proteins whereas it does differ in others. The PLH–Cu(II) system thus constitutes at best a partial model for a binding site in copper-containing proteins. It is possible that the similarities observed stem from a similarity in the way Cu(II) is bound, *i.e.*, at least partly at the imidazole groups.

Substrate Specificity of Farnesyl Pyrophosphate Synthetase

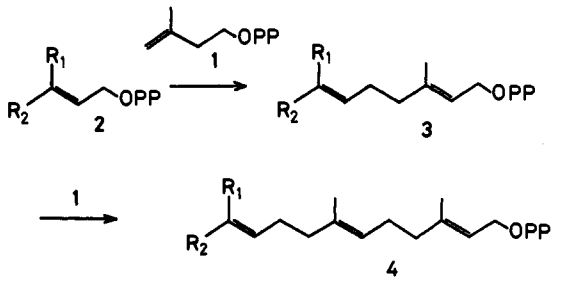
Tokuzo Nishino, Kyozo Ogura,* and Shuichi Seto

Contribution from the Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai, Japan. *Received February 2, 1972*

Abstract: The substrate specificity of farnesyl pyrophosphate synthetase of pumpkin fruit was studied with artificial allylic pyrophosphates. In order to determine the upper size limit of the reactive allylic pyrophosphate, *trans*-3-methyl-2-undecenyl (**2a**), *trans*-3-methyl-2-dodecenyl (**2b**), and *trans*-3-methyl-2-tetradecenyl pyrophosphate (**2c**) were assayed in the enzymatic reaction with isopentenyl pyrophosphate (**1**). **2a** and **2b** were reactive, the latter being far less so, whereas **2c** was no longer reactive. Replacement of the methyl group in 3-methyl-2-alkenyl pyrophosphate by ethyl did not cause marked change in the reactivity. *trans*-3-Ethyl-2-heptenyl (**2d**), *trans*-3-ethyl-2-octenyl (**2e**), and *trans*-3-ethyl-2-decenyl pyrophosphate (**2f**) were all reactive. However, branching of the alkyl group in 3-methyl-2-alkenyl pyrophosphate caused a remarkable decrease in the reactivity. Reactivities of *trans*-3,4-dimethyl-2-pentenyl (**5a**), *trans*-3,4-dimethyl-2-hexenyl (**5f**), and 3,6-dimethyl-2-heptenyl (**5c**) pyrophosphate were negligible.

Studies with artificial substrates for farnesyl pyrophosphate synthetase of pig liver and pumpkin fruit[1–5] have shown that the longest carbon chain homolog formed by pumpkin farnesyl pyrophosphate synthetase is a C_{18} compound, trishomofarnesyl pyrophosphate (**4**, $R_1 = CH_3$, $R_2 = n\text{-}C_4H_9$ or $R_1 = n\text{-}C_4H_9$, $R_2 = CH_3$) (see Scheme I) which results from the condensation of two molecules of isopentenyl pyrophosphate (**1**) with *trans*- (**2**, $R_1 = CH_3$; $R_2 = n\text{-}C_4H_9$) or *cis*-3-methyl-2-heptenyl pyrophosphate (**2**, $R_1 = n\text{-}C_4H_9$; $R_2 = CH_3$).[3] It was shown that the longer homolog of the cis series (**2**, $R_1 = n\text{-}C_5H_{11}$; $R_2 = CH_3$) was inactive and that the longer homologs of the trans series (at least up to $R_1 = CH_3$; $R_2 = n\text{-}C_7H_{15}$ in **2**) reacted with one molecule of **1** to give the corresponding geranyl pyrophosphate homologs (**3**),[3] but the longer limit of the trans series remains to be defined. The previous observation that *trans*-3,5-dimethyl-2-hexenyl pyrophosphate (**5b**) cannot be a substrate in contrast to the reactivity of the nonbranching isomer[3] also led us to study the effect of the branching of the alkyl group in 3-methyl-2-alkenyl pyrophosphate on the reactivity as a substrate. The present paper describes these results.

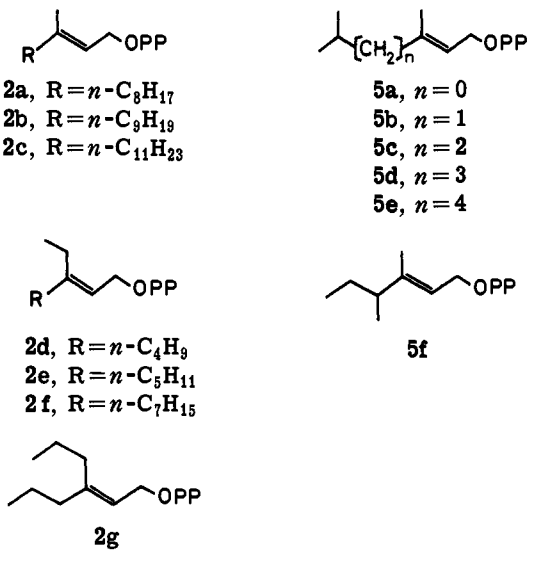
Scheme I



$-OPP = -OP_2O_6^{3-}$

In order to define the longer limit of the reactive homolog, *trans*-3-methyl-2-undecenyl (**2a**), *trans*-3-methyl-2-dodecenyl (**2b**), and *trans*-3-methyl-2-tetradecenyl pyrophosphate (**2c**) were synthesized by a method similar to that reported previously[3] (Scheme II). The Witting reaction of 2-decanone, 2-undecanone, and 2-tridecanone with diethyl methoxycarbonylmethyl phosphonate gave mixtures of methyl *cis*- and *trans*-3-methyl-2-alkenoates. The mixture of the esters was hydrolyzed to the free acids, from which the trans isomers were purified by recrystallization.

Scheme II



$-OPP = -OP_2O_6^{3-}$

(1) G. Popják, P. W. Holloway, and J. M. Baron, *Biochem. J.*, **111**, 325 (1969).
(2) G. Popják, J. L. Rabinowitz, and J. M. Baron, *ibid.*, **113**, 861 (1969).
(3) K. Ogura, T. Nishino, T. Koyama, and S. Seto, *J. Amer. Chem. Soc.*, **92**, 6036 (1970).
(4) T. Nishino, K. Ogura, and S. Seto, *ibid.*, **93**, 794 (1971).
(5) T. Nishino, K. Ogura, and S. Seto, *Biochim. Biophys. Acta*, **235**, 322 (1971).

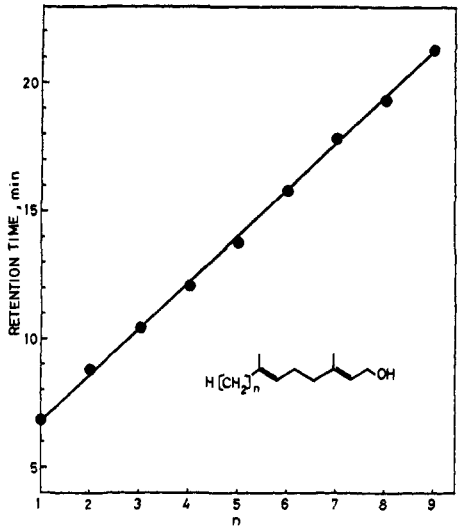


Figure 1. Retention time in the gas chromatography of geraniol and its homologs. The gas chromatography was carried out at linear programmed temperature at a rate of 4°/min from 140 to 245° on a 1-m column of PEG 20M with helium gas at a flow rate of 30 ml/min.

The alcohols derived from the trans acids were phosphorylated to give the corresponding pyrophosphates, **2a**, **2b**, and **2c**. Enzymatic reaction of the artificial substrates was assayed as described in the previous paper[3] by determining the incorporation of [^{14}C]isopentenyl pyrophosphate into the acid-labile allylic pyrophosphate formed by the condensation reaction. For analysis of the products of the enzymatic reaction, the radioactive alcohols liberated by alkaline phosphatase hydrolysis were subjected to radiogas chromatography with suitable reference prenols.

As shown in Table I, adequate reactivity of **2a** with **1** was observed. Although the reactivity of **2b** was far less as compared with that of **2a**, the conversion was significant, since the analysis of the products obtained by a large scale incubation revealed the formation of the corresponding geranyl pyrophosphate homolog (**3**, $R_1 = CH_3$; $R_2 = n\text{-}C_9H_{19}$). However, the reaction of **2c** with **1** was equal to that in the control experiment with **1** alone. The retention times by gas chromatography of the radioactive alcohols obtained by the alkaline phosphatase treatment of the products derived from **2a** and from **2b** were 19.3 and 21.3 min, respectively. These were reasonable for heptakishomogeraniol and octakishomogeraniol, because they satisfy the linear relation between chain lengths and retention times of geraniol and its homologs as shown in Figure 1. Thus, all the possible 3-methyl-2-alkenyl pyrophosphates that are enzymatically active are now known. Figure 2 shows the reactivities of these homologs relative to that of the natural substrate, dimethylallyl pyrophosphate.

Table I. Conversion of [^{14}C]Isopentenyl Pyrophosphate (**1**) into Acid-Labile Material

Substrate	Acid-labile material, cpm
1 + **2a**	8800
1 + **2b**	460
1 + **2c**	70
1 alone (control)	80

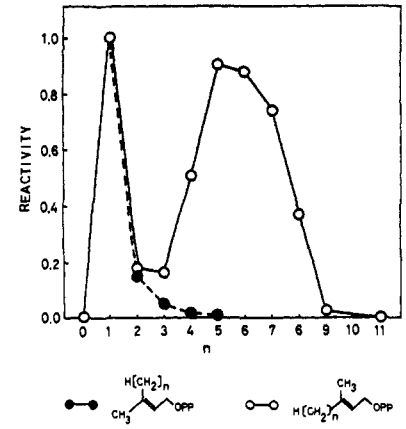


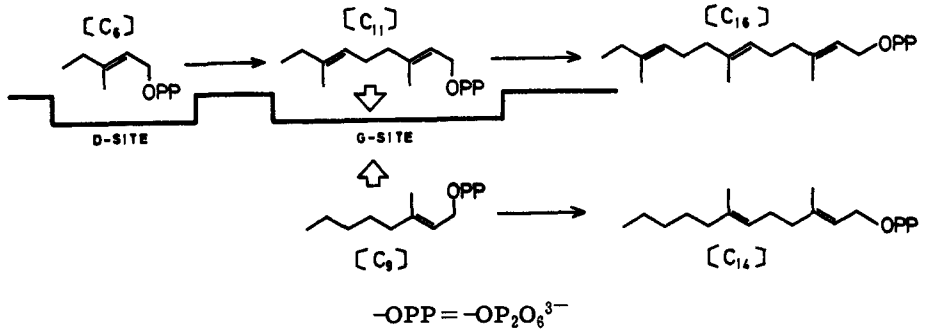
Figure 2. Reactivity of 3-methyl-2-alkenyl pyrophosphates as a function of the chain length of the alkyl group. The reactivity is expressed as the relative amount of condensation with [^{14}C]isopentenyl pyrophosphate to give acid-labile allylic pyrophosphate under standard conditions as described in the Experimental Section. The conversion of the natural substrate, *trans*-3-methyl-2-butenyl pyrophosphate, is taken as a standard.

The reactivity of *trans*-3-methyl-2-tridecenyl pyrophosphate (**2**, $R_1 = CH_3$; $R_2 = n\text{-}C_{10}H_{21}$), though not examined, would be negligible, and the C_{13} compound **2b** can be considered as the longest homolog that can be a substrate. It is also concluded that the C_{18} compound is the longest product formed by farnesyl pyrophosphate synthetase of pumpkin, regardless of whether the product is a homolog of the geranyl type **3** or the farnesyl type **4**.

The profile of the relation between the chain length and the reactivity (Figure 2), showing two maxima for the trans and only one for the cis isomers, suggests that two different sites responsible for the shorter and the longer substrates may be present in the enzyme. Namely, dimethylallyl pyrophosphate is expected to react with isopentenyl pyrophosphate (**1**) at the former site (dimethylallyl-transferring site) to give geranyl pyrophosphate, which would in turn migrate to the latter site (geranyl-transferring site) for conversion to farnesyl pyrophosphate. This assumption was supported by the study of a mixed incubation containing both *trans*-3-methyl-2-pentenyl pyrophosphate (C_6 substrate), capable of reacting with two molecules of **1**, and *trans*-3-methyl-2-octenyl pyrophosphate (C_9 substrate), which reacted with only one molecule of **1**. As seen in Figure 3, in the presence of both the C_6 substrate and the C_9 substrate, the elongation of the former to the C_{16} compound was suppressed and the synthesis of the C_{14} compound from the C_9 substrate was dominant. The radioactive carbon content of the C_{11} peak relative to that for the C_{16} peak was undoubtedly larger when the C_6 substrate was incubated in the presence of the C_9 substrate than during its absence. These results suggest that the added C_9 substrate competes with the C_{11} intermediate derived from the C_6 substrate and **1** (Scheme III).

In order to determine the effect of replacement of the methyl group at the 3 position of these homologs by an ethyl group, *trans*-3-ethyl-2-alkenyl pyrophosphates were synthesized by a method similar to that for the *trans*-3-methyl-2-alkenyl pyrophosphates, and

Scheme III



trans-3-ethyl-2-heptenyl (**2d**), *trans*-3-ethyl-2-octenyl (**2e**), and *trans*-3-ethyl-2-decenyl pyrophosphate (**2f**) were also found to be reactive. Radioactive alcohols obtained by alkaline phosphatase treatment of the products from **2d**, **2e**, and **2f** showed retention times of 13.1, 14.6, and 18.4 min in the radiogas chromatography (conditions as in Figure 1). These values are reasonable for the C_{14}, C_{15}, and C_{17} alcohols, respectively. The reactivities of **2d**, **2e**, and **2f** relative to that of dimethylallyl pyrophosphate were 0.17, 0.60, and 0.47, respectively. 3-Propyl-2-hexenyl pyrophosphate (**2g**) was also synthesized and examined, but this compound was found to be inactive.

Several allylic pyrophosphates having a hydrogen atom at the 3 position have been tested, and none of them are accepted as a substrate by either liver or pumpkin enzyme.[2,6]

The data in Figure 2 which show that *n*-C_5H_{11} or *n*-C_6H_{13} at the 3 position of the allylic pyrophosphate is most favored by the enzyme led us to test *trans*-2-octenyl (**2**, R_1 = H; R_2 = *n*-C_5H_{11}) and *trans*-2-nonenyl pyrophosphate (**2**, R_1 = H; R_2 = *n*-C_6H_{13}). However, they were both inactive. These results indicate that, for reaction, disubstitution at the 3 position is essential, regardless of the chain length of the alkyl group.

In order to test the effect of branching of the alkyl group of the *trans*-3-methyl-2-alkenyl pyrophosphate, a series of compounds of type **5** was similarly synthesized. As seen in Table II, 6,7-dihydrogeranyl pyrophosphate (**5d**)[7] and 3,8-dimethyl-2-nonenyl pyrophosphate (**5e**) showed fairly high reactivity, but *trans*-3,4-dimethyl-2-pentenyl (**5a**) and *trans*-3,6-dimethyl-2-heptenyl pyrophosphate (**5c**) as well as *trans*-3,5-dimethyl-2-hexenyl pyrophosphate (**5b**)[3] were far less reactive as compared with **5d** and **5e**. *trans*-3,4-Dimethyl-2-hexenyl pyrophosphate (**5f**) was also found to be inactive. The radioactive alcohols obtained by alkaline phosphatase treatment of the products from **5d** and **5e** showed retention times of 14.5 and 16.5 min, respectively, which were reasonable for dihydrofarnesol[1] and its homo derivative. Comparison of the reactivity of each compound with its nonbranching isomer reveals that the branching of the alkyl group is unfavorable for reactivity as the substrate.

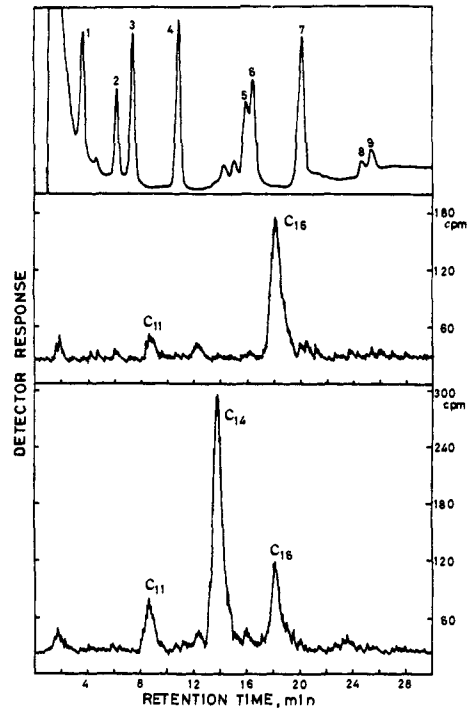


Figure 3. Radiogas chromatograms of the alcohols obtained by alkaline phosphatase hydrolysis of the products synthesized on incubation of farnesyl pyrophosphate synthetase with *trans*-3-methyl-2-pentenyl pyrophosphate (C_6 substrate) and [^{14}C]isopentenyl pyrophosphate (**1**) in the absence (middle) or the presence (bottom) of *trans*-3-methyl-2-octenyl pyrophosphate (C_9 substrate). Reference prenols in the gas chromatogram (top): 1, linalool; 2, citronellol; 3, geraniol; 4, *trans*-nerolidol; 5, *cis,trans*-farnesol; 6, *trans,trans*-farnesol; 7, *trans,trans*-geranyllinalool; 8, *cis,trans,-trans*-geranylgeraniol; 9, *all-trans*-geranylgeraniol.

Table II. Conversion of [^{14}C]Isopentenyl Pyrophosphate (**1**) into Acid-Labile Material

Substrate	Acid-labile material, cpm
1 + **5a**	300
1 + **5b**	180
1 + **5c**	90
1 + **5d**	6400
1 + **5e**	2940
1 + **5f**	40
1 alone	40

Experimental Section

Materials. Farnesyl pyrophosphate synthetase was obtained from pumpkin fruit by a method reported previously.[8] [^{14}C]Isopentenyl pyrophosphate (specific activity, 1.2 μCi/μmol) was the same preparation as in the previous study.[8] Ketones for the

(6) K. Ogura, T. Koyama, T. Shibuya, T. Nishino, and S. Seto, *J. Biochem.* (*Tokyo*), **66**, 117 (1969).

(7) Popják, *et al.*, have shown that **5d** can be a substrate for liver farnesyl pyrophosphate synthetase to give 10,11-dihydrofarnesyl pyrophosphate.[1]

(8) K. Ogura, T. Nishino, and S. Seto, *J. Biochem.* (*Tokyo*), **64**, 197 (1968).

Table III. Characteristics of Compounds

Compd, R =	δ (ppm) in nmr[a] $CH_3C=$	HC=	$(CH_3)_2CH$	Retention time in glpc, min	Mp, °C
trans-$R(CH_3)C=CHCO_2CH_3$					
n-C_8H_{17}	2.13	5.60		7.1[b]	
n-C_9H_{19}	2.15	5.70		10.1[b]	
n-$C_{11}H_{23}$	2.15	5.66		21.6[b]	
$(CH_3)_2CH$	2.08	5.57	1.05	2.1[c]	
$C_2H_5(CH_3)CH$	2.06	5.56		3.0[c]	
$(CH_3)_2CH(CH_2)_2$	2.12	5.57	0.90	4.3[c]	
$(CH_3)_2CH(CH_2)_3$	2.13	5.59	0.89	6.3[c]	
$(CH_3)_2CH(CH_2)_4$	2.12	5.58	0.87	9.4[c]	
trans-$R(CH_3)C=CHCOOH$					
n-C_8H_{17}	2.16	5.64			10.0–11.0
n-C_9H_{19}	2.16	5.70			36.5–37.5
n-$C_{11}H_{23}$	2.18	5.70			48.5–49.0
$(CH_3)_2CH$	2.12	5.67	1.08		35.5–36.0
$C_2H_5(CH_3)CH$	2.11	5.65			35.0–36.0
$(CH_3)_2CH(CH_2)_2$	2.17	5.69	0.92		23.0–24.0
$(CH_3)_2CH(CH_2)_3$	2.16	5.64	0.89		35.0–36.0
$(CH_3)_2CH(CH_2)_4$	2.17	5.67	0.88		

[a] The nmr spectra were measured on samples in carbon tetrachloride with tetramethylsilane as internal standard with a JNM-C 60HL nmr instrument (Japan Electron Optics Laboratory Co., Ltd.). [b] The gas chromatography was carried out with a Shimadzu gas chromatograph GC-4APT on a 1.5-m column packed with 20% PEG 20M on 60–80 mesh Chromosorb AW with helium gas at a flow rate of 26 ml/min. The column temperature was 165°. [c] Conditions were the same as described above except that the column temperature was 140°.

Table IV. Characteristics of Compounds

Compd R =	δ (ppm) in nmr[a] $-CH_2C(C_2H_5)=$	$CH_3CH_2C=$	HC=	Retention time in glpc, min[b]	Mp, °C
trans-$R(C_2H_5)C=CHCO_2CH_3$					
n-C_4H_9	2.18 (t)	2.65 (q)	5.58	4.1	
n-C_5H_{11}	2.15 (t)	2.66 (q)	5.65	6.0	
n-C_7H_{15}	2.15 (t)	2.63 (q)	5.59	13.7	
trans-$R(C_2H_5)C=CHCOOH$					
n-C_4H_9	2.21 (t)	2.68 (q)	5.68		10.0–11.5
n-C_5H_{11}	2.19 (t)	2.65 (q)	5.62		19.0–20.5
n-C_7H_{15}	2.18 (t)	2.64 (q)	5.60		19.5–20.5

[a] See Table III, footnote *a*. [b] See Table III, footnote *c*.

Table V. Characteristics of Compounds

Compd R =	δ (ppm) in nmr[a] $CH_3C=$	HC=	$-CH_2O$	$-CH_2C=$	CH_3CH_2	Retention time in glpc, min
trans-$R(CH_3)C=CHCH_2OH$						
n-C_8H_{17}	1.63	5.31	4.00	2.00	0.88	10.4[b]
n-C_9H_{19}	1.63	5.36	4.04	1.99	0.89	15.7[b]
n-$C_{11}H_{23}$	1.62	5.35	4.03	2.00	0.88	33.9[b]
$(CH_3)_2CH$	1.62	5.38	4.08			3.4[c]
$C_2H_5(CH_3)CH$	1.54	5.52	4.04			4.8[c]
$(CH_3)_2CH(CH_2)_2$	1.65	5.37	4.06			7.2[c]
$(CH_3)_2CH(CH_2)_3$	1.64	5.36	4.06			10.5[c]
$(CH_3)_2CH(CH_2)_4$	1.65	5.36	4.09			16.4[c]

[a] See Table III, footnote *a*. [b] See Table III, footnote *b*. [c] See Table III, footnote *c*.

synthesis of the artificial substrates were commercial products, unless otherwise stated.

General Procedure of Synthesis. ***trans*-3-Alkyl-2-alkenoic Acids.** A ketone was treated with diethyl methoxycarbonylmethyl phosphonate in the presence of sodium methoxide in the same manner as described in the preceding paper,[3] and the mixture of methyl *cis*- and *trans*-3-alkyl-2-alkenoates was obtained. The mixture of the esters was stirred in 1.2 equiv of 1 *N* sodium hydroxide at 70° until solution was complete (5–7 hr). The resulting solution was washed with ether, acidified with dilute hydrochloric acid, and then extracted with petroleum ether. Evaporation of the solvent left colorless crystals on cooling, which were recrystallized from methanol or aqueous methanol. The purity of each trans acid was confirmed by glpc and nmr of its methyl ester obtained by treatment of a part of the specimen with diazomethane. For the synthesis of 3-methyl-2-undecenoic acid, 2-decanone was obtained by chromic acid oxidation of commercially available 2-decanol. For the synthesis of 3,7-dimethyl-2-octenoic acid, 6-methylheptanone-2 was obtained by catalytic hydrogenation of 6-methyl-5-heptenone-2 in the presence of palladium/charcoal. 7-Methyloctanone-2 for the synthesis of 3,8-dimethyl-2-nonenoic acid was obtained by the reaction of 1-bromo-4-methylpentane with ethyl acetoacetate in the presence of sodium ethoxide followed by hydrolysis and decarboxylation.

***trans*-3-Alkyl-2-alkenyl Alcohol.** A solution of *trans*-3-alkyl-2-alkenoic acid in dry ether was added dropwise into an ice-cooled suspension of lithium aluminum hydride (1.2 equiv) in ether with stirring. After the complete addition, the product was worked up in the usual way. The purity was examined by glpc and nmr, and the data are summarized in Tables III–VI.

Table VI. Characteristics of Compounds

Compd R =	δ (ppm) in nmr[a] $CH_3CH_2C=$	HC=	$-CH_2O$	Retention time in glpc, min[b]
trans-$R(C_2H_5)C=CHCH_2OH$				
n-C_4H_9	2.00	5.35	4.02	7.5
n-C_5H_{11}	2.00	5.25	4.01	11.1
n-C_7H_{15}	2.00	5.25	4.01	25.4

[a] See Table III, footnote *a*. [b] See Table III, footnote *c*.

trans-**3-Alkyl-2-alkenyl Pyrophosphates.** *trans*-3-Alkyl-2-alkenyl alcohols were phosphorylated in a 1-mmol scale essentially by the method of Cramer and Böhm[9] as modified by Kandutsch, *et al.*[10] To the reaction mixture of the phosphorylation was added 5 ml of ether, and the mixture was extracted four times with 1-ml portions of 1% aqueous ammonia. After the combined aqueous extract was washed four times with 5-ml portions of ether, 0.5 ml of cyclohexylamine was added. Then the solution was made *ca.* 50% acetone–water by the addition of acetone and allowed to stand at 4° overnight. After removal of the crystalline monophosphate cyclohexylammonium salt by filtration, a few drops of a saturated lithium chloride solution were added to the filtrate. After standing for several hours at 4°, the precipitate of the lithium salt of the pyrophosphate ester was collected by filtration and washed with a small volume of ice-cooled 50% acetone–water and then with a few drops of cold water. The ir spectrum indicated that this precipitate was almost free from the monophosphate ester. The contamination with the monophosphate was checked mainly on the basis of the fact that the lithium salts of the pyrophosphates showed absorptions at 1115–1125, 930–940, and 720–735 cm^{-1} and the lithium salts of the monophosphates at 1100–1160 and 1010–1030 cm^{-1}.

trans-2-Alkenyl pyrophosphates were obtained similarly from *trans*-2-alkenols synthesized by the malonic acid condensation of the corresponding aldehydes.

Enzymatic Reaction. In the standard experiments, the incubation mixture contained, in a final volume of 1.0 ml, 40 μmol of phosphate buffer, pH 7.0, 5 μmol of magnesium chloride, 25 nmol of [^{14}C]isopentenyl pyrophosphate (30 nCi), 25 nmol of an allylic pyrophosphate to be examined, and 0.1 mg of the enzyme. After the mixture had been incubated at 37° for 30 min, the reaction was stopped by the addition of 0.3 ml of 1 *N* hydrochloric acid, and the mixture was incubated at the same temperature for 15 min to complete the hydrolysis of allylic pyrophosphates. The mixture was made alkaline with 0.35 ml of 1 *N* sodium hydroxide, and extracted with 5 ml of *n*-hexane. After washing with water the radioactivity in the extracts was determined in a toluene scintillator with a Kobekogyo liquid scintillation counter GCL-111. The efficiency of counting ^{14}C was 86%.

Analysis of Products. For preparing the samples for gas chromatographic analysis, large scale incubations (three–ten times as much as the standard incubation) were made for 2 hr. The reaction mixture was then adjusted to pH 9.0 with Tris-HCl buffer, and intestinal alkaline phosphatase (10 μl, Boehringer, grade II, 10 mg/ml) was added. After the incubation at 37° for 3 hr, the mixture was extracted with petroleum ether. The extracts were subjected to gas chromatographic analysis. The analysis was carried out with a Shimadzu radiogas chromatograph RID at linear programmed temperature at a rate of 4°/min from 140 to 245° on a 1-m column packed with PEG 20M on Chromosorb AW. Helium gas was used as a carrier at a rate of 30 ml/min. A mixture of prenols (geraniol, farnesol, and geranylgeraniol) was usually used for the reference.

In the mixed incubation in Figure 3, the incubation mixture contained the same as that in the standard incubation except that 25 nmol of *trans*-3-methyl-2-octenyl pyrophosphate was added in addition to *trans*-3-methyl-2-pentenyl pyrophosphate. After incubation for 35 min, the products were analyzed as described above.

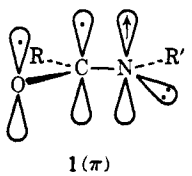
(9) F. Cramer and W. Böhm, *Angew. Chem.*, **71**, 775 (1959).
(10) A. A. Kandutsch, H. Paulus, E. Levin, and K. Bloch, *J. Biol. Chem.*, **239**, 2507 (1964).

Communications to the Editor

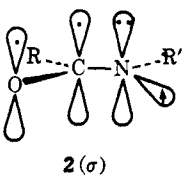
Nitrogen-Centered Free Radicals. V. Electron Spin Resonance Evidence for a π Electronic Ground State of Transient Amido Free Radicals[1]

Sir:

We wish to report the first unequivocal identification of simple amido radicals, R–CO–$\dot{N}$–R′, by electron spin resonance spectroscopy. Amido radicals have been the subject of considerable controversy due to the possibility of either a π or σ electronic ground state for this type of radical (*cf.* **1** and **2**). The basic question has been whether the difference in energy resulting from the delocalization of a pair of electrons in a p orbital would be sufficiently great to overcome the promotional energy of an electron in a hybrid orbital to the p orbital. Purported evidence for both a π[2–6] and a σ[7–10] structure



1 (π)



2 (σ)

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