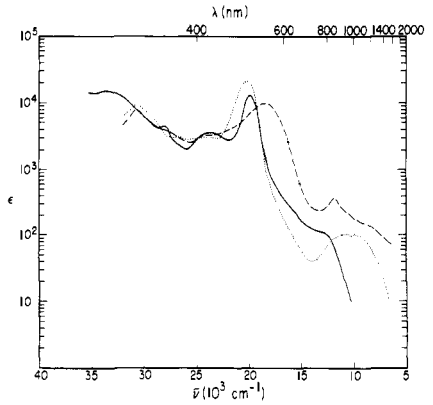

Figure 1. Electronic absorption spectra of bis(fulvalene)dinickel, II-Ni ($z = 0$) (—) in benzene; ($z = +1$) (- - -) and ($z = +2$) (· · ·) as hexafluorophosphate salts in acetone.

We have found that both II-Co ($z = 0, +1$) exhibit very similar infrared absorbances at 980 nm (ϵ 1150 and 7000, respectively), with shoulders at lower energy. These bands are absent in cobaltocene and the cobalticinium ion. The electronic spectra of the II-Ni system in Figure 1 indicate the presence of somewhat similar near-infrared absorbances for the three oxidation levels thus far isolated. These bands are absent in the "parent" nickelocene[11] and nickelocinium ion.[10] *Although these bands are the most intense in the mixed-valence derivative of cobalt and nickel, the presence of seemingly analogous near-infrared bands in other derivatives suggests that they are not intervalence transfer transitions associated with electron transfer from one localized metal center to another.*

Magnetic susceptibility measurements of solid samples of II-Fe,[1c,d] Co,[10] Ni[12] ($z = 0, +2$) show them to be diamagnetic at room temperature. The mixed-valence II-Co,[3c] Ni ($z = +1$) have $S = \frac{1}{2}$ ground states with magnetic moments close to that of the free electron value. The susceptibility of II-Ni ($z = +1$) tetraphenylborate follows Curie law from 3.5 to 82.0 K with $\mu_{eff} = 1.79\ \mu_B$. A $\mu_{eff} = 1.7\ \mu_B$ at 300 K was found for the hexafluorophosphate salt by the Evans NMR method.[13] These results indicate that complete magnetic coupling is facilitated in the bis(fulvalene)dimetal system containing from 34 to 40 valence electrons. To what degree this coupling is the result of direct metal–metal exchange or is propagated by the bridging ligands remains to be determined. However, a comparison of ultraviolet and visible spectra indicates that there are qualitative differences among the different oxidation levels of the cobalt and nickel complexes, as well as their "parent" metallocenes. These observations suggest that the bis(fulvalene) dimetal systems have electronic structures that are distinctly different from metallocenes.

Further evidence for geometric and electronic structural differences in these compounds is provided by a comparison of their infrared spectra. A variation in the number of bands in the carbon–carbon stretching region, as well as distinct differences in the lower energy region, is observed for each oxidation level of both II-Co, Ni, systems. These observations suggest that a ligand propogated exchange is occurring in bis(fulvalene)dimetal complexes containing more than 36 valence electrons, with concurrent changes occurring in the ligand geometry. A complete understanding of the structure and bonding of this interesting class of compounds will require further physical and structural studies, and will be aided by the synthesis of other bis(fulvalene)dimetal and bimetallocene derivatives.

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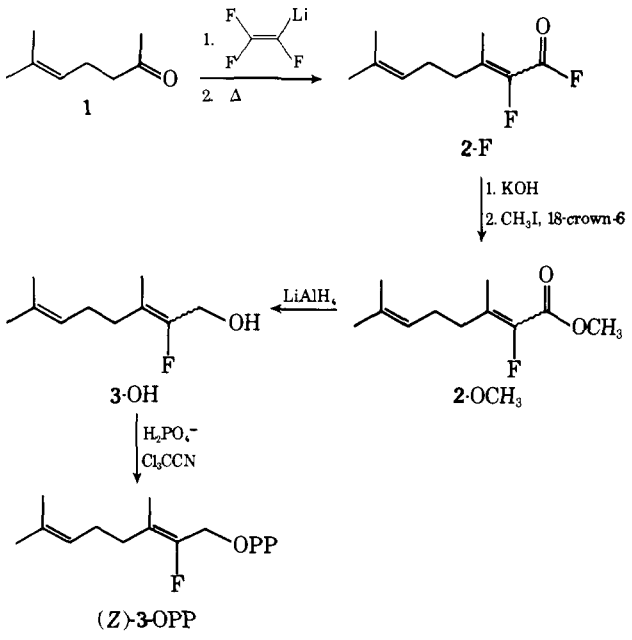
Prenyltransferase. New Evidence for an Ionization–Condensation–Elimination Mechanism with 2-Fluorogeranyl Pyrophosphate[1]

Sir:

The mechanism of the head-to-tail condensation between isopentenyl pyrophosphate (IPP) and an allylic pyrophosphate catalyzed by prenyltransferase (EC 2.5.1.1) has been the subject of speculation since the biosynthetic pathway was first uncovered over 20 years ago.[2] The earliest proposals envisioned carbon–carbon bond formation between C(4) of isopentenyl pyrophosphate and C(1) of the allylic substrate via cationic intermediates.[3] About ten years ago the ionization–condensation–elimination mechanism was replaced by the "X-group" mechanism (a displacement–elimination sequence), which was thought to be more compatible with the stereochemistry of the prenyltransfer reaction.[4] After examining the data which had been published we decided that it was not possible to distinguish between the two mechanisms. Although the stereochemistry of the enzyme-catalyzed reaction is compatible with that of the individual steps of the displacement–elimination mechanism,[4c] it is quite possible that the stereospecificity found for the reaction is dictated by the topology of the active site of prenyltransferase.[5]

We reasoned that it would be possible to distinguish between the two mechanisms by selectively substituting hydrogen with fluorine in the allylic substrate. The powerful electron withdrawing effect of fluorine should retard ionization of the allylic pyrophosphate, while having little influence on the rate of a direct nucleophilic displacement.[6] We recently reported that

Scheme I



(*E*)-3-trifluoromethyl-2-buten-1-yl pyrophosphate (an analogue for dimethylallyl pyrophosphate) was at least 10^6 times less reactive than the normal substrate during the prenyltransfer reaction.[7] However, some ambiguities remained. Inhibition studies with the C(5) analogue against geranyl pyrophosphate showed a "mixed-linear" pattern[8] with a fairly large inhibition constant, $K_i \simeq 51$ μM, and condensation of isopentenyl pyrophosphate with the fluoro analogue was too slow to permit isolation and characterization of a product. We have circumvented these problems with 2-fluorogeranyl pyrophosphate, and in this communication present new evidence for an ionization–condensation–elimination mechanism with farnesyl pyrophosphate synthetase (a C(5) → C(15) prenyltransferase) from porcine liver.

2-Fluorogeranyl pyrophosphate ((*Z*)-**3**-OPP) was prepared from 6-methyl-5-hepten-2-one (**1**) as shown in Scheme I. (*E*)- and (*Z*)-2-fluoro-3,7-dimethyl-2,6-octadienoyl fluoride (**2**-F, 35:65, respectively) were obtained from 6-methyl-5-hepten-2-one by the procedure of Drakesmith and coworkers.[9] The mixture of acid fluorides was converted to the corresponding methyl esters, followed by reduction with lithium aluminum hydride to a mixture of 2-fluoronerol ((*E*)-**3**-OH) and 2-fluorogeraniol ((*Z*)-**3**-OH). The alcohols were cleanly separated by medium pressure chromatography on silica gel, and (*Z*)-**3**-OH was phosphorylated according to the procedure of Cramer.[10,11]

The stereochemistry of the double bond at C(2) was determined from chemical shift data (see Table I). For acid fluorides **2**-F, carboxylic acids **2**-OH, and methyl esters **2**-OCH_3, the methyl group at C(3) in the *Z* isomers is deshielded by slightly more than 0.2 ppm.[12] We also found that the four-bond coupling constants ($^4J_{^1H-^{19}F}$) for the fluorine at C(2) and the hydrogens of the C(3) methyl group follow a regular pattern with $E(^4J_{^1H-^{19}F}) > Z(^4J_{^1H-^{19}F})$.[14] Overlapping peaks obscured the coupling constants for (*E*)- and (*Z*)-**3**-OH, but the pattern reemerged when the alcohols were each converted to benzoate esters, although the difference between the four-bond couplings had diminished. Our assignments were reconfirmed with 2-fluoro-3-methyl-2-buten-1-ol. In deuteriochloroform both methyl groups appear at 1.69 ppm. Upon addition of $Eu(fod)_3$, one methyl moves to lower field (2.76 ppm/equiv of $Eu(fod)_3$) significantly faster than the other (1.93 ppm/equiv of $Eu(fod)_3$), and the faster moving methyl has a smaller hydrogen–fluorine coupling constant ($^4J_{^1H-^{19}F}$ = 3.0 Hz vs. $^4J_{^1H-^{19}F}$ = 3.3 Hz) in agreement with our previous observations.

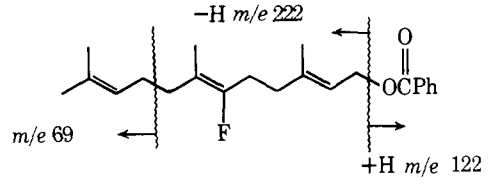
Table I. Chemical Shifts and ^1H–^{19}F Coupling Constants for the Methyl Group at C(3)[a]

Compd	δ, ppm	$^4J_{^1H-^{19}F}$, Hz
(*E*)-**2**-F	1.97	4.5
(*Z*)-**2**-F	2.19	3.6
(*E*)-**2**-OH	1.87	4.5
(*Z*)-**2**-OH	2.12	3.3
(*E*)-**2**-OCH_3	1.86	4.5
(*Z*)-**2**-OCH_3	2.07	3.4
(*E*)-**3**-OH	1.67	*b*
(*Z*)-**3**-OH	1.67	*b*
(*E*)-**3**-OCOPh	1.75	3.4
(*Z*)-**3**-OCOPh	1.77	3.0

[a] Spectra were obtained on a Varian EM-390 NMR spectrometer using $CDCl_3$ as a solvent. [b] Obscured by overlapping peaks.

2-Fluorogeranyl pyrophosphate (8.3 μmol) was incubated with isopentenyl-^{14}C pyrophosphate (4.1 μmol, 0.075 μC/μmol) and 2.5 mg of porcine liver farnesyl pyrophosphate synthetase (SA 300)[16] at 37 °C in 30 mL of a buffer consisting of 10 mM potassium phosphate, 1.0 mM magnesium chloride, and 0.1 mM dithiothreitol, pH 7.4. After 70 h[17] water was removed by freeze drying, and the residue was stirred overnight with 4 mL of isobutyl alcohol and 4 mL of saturated ammonium sulfate. The isobutyl alcohol layer was blown dry, and the residue was dissolved in 10 mL of 100 mM lysine buffer, pH 10.4. Alkaline phosphatase (5 mg) was added, and the solution was incubated for 48 h at 37 °C. The mixture was then extracted with hexane, and the hexane-soluble material was treated with benzoyl chloride and pyridine. The radioactive material was purified by high pressure liquid chromatography with an overall recovery of 37% based on unreacted IPP.

The radioactive material is judged to be C(15) fluorine containing terpene from GLC–MS data. The product eluted as a single, sharp peak at 180 °C on a 3-ft OV-17 column, as compared with an elution temperature of 138 °C for (*Z*)-**3**-OCOPh. The base peak in the mass spectrum occurs at *m/e* 69,



and represents loss of a 3-methyl-2-butenyl unit. Although a molecular ion at *m/e* 344 is not seen, two dianogistic peaks are found at *m/e* 122 (23% of base) and 222 (3% of base). We believe that these peaks arise from rupture of the alkyl–oxygen bond with transfer of a hydrogen from the hydrocarbon moiety to the benzoate group. A similar fragmentation is seen in farnesyl benzoate, *m/e* 122 (9% of base) and 204 (4% of base). These data and the known sterochemistry of condensation catalyzed by the pig liver enzyme[4a,b,c,19] suggest that condensation of (*Z*)-**3**-OPP with IPP gives (*Z*)-6-fluorofarnesyl pyrophosphate.[20]

From initial velocity measurements,[21] we determined $V_{max}^{GPP} = 370 \pm 30$ nmol/min mg and $V_{max}^{(Z)\text{-}3\text{-}OPP} = 0.31 \pm 0.02$ nmol/min mg. The rate retardation of the enzyme-catalyzed reaction by the 2-fluoro substituent (8.4×10^{-4}) is remarkably similar to that found for solvolysis of geranyl and 2-fluorogeranyl methanesulfonates (4.4×10^{-3}).[22] Michaelis constants for both reactions[23] ($K_{GPP}^{IPP} = 0.5 \pm 0.1$, $K_{IPP}^{GPP} = 0.8 \pm 0.2$, $K_{(Z)\text{-}3\text{-}OPP}^{IPP} = 0.35 \pm 0.1$, $K_{IPP}^{(Z)\text{-}3\text{-}OPP} = 1.1$

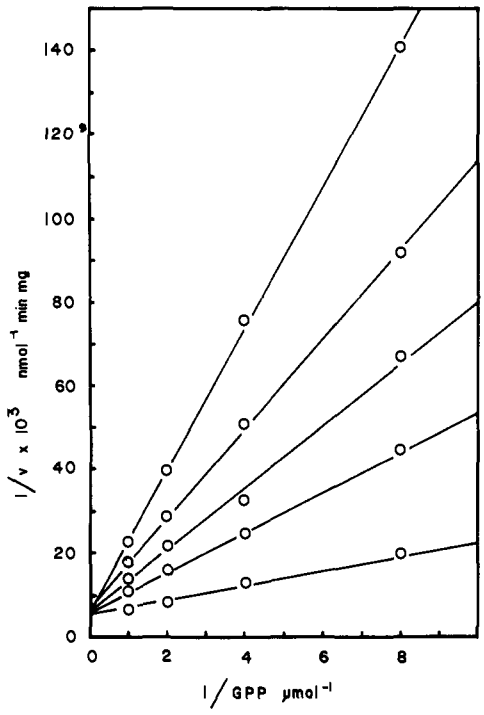


Figure 1. Inhibition of the enzyme with (*Z*)-3-OPP. Incubations were at 37 °C in 200 μL of 10 mM potassium phosphate buffer, pH 7.4, 1 mM $MgCl_2$, 0.1 mM dithiothreitol, 1 μM NaN_3, and 0.5 μM IPP with 26 ng of prenyltransferase and the indicated concentrations of GPP. Determinations were in duplicate. Concentrations of (*Z*)-3-OPP: none, 2.5, 5, 10, and 20 μM.

± 0.2 μM) suggest that 2-fluorogeranyl pyrophosphate is tightly bound by the enzyme. This observation is supported by inhibition kinetics, which show that (*Z*)-3-OPP is a *competitive inhibitor* (see Figure 1) of geranyl pyrophosphate with K_i = 2.4 ± 0.5 μM.

In summary, 2-fluorogeranyl pyrophosphate reacts with isopentenyl pyrophosphate in the presence of prenyltransferase to yield a C(15) fluorine containing homologue. The substrate analogue binds specifically to the allylic site, and kinetic behavior suggests that the binding is almost as tight as that of the natural substrate. Finally, replacing the C(2) hydrogen in the geranyl system by fluorine retards the rate of solvolysis, a reaction known to proceed through a carbonium ion intermediate, and the V_{max} of the prenyltransfer reaction by similar amounts.[25] We conclude that the head-to-tail coupling reaction catalyzed by prenyltransferase proceeds by an ionization–condensation–elimination mechanism. Experiments are underway in our laboratory to determine the timing of the individual steps.

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(11) Satisfactory IR and NMR spectra were obtained for all compounds. (*Z*)-**2**-OCH_3 and (*Z*)-**3**-OH gave satisfactory carbon–hydrogen analyses. Pyrophosphate (*Z*)-**3**-OPP gave a single spot on silica gel H plates (R_f 0.55 with $CHCl_3$/*MeOH*/H_2O 50:50:10). In the same solvent system the R_f's of geranyl phosphate and geranyl pyrophosphate were 0.72 and 0.54, respectively.
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(17) By 48 h the reaction had essentially stopped at two-thirds completion,[18] based on unreacted isopentenyl pyrophosphate. The enzyme was still active, and presumably the reaction stopped because of product inhibition.
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(21) All incubations were at 37 °C in 10 mM potassium phosphate buffer with 1.0 mM magnesium chloride and 0.1 mM dithiothreitol, pH 7.4. Total volume was 200 μL.
(22) Kinetics were measured conductiometrically in 90% acetone/water, $k_{(Z)\text{-}3\text{-}OMs}^{60°C} = (2.29 \pm 0.03) \times 10^{-3}$, $k_{GOMs}^{0°C} = (1.74 \pm 0.07) \times 10^{-3}$, $k_{GOMs}^{25°C} = (2.47 \pm 0.03) \times 10^{-2}$ s^{-1}. Extrapolation to 60 °C gives $k_{GOMs}^{60°C} = 5.2 \times 10^{-1}$ s^{-1}.
(23) Our values for IPP and GPP are similar to those reported for the avian liver enzyme[19] and considerably below those previously reported for porcine liver farnesyl pyrophosphate synthetase.[10,24] The superscripts refer to the variable substrates and the subscripts to the fixed substrates in runs from which the Michaelis constants were determined.
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(26) (a) Alfred P. Sloan Fellow; (b) Career Development Award from the National Institutes of Health, HL00084.

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Formation of Fused, Spiro, and Metacyclophane Rings via Intramolecular Carbanion Attack on Arene–Chromium Complexes

Sir:

The activating effect of π-bonded transition metals in the addition of nucleophiles to arene ligands is well established.[1] Combined with mild oxidation of the intermediate η^5-(alkylcyclohexadienyl)chromium tricarbonyl anion,[2] this process has been shown in simple examples to be an efficient means of formal nucleophilic substitution for hydrogen.[3] Here we report intramolecular reaction of carbanions onto π-arene ligands which provide examples of more complex conversions appropriate for organic synthesis, unexpected examples of thermodynamic vs. kinetic control over ring size, and the formation of a [3.3]metacyclophane.

Successful intermolecular additions to π-benzenechromium tricarbonyl have been observed with carbanions stabilized by carboalkoxy,[3] nitrile,[3] sulfur,[3] keto,[4] and imino[4] units, as well as a few examples of simple organolithium reagents.[3,4] We find that ester enolates fail in intramolecular addition to π-arene ligands,[5] while the anion of 1,3-dithiane (and, presumably, anions derived from still less acidic carbon acids) cannot be generated efficiently by direct proton abstraction in the presence of a π-arene unit.[6] However, nitrile-stabilized anions, such