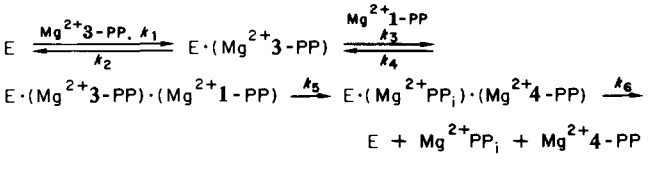
Scheme II. Binding Mechanism for 1′–4 Condensation



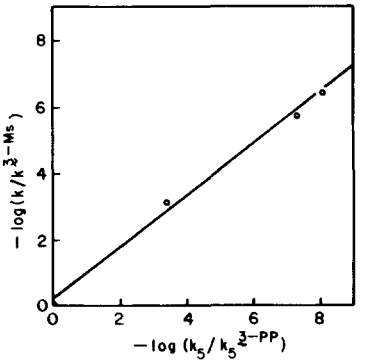


Figure 1. A Hammett plot of the ratio of rate constants for the catalytic step in 1′–4 condensation between **1**-PP and allylic substrates **3**-PP, **5**-PP, **6**-PP, and **7**-PP ($k_5/k_5^{3\text{-PP}}$) and the ratio of rate constants for solvolysis of **3**-Ms, **5**-Ms, **6**-Ms, and **7**-Ms ($k/k^{3\text{-Ms}}$).

yielding a geranyl cation–PP_i ion pair, and that this reactive species subsequently alkylates the double bond in **1**-PP.

Three analogues of **3**-PP—3-(fluoromethyl)-7-methyl-2,6-octadienyl pyrophosphate (3′-fluorogeranyl-PP, **5**-PP), 3-(difluoromethyl)-7-methyl-2,6-octadienyl pyrophosphate (3′,3′-difluorogeranyl-PP, **6**-PP), and 3-(trifluoromethyl)-7-methyl-2,6-octadienyl pyrophosphate (3′,3′,3′-trifluorogeranyl-PP, **7**-PP)—were prepared from the corresponding alcohols.[14,15] Maximum velocities (V) were measured by the acid lability method[16] using crystalline enzyme from avian liver,[17] specific activity 1.5 units/mg. Saturating concentrations of [1-^{14}C]isopentenyl-PP (20 μM, 56 μCi/μmol) and allylic substrate (400 μM) were used. Each run was accompanied by a blank determination with only the allylic pyrophosphate omitted from the buffer. The production of acid labile counts was linear up to ca. 20% conversion, and V (see Table I) was calculated from initial velocities in the linear region of the curve.[18] Michaelis constants (K_M) were also evaluated for **1**-PP with **3**-PP and the fluorinated analogues. The values are all similar and indicate that the replacement of **3**-PP in the active site by the analogues does not significantly perturb binding of **1**-PP to the enzyme, although the V's for **3**-PP and **7**-PP span a range almost of 10^8!

The effect of the fluorinated substituents on the rates for ionization of geranyl derivatives was evaluated in a model reaction where participation by π electrons is not possible by measuring the rate constants for solvolysis of methanesulfonates **3**-Ms, **5**-Ms, **6**-Ms, and **7**-Ms in acetone–water.[7] The values listed in Table II cover a range of more than 10^6. Two lines of evidence indicate that the cationic mechanism for solvolysis of **3**-Ms does not change as the system is destabilized by fluorine. A plot of log $k/k^{3\text{-Ms}}$ against σ_R[19,20] is linear ($R^2 = 0.995$), and the sensitivities of the less reactive analogues (**6**-Ms and **7**-Ms) to changes in the composition of the solvent are in the range expected for limiting solvolysis reactions according to Winstein-Grunwald m values.[6,21,22]

Farnesylpyrophosphate synthetase catalyzes the 1′–4 condensation reaction by the ordered, sequential mechanism shown in Scheme II,[23] and at steady state the maximum velocity is given by eq 1.[24] Furthermore, the rate constant for the catalytic step

$$V = k_5k_6E_t/(k_5 + k_6) \quad (1)$$

(k_5) is 47 times slower than the rate-limiting step k_6.[23] Assuming that the fluorinated farnesyl derivatives produced from **5**-PP, **6**-PP, and **7**-PP are released at least as rapidly as **4**-PP (i.e., $k_6^{\text{analogues}} \geq k_6^{4\text{-PP}}$), the decrease in V we observed for the fluorinated substrates must result from a situation where k_5 is significantly less than k_6, in which case $V = k_5E_t$. On the basis of this assumption, values for $k_5/k_5^{3\text{-PP}}$ were calculated and are listed in Table I.

A Hammett plot of $k_5/k_5^{3\text{-PP}}$ vs. $k/k^{3\text{-Ms}}$ (see Figure 1) is particularly informative. Since the rate ratios for 1′–4 condensation and solvolysis correlate linearly ($R^2 = 0.993$) over the entire range of reactivities, we have not traversed a threshold for π participation, even with the less reactive analogues. Also, the slope of the plot (0.77) demonstrates that 1′–4 condensation is slightly *more* sensitive to the electron-withdrawing groups at C(3) in the geranyl analogues than is the model solvolysis reaction. If π participation were important for the enzymatic reaction, one would expect the slope in Figure 1 would be considerably greater than unity.[8,25] We conclude, therefore, that (a) ionization and (b) condensation are not concerted. In view of the spatial limitations expected in the active site, we further conclude that an allylic cation–PP_i ion pair is the reactive species which alkylates **1**-PP. Experiments are now under way to determine if the changes in covalent bonding that occur during the condensation and elimination phases are stepwise or concerted.

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Farnesylpyrophosphate Synthetase. Evidence for a Rigid Geranyl Cation–Pyrophosphate Anion Pair[1,2]

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Received October 14, 1980

The terpene biosynthetic pathway is unique among major metabolic pathways in that carbon–carbon bonds are formed by electrophilic attack on a π-electron functional group. This general biosynthetic strategy was first deduced from the remarkable parallel that exists between the structures of natural isoprenoids and products of putative carbocationic precursors.[3,4] More re-

†University of Utah Graduate Research Fellow, 1977–1980.
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(1) Support of this research by the National Institutes of Health, GM-21328, is gratefully acknowledged.

(2) Abbreviations used in this communication are farnesyl-PP, farnesyl pyrophosphate; 2-fluoroisopentenyl-PP, 2-fluoroisopentenyl pyrophosphate; GC/MS, gas chromatography/mass spectroscopy; geranyl-PP, geranyl pyrophosphate; isopentenyl-PP, isopentenyl pyrophosphate; Pipes, piperazine-*N*,*N*′-bis(2-ethanesulfonic acid); PP_i, inorganic pyrophosphate.
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0002-7863/81/1503-3927$01.25/0

Table I. Incubation of [1-^{18}O]Geranyl-PP with Avian Liver Farnesylpyrophosphate Synthetase at 37 °C in the Presence of Various Cosubstrates

acceptor	concn, μM: acceptor	concn, μM: [1-^{18}O] 1-PP	pH	V_{rel}	1-PP consumed, %	^{18}O remaining at C(1) in recovered 1-PP, %
none		14	7.0[a]	0		94
[1-^{14}C] 2-PP[b]	10	14	7.0[a]	1	71	94
[1-^{14}C] 2-PP[b]	10	16	4.75[c]	0.011	63	95
[1-^{3}H] 3-PP[d]	22	20	7.0[a]	0.24	55	94

[a] 5 mM pipes, 1 mM magnesium chloride, 10 mM β-mercaptoethanol. [b] 10 μCi/μmol. [c] 20 mM potassium acetate, 1 mM magnesium chloride, 10 mM β-mercaptoethanol. [d] 1.5 μCi/μmol.

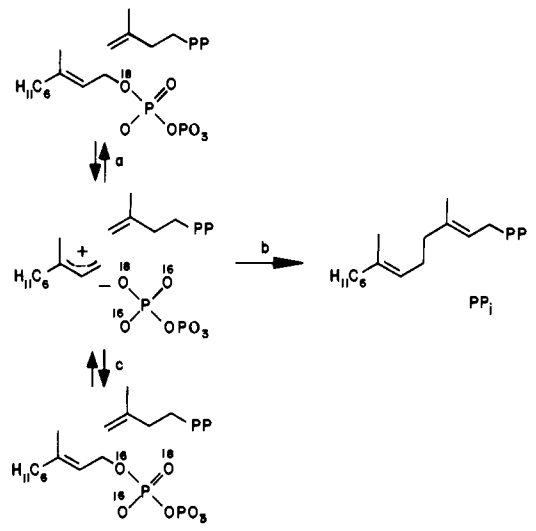
cently, linear free energy correlations were used[5-8] to establish an electrophilic mechanism for the 1′–4 condensation[9] between geranyl-PP (**1**-PP), an electrophilic prenyl donor, and isopentenyl-PP (**2**-PP), a π-electron prenyl acceptor, catalyzed by farnesylpyrophosphate synthetase. Although the generality of the electrophilic mechanism has not been established, it may be operating in other prenyl transfer reactions,[10,11] including examples where the electron-rich moiety in the prenyl acceptor is aromatic or a heteroatom.[12]

One of the remarkable features of terpene metabolism is the variety of products which different enzymes can synthesize from a single substrate. The conformation of the substrate in an E·S complex prior to catalysis is undoubtedly an important consideration. There is, however, a growing awareness that enzymes in the terpene pathway can also exert regiocontrol via electrostatic interactions between the carbocationic intermediates and appropriate counterions.[10,11,13-15] Recent experiments indicate that enzyme bound ion pairs are intermediates during cyclization of **1**-PP to bornyl-PP[16,17] and during isomerization of farnesyl-PP to nerolidyl-PP.[14,15] In both cases, considerable movement of the positive and negative partners occurs during the reaction. In particular, the primary-to-tertiary isomerization studied by Cane and Iyengar[14] was accompanied by complete scrambling of the oxygen originally attached to C(1) in farnesyl-PP with the two nonbridging oxygens at P_α. In the preceding communication, we reported that a geranyl cation–PP_i ion pair is an enzyme bound intermediate during the biosynthesis of farnesyl-PP.[8] We now present evidence concerning the structure of the ion pair.

Three options open to the geranyl cation are illustrated in Scheme I. Reaction a, regiospecific ion pair return to the labeled oxygen, and reaction b, alkylation of the double bond in **2**-PP, require very little movement of the positive and negative centers in the ion pair, whereas, reaction c, ion pair return to the unlabeled nonbridge oxygens in PP_i, is analogous to previously studied ion pairs where movement is required to obtain the observed products. The latter reaction can be detected by incubating farnesylpyrophosphate synthetase with **2**-PP and an excess of [1-^{18}O]**1**-PP until **2**-PP has been consumed, followed by analysis of distribution of ^{18}O in residual **1**-PP.

[^{18}O]Geraniol ([^{18}O]**1**-OH) was prepared from the corresponding chloride[18] and potassium [$^{18}O_2$]acetate,[19] followed by

Scheme I. Potential Reactions of the Geranyl Cation during 1′–4 Condensation



hydrolysis of the resulting acetate with potassium carbonate in methanol. The labeled alcohol was converted to [1-^{18}O]**1**-PP by the method of Cramer.[20,21] All incubations utilized crystalline farnesylpyrophosphate synthetase from avian liver (specific activity 1.5 units/mg)[22] in 20 mL of buffer at 37 °C. The following blank determination was used to establish the analytical procedure. A 1.5-mL portion of 1.5 M lysine (pH 10.4) was added to a solution of [1-^{3}H,1-^{18}O]**1**-PP (20 μM, 1.9 μCi/μmol). The sample was heated at 75 °C for 10 min[23] and equilibrated at 37° before addition of 10 mg of calf intestine alkaline phosphatase (Sigma).[24] Progress of the hydrolysis reaction was monitored by measuring the increase in hexane-soluble counts with time. Upon completion (usually 2 h), the aqueous layer was extracted with pentane; the pentane extracts were dried over magnesium sulfate and filtered; and the volume of the sample was reduced to ca. 100 μL with a stream of dry nitrogen. Bis(trimethylsilyl)acetamide was added, and the resulting trimethylsilyl ether of geraniol (**1**-$SiMe_3$) was analyzed by GC/MS.[25] The peak at m/z 228 for the molecular ion of [1-^{18}O]**1**-$SiMe_3$ is weak; however, a major peak at m/z 213, presumably resulting from the loss of methyl radical from silicon, is free from interfering peaks. Therefore, the $^{16}O/^{18}O$ ratio in [1-^{18}O]^{1}-$SiMe_3$ could be determined by selective ion monitoring of the peaks at m/z 211 and 213. Identical ratios were obtained

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for samples prepared from [1-^{18}O]1-PP or directly from [1-^{18}O]1-OH.

The results of our experiments with [1-^{18}O]1-PP using 2-PP and 2-fluoroisopentenyl-PP (3-PP)[26] as prenyl acceptors are summarized in Table I. The progress of each reaction was followed by the acid lability method,[27] and each reaction was run until the prenyl acceptor was consumed.[28] The 1′-4 condensation between 1-PP and 2-PP was not accompanied by scrambling of ^{18}O from a bridging to a nonbridging position when the incubation was carried out at the pH optimum of the enzyme (7.0). It is, however, necessary to show that this result is not simply an artifact resulting from insufficient quantities of 1-PP escaping from the active site before catalysis, once 2-PP has added to the enzyme. When the concentrations for 1-PP and 2-PP presented in Table I along with the known individual rate constants for the reaction[29] were used, it was possible to calculate by numerical integration[30] of the kinetic expression for the reaction[29] that 37% of the 1-PP which remained at the end of the reaction at pH 7 had been released from the ternary complex. We conservatively estimate the accuracy of the GC/MS analyses at ±1% and conclude that as little as 8% of exchange of ^{18}O into a nonbridging position in 1-PP would have been detected. An experiment with [1-^{18}O]1-PP and 2-PP was also conducted at pH 4.75,[31] where the initial velocity is only 1% of the value at pH 7.0, in an unsuccessful effort to detect scrambling by optimizing release of 1-PP from the ternary complex. Finally, 3-PP was employed as a prenyl acceptor. The fluorine at C(2) in 3-PP deactivates the adjacent double bond to electrophilic attack[26,32] and should enhance the possibility for bridge to nonbridge scrambling. Again, no exchange was detected in recovered 1-PP.

Our experiments with [1-^{18}O]1-PP clearly establish that the geranyl cation–PP_i ion pair does not react via path c (Scheme I). The question of whether path a competes favorably with b depends on the relative nucleophilicities of PP_i and the double bond in 2-PP. Although data are not available for these two specific moieties, negatively charged nucleophiles are usually considerably more reactive than their neutral counterparts.[33] Also, in an extensive series of studies, Goering[34] found that *p*-nitrobenzoate competes effectively with water for allylic cations in intimate ion pairs. One would expect that carbon–carbon double bonds are considerably less nucleophilic than any of these oxygen-containing species. We therefore submit that ion pair return does occur during the enzymatic reaction but is not detected because of topological constraints which restrict movement of the two partners.

A highly structured ion pair would have specific advantages with respect to the 1′–4 condensation reaction. A symmetrically solvated geranyl cation is a charge-delocalized species with significantly higher charge at C(3) than at C(1).[35] However, the distribution of charge in the allylic moiety will be altered substantially in a structure where the geranyl cation is sandwiched between 2-PP and PP_i, with a negatively charged oxygen near C(1).[36] The resulting increase in charge at C(1) and concommitant decrease at C(3) will enhance the reactivity of the primary center relative to C(3). This phenomenon has important implications with regard to reactivity and regiocontrol in electrophilic reactions. In the case of farnesylpyrophosphate synthetase, the desired selectivity is best accomplished in an enzyme bound ion pair complex whose topology is similar to that of the covalent substrates. Other enzymes, such as bornyl synthetase and farnesyl-PP:nerolidylpyrophosphate isomerase, may rely on an enzyme-mediated relocation of PP_i to regulate regiochemistry.[37]

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Synthesis and Complexing Properties of Chiral Macrocycles Containing Enforced Cavities[1]

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Synthetic organic compounds containing enforced cavities large enough to embrace molecules or ions larger than H^+, Li^+, or Mg^{2+} are virtually unknown. Crowns or cryptands in the uncomplexed state fill their own potential cavities with inward-turning CH_2 groups when their rings are large enough to accommodate such conformations.[2] Crowns whose rings are too small to accommodate inward-turned CH_2 groups possess cavities too small to embrace guests larger than the smallest ions.[2] In space-filling molecular models (CPK), compounds such as [1.2.1.2]paracyclophane[3a] or its analogues[3b-d] possess conformations in which their potential cavities can be filled with halves of aryl groups. Even the bicyclophane 1,3,5-C_6H_3(1,4-CH=CHC_6H_4CH=CH)$_3C_6H_3$-1,3,5 in molecular models possesses a cavity-free conformation. Models of the cyclic oligomers [2,6-$CH_2C_6H_3$(OH)CH_2]$_n$ with n = 4 to 8 (the calixarenes)[4] in some conformations contain substantial cavities which disappear in others. Kekulene[5] contains a disk-shaped cavity of about 3.4-Å depth whose existence is enforced by the rigidity of the fused aryl groups. The spherands contain enforced cavities, but in those reported to date, the cavities are large enough to capsularly complex ions only as small as Li^+ or Na^+.[6,7] Thus no synthetic organic compounds have been reported that contain enforced cavities the sizes of those in the cyclodextrins[8] or proteases[9] that contain lipophilic pockets. We report here stereochemically directed syntheses of such com-

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