bromo-2-methyl-1-pentene[9] to give the triethyl ester **8** of **2**[10] in 26% yield or with 5-bromo-2-methyl-2-pentene[11] to give the triethyl ester **9** of **3**[12] in 66% yield. After deprotection with bromotrimethylsilane, the analogues were isolated as their crystalline ammonium salts.[10,12]

Phosphonylphosphinates **2** and **3** were evaluated as inhibitors of the 1'-4-condensation between isopentenyl diphosphate (**4**) and geranyl diphosphate (**10**) catalyzed by avian liver farnesyl diphosphate synthetase. Under standard assay conditions,[13] isopentenyl analogue **2** was a competitive inhibitor against **4**, $K_{i(2)} = 19 \pm 7$ μM, and diemethylallyl analogue **3** was a competitive inhibitor against **10**, $K_{i(3)} = 71 \pm 9$ μM. These values can be compared with $K_d = 2.4$ and $K_d = 2.5$ μM for the magnesium salts of **4** and **5**, respectively.[14] The reduced binding of these analogues, relative to the natural compounds, probably reflects

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(8) ^{1}H NMR ($CDCl_3$) δ 1.21 and 1.26 (12 H, dt, -O-CH_2-CH_3, $J_{H,H}$ = 7), 2.14 (2 H, dd, P-CH_2-P, $J_{H,P}$ = 4.8 Hz, $J_{H,P'}$ = 19.8 Hz), 3.60-4.27 ppm (8 H, m, -O-CH_2-CH_3); lit.[6] (benzene), P-CH_2-P, δ 2.16 (dd, $J_{H,P}$ = 20 Hz, $J_{HP'}$ = 4 Hz); ^{31}P NMR (^{1}H decoupled, benzene/$CDCl_3$, internal reference $(CH_3O)_3P$ taken as +140.7) δ + 23.6 (d, phosphonyl), +164.9 (d, phosphonite), $J_{PP'}$ = 40 Hz; lit. 6 (neat) δ +25, +164, J = 38 Hz.
(9) This material was synthesized from 4-methyl-4-penten-1-ol (Wiley Organics) according to a published procedure: van der Gen, A.; Wiedhaup, K.; Swoboda, J.; Dunathan, H. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1979**, *95*, 2656.
(10) ^{1}H NMR (D_2O) δ 1.48 (4 H, m, $-CH_2$-s), 1.55 (3 H, s, $-CH_3$), 1.85 (2 H, dd, P-CH_2-P, $J_{H,P}$ = 17.1 Hz, $J_{H,P'}$ = 18.8 Hz), 1.94 (2 H, m, $-CH_2$-), the vinyl protons were obscured by the HOD peak at 4.55-4.75 ppm; ^{31}P NMR (D_2O, 85% H_3PO_4 reference, ^{1}H-decoupled) δ +36.59 (d, phosphinyl), and +12.73 ppm (d, phosphonyl), $J_{P,P'}$ = 5 Hz. Anal. Calcd for the monoammonium salt, $C_7H_{19}NO_5P_2$: C, 32.44; H, 7.39; N, 5.40; P, 23.90. Found: C, 30.62; H, 7.21; N, 5.33; P, 23.81. Triethyl ester **8** gave appropriate ^{1}H NMR, ^{31}P NMR, and GCMS spectra.
(11) This compound is commercially available, but we made it by acidification of 5-bromo-2-methyl-1-pentene, which was synthesized as described above.[9] The boiling point and ^{1}H NMR were identical with those of the commerical product.
(12) ^{1}H NMR (D_2O) δ 1.47 (3 H, s, $-CH_3$), 1.52 (3 H, s, $-CH_3$), 1.55 (2 H, br m, $-CHCH_2$-P, under $-CH_3$ groups), 1.87 (2 H, dd, P-CH_2-P, $J_{H,P}$ = 16.5 Hz, $J_{H,P'}$ = 19.0 Hz), 2.03 (2 H, q, =CH-CH_2-CH_2, $J_{apparent}$ = 7.5 Hz), 5.08 (1 H, dt, = CH-, $J_{H,H}$ = 6 Hz, J_{HCCP} = 1 Hz); ^{31}P NMR (D_2O, 85% H_3PO_4 reference, ^{1}H-decoupled) δ +35.23 (d, phosphinyl) and +12.92 ppm (d, phosphonyl), $J_{P,P'}$ = 4.3 Hz. Anal. Calcd for the monoammonium salt, $C_7H_{19}NO_5P_2$: C, 32.44; H, 7.39; N, 5.40; P, 23.90. Found: C, 30.46; H, 7.23; N, 5.45; P, 23.73. Triethyl ester **9** gave appropriate ^{1}H NMR, ^{31}P NMR, and GCMS spectra.
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