$C_{13}H_{20}O_4S$ 272.10850)] and the double-bond isomer **28** [R_f 0.26; 13 mg; 38%; IR (CCl_4) 2965 (s), 2955 (s), 2900 (s), 2880 (s), 2840 (s), 1730 (s), 1635 (w), 1460 (s), 1370 (m), 1320 (m), 1300 (s), 1240 (m), 1130 (m), 1110 (m), 1085 (m), 1010 (m) cm^{-1}; NMR (CCl_4) δ 6.75 (1 H, q, J = 6.5 Hz), 5.7 (2 H, m), 4.2 (2 H, q, J = 7 Hz), 2.5 (6 H, m), 1.9 (3 H, d, J = 6.5 Hz), 1.55 (3 H, s), 1.3 (3 H, t, J = 7 Hz); m/e 272.10772 (m/e calcd for $C_{13}H_{20}O_4S$ 272.10850)].

Acknowledgment. This work was supported by grants from the National Science Foundation (GD 43891X) and the National Institutes of Health (CA 17918).

Registry No. 1 isomer A, 71031-77-1; 1 isomer B, 71031-78-2; 2 isomer A, 71031-79-3; 2 isomer B, 71031-80-6; 4, 71031-81-7; 5, 71031-82-8; 6, 71031-83-9; 8, 71031-84-0; 9, 71031-86-2; 11, 26505-44-2; 12, 70475-68-2; 13, 71031-87-3; 14, 71031-88-4; 15 isomer A, 71031-89-5; 15 isomer B, 71031-90-8; 17, 53799-54-5; 18, 71031-91-9; 19, 15224-05-2; 21, 71031-92-0; 22, 71031-93-1; 24, 71031-94-2; 26, 71031-95-3; 27, 71031-96-4; 28, 71031-97-5; 30, 71031-98-6; 31 isomer A, 71031-99-7; 31 isomer B, 71032-00-3; 32, 71032-01-4; 33, 71032-02-5; 34, 71032-03-6; 35, 71032-04-7; 37, 71032-05-8; 38, 71032-06-9; 39, 71032-07-0; 40, 71032-08-1; 43, 71032-09-2; 4-bromo-1-butanol, 33036-62-3; 4-bromobutanal, 38694-47-2; ethyl 6-bromo-hex-2-enoate, 71032-10-5; 6-bromohex-2-enol, 71032-11-6; 6-bromohex-2-enyl tetrahydropyranyl ether, 71032-12-7; methyl (methylthio)acetate, 16630-66-3; methyl thioglycolate, 2365-48-2; methyl 2-(butylthio)propionate, 71032-13-8; carbonodithioic acid *O,O'*-2,6-octadiene-1,8-diyl *S,S'*-dimethyl ester, 71032-14-9; allyl tetrahydropyranyl sulfide, 56393-74-9; allyl mercaptan, 870-23-5; (carboethoxy)methyl trifluoromethanesulfonate, 61836-02-0; 2-(carboethoxy)-2-methyl-1,1-dioxo-8-vinylthiacyclooct-4-ene, 71032-15-0; dihydropyran, 25512-65-6.

Cyclization and Allylic Rearrangement in Solvolyses of Monoterpenoids

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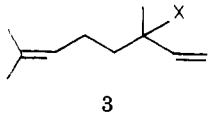
Hydrolysis and methanolysis of chlorides, phosphates, and pyrophosphates are examined. Solvolyses of geranyl derivatives give predominantly acyclic primary and tertiary substitution products, and the S_N1 reaction involves extensive allylic delocalization in the forming carbocation. Cyclic products formed with π participation predominate in solvolyses of neryl derivatives, but acyclic product formation involves allylic delocalization. The conformational requirements for π participation and allylic delocalization are different, and the rates, products, and kinetic secondary hydrogen isotope effects can be explained in terms of the initial state conformations and the transition state geometries. Decrease of solvent polarity favors elimination over substitution, and increasing nucleophilicity of the solvent favors formation of primary over tertiary products, but $LiClO_4$ has the opposite effect. These differences appear to depend upon the lifetime of the carbocation and its attaining the most stable conformation.

There has been considerable interest in mechanisms of solvolyses of the open chain monoterpenoid neryl (**1**) and geranyl (**2**) derivatives. Neryl derivatives readily give cyclic products, whereas predominantly open chain products are formed from geranyl derivatives.[1-9] At the simplest level, observations have been rationalized in terms of π participation in reactions of neryl derivatives (Scheme I).[10] Linalyl derivatives (**3**) are the most important substitution



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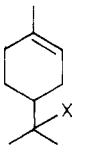
products in solvolyses of **2**. These reactions have also been considered as models for the biosynthesis of cyclic monoterpenes, and in some biological systems neryl, but not geranyl, pyrophosphate is a precursor of monocyclic terpenoids.[9,11,12] The nonbiological reactions have all the characteristics of S_N1 reactions, but the partial product specificity shows that the intermediate carbocations, or their ion pairs, do not undergo rapid trans-cis interconversion by rotation about the allylic double bond of the cation.

Scheme I is inadequate in that some acyclic products are always formed in solvolyses of neryl substrates (**1**), and some cyclic products are generally formed in solvolyses of geranyl substrates (**2**),[2-8] although terpinyl derivatives (**4**)



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are the predominant products in solvolyses of **1**.

Not only is the specificity incomplete, but the rates of solvolyses of neryl and geranyl substrates are often very similar despite product and kinetic isotope evidence for π participation in solvolyses of neryl substrates.[3-8] It is necessary to include additional steps to those shown in

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(1) O. Zeitschel, *Ber. Dtsch. Ges.*, **39**, 1780 (1906).
(2) J. A. Miller and H. C. S. Wood, *Angew. Chem.*, **76**, 301 (1964); R. C. Haley, J. A. Miller, and H. C. S. Wood, *J. Chem. Soc. C*, 264 (1969).
(3) P. Valenzuela and O. Cori, *Tetrahedron Lett.*, 3089 (1967).
(4) F. Cramer and W. Rittersdorf, *Tetrahedron*, **23**, 3015, 3023 (1967).
(5) W. Rittersdorf and F. Cramer, *Tetrahedron*, **24**, 43 (1968).
(6) C. A. Bunton, D. Hachey, and J.-P. Leresche, *J. Org. Chem.*, **37**, 4036 (1972).
(7) (a) C. A. Bunton, J.-P. Leresche, and D. Hachey, *Tetrahedron Lett.*, 2431 (1972); (b) D. Hachey, Ph.D. Thesis, University of California, Santa Barbara.
(8) K. B. Astin and M. C. Whiting, *J. Chem. Soc., Perkin Trans. 2*, 1160 (1976).
(9) T. Money, *Prog. Org. Chem.*, **8**, 29 (1973).
(10) In Scheme I, the neryl derivatives are shown in both the extended conformation, **1**, and as **1'**, which has a conformation which is similar to that of the transition state for ionization with π participation.
(11) O. Cori, *Arch. Biochem. Biophys.*, **135**, 416 (1969); R. Croteau and F. Karp, *ibid.*, **176**, 734 (1976).
(12) D. V. Banthorpe, B. V. Charlwood, and M. J. O. Francis, *Chem. Rev.*, **72**, 115 (1972).

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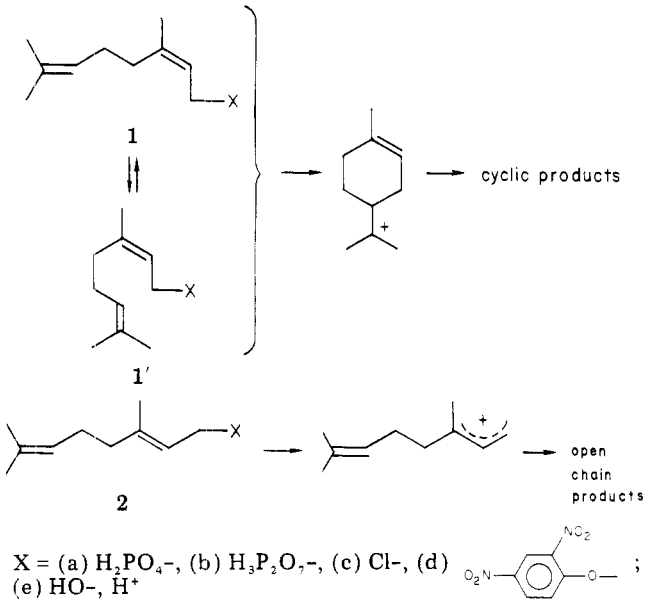
Scheme I



X = (a) H_2PO_4-, (b) $H_3P_2O_7$-, (c) Cl-, (d) ; (e) HO-, H^+

Scheme I, and the role of ion pairing has been stressed in discussions of acetolyses of the 2,4-dinitrophenyl ethers[8] and hydrolysis of *p*-nitrobenzoates in aqueous acetone.[13] However, the importance of ion pairing should decrease as the solvent becomes more aqueous; in addition, the rearrangements of the corresponding alcohols in aqueous solution give products similar to those of solvolysis,[1,3] but ion pairs should not be intermediates in the alcohol reactions.

Cramer and Rittersdorf postulated the existence of three carbocations formed directly by substrate ionization.[4] Geranyl derivatives could form an allylic cation, whereas neryl derivatives could generate both an allylic cation and a terpinyl-like cation. They considered ion pairing to be relatively unimportant for hydrolyses of the phosphates and pyrophosphates in water.

We had several aims in the present work: (i) to vary the leaving group, (ii) to attempt to promote the formation of ion paired intermediates in polar hydroxylic solvents, and (iii) to examine the effects of medium changes on the products. As leaving groups we used chloride, phosphate, and pyrophosphate, and we also examined the effects of micelle-forming surfactants.[14] We also attempted to reconcile the available product and kinetic evidence, especially with regard to the similarity of the reaction rates of **1** and **2** and the kinetic hydrogen isotopic evidence for π participation in solvolyses of neryl substrates.[7]

Experimental Section

Materials. Nerol and geraniol (Fluka, Chemical Samples Co. or Columbia Organics) were analyzed by GLC, were >95% pure, and did not contain the other geometrical isomer. α-Terpineol and limonene (MCB) were 98% pure by GLC.

The phosphates and pyrophosphates were prepared by standard methods[3-6] and isolated as lithium or cyclohexylammonium salts. They were quantitatively hydrolyzed using *E. coli* alkaline phosphatase giving alcohols which contained less than 1% impurity (GLC).

Neryl and geranyl chlorides (**1c** and **2c**) were prepared by reaction of the alcohols with methanesulfonyl chloride and pyridine in pentane at −5 °C.[6] This procedure is similar to, but simpler than, that of Stork which involves treatment of geraniol with *n*-BuLi in ether followed by tosyl chloride in hexamethylphosphoramide.[15] The chlorides prepared by our method were isomerically pure in that we did not detect the other isomer by kinetic analysis[7] or by infrared or NMR spectrometry.[6] (The chlorides and the amines had an infrared peak at 1670 cm^{-1}, characteristic of a carbon–carbon double bond. There is a typographical error in ref 6 where a frequency of 1750 cm^{-1} is given.) In addition, the amines prepared from the chlorides were isomerically pure.[6] The preparation of geranyl chloride by treatment of the alcohol with $SOCl_2$ or PCl_5 has been reported,[16] but in our hands these methods gave mixtures of the isomeric chlorides.

α-Terpinyl chloride (**4c**) was prepared from limonene (20 g) and dry HCl gas in hexane at −5 °C. The crude product was washed with water and $NaHCO_3$, and the solution was dried ($MgSO_4$). Vacuum distillation (bp 52–53 °C (0.3 mm)) gave the chloride in 20% yield. Analysis by GLC (7 ft. × $^1/_8$ in., 5% Carbowax-4000, 90 °C) showed that the product contained 6% impurity with the retention time expected for a monocyclic chloride. The NMR spectra in the vinyl region suggested that the product contained ca. 6% of the β-terpinyl chloride.

The kinetic solvents were made up from distilled water and acetone which had been dried (molecular sieve) and redistilled. Methanol was dried in the same way. The surfactants, cetyltrimethylammonium bromide (CTABr) and sodium lauryl sulfate (NaLS), were recrystallized (H_2O–EtOH) before use.

Products. The organic products were extracted and analyzed by GLC following methods already described.[6] The peak areas were determined using a Disc integrator, and peaks were identified by injection with known compounds. We were usually able to identify more than 90% of the material, and the unidentified peaks did not correspond to any of the common bicyclic terpenes. The total amount of alkenes noted in the tables of products is sometimes greater than the sum of the identified alkenes. The retention times of the unidentified products were similar to those of the identified alkenes.

Table I. Hydrolysis of Neryl and Geranyl Chloride[a]

	H_2O vol %							
	95		50		30		10	
product	NCl[b]	GCl	NCl	GCl	NCl	GCl	NCl	GCl
limonene	3		7		16		32	
terpinolene	2		4		8		12	
myrcene		1		1		4		9
ocimene		1		2		7		11
linalool	20	81	19	79	19	72	16	64
nerol	2		2		2		1	
geraniol		10		12		12		12
α-terpineol	72	7	67	6	52	5	37	4
alkenes, %	6	2	12	3	27	11	45	20

[a] At 25 °C in aqueous acetone. [b] Reference 6.

Table II. Hydrolysis of α-Terpinyl Chloride[a]

	H_2O vol %						
product	100[b]	100[c]	95	50	30	30[d]	30[e]
α-terpineol	76	64	99	84	51	13	33
limonene	10	17	1	12	36	58	25
terpinolene	11	18	1	4	13	21	29
alkenes, %	22	35	2	16	49	87	68

[a] At 25.0 °C in water or aqueous acetone. [b] 0.2 M NaLS. [c] 0.2 M CTABr. [d] 4 M $LiClO_4$; the products also contained 8% unidentified alkene and 1% unidentified alcohol. [e] 0.1 M $AgClO_4$–4 M $LiClO_4$; the products also contained 12% unidentified alkene.

(13) S. Winstein, S. Valkanas, and C. F. Wilcox, Jr., *J. Am. Chem. Soc.*, **94**, 2286 (1972).

(14) E. H. Cordes and C. Gitler, *Prog. Bioorg. Chem.*, **2**, 1 (1973); C. A. Bunton, *Pure Appl. Chem.*, **49**, 969 (1977); E. J. Fendler and J. H. Fendler, "Catalysis in Micellar and Macromolecular Systems", Academic Press, New York, 1975.

(15) G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Lett.*, 1393 (1969).

(16) J. L. Simonsen, "The Terpenes", Vol. 1, Cambridge University Press, London, 1953, p 50.

Table III. Solute Effects on the Products of Hydrolysis of Neryl Chloride[a]

product	0.2 M NaLS[b]	Ag_2O[c]	3.5 M $LiClO_4$[d]
limonene	15	19 (7)	14 (16)
terpinolene	6	9 (4)	15 (8)
acylic alkenes	1	4	10
linalool	17	13 (19)	1 (19)
nerol		1 (2)	(2)
geraniol		trace	
α-terpineol	60	53 (67)	58 (52)
alkenes, %	22	32 (12)	39 (27)

[a] The values in parentheses are in the absence of added solute. [b] In H_2O. [c] In Me_2CO–H_2O 50:50 (v/v). [d] In Me_2CO–H_2O 70:30 (v/v).

Table IV. Solute Effects on the Products of Hydrolysis of Geranyl Chloride[a]

product	0.2 M NaLS[b]	Ag_2O[c]
limonene	0.5	0.7
terpinolene	trace	0.5
acylic alkenes	trace	2.5 (3)
linalool	83	80 (79)
geraniol	6	8 (12)
α-terpineol		(6)
elimination, %	1	4 (3)

[a] The values in parentheses are in the absence of added solute. [b] In H_2O. [c] In Me_2CO–H_2O 50:50 (v/v).

Results and Discussion

Reactions of the Chlorides in Aqueous Solvents. We found both substitution and elimination products with the former predominating, especially in the more aqueous solvents (Tables I and II). The product compositions for neryl (**1c**) and geranyl (**2c**) chloride in water–acetone 70:30 (v/v) differ from those quoted in ref 6 where the amount of elimination was underestimated. There is consistently more elimination with neryl and terpinyl (**4c**) chloride than with geranyl chloride, which is understandable because solvolyses of neryl and terpinyl substrates give products derived almost wholly from tertiary carbocations.

The solvent effect upon the ratio of substitution to elimination is typical of S_N1-E1 reactions.[17] Elimination from neryl and terpinyl chloride is also favored when reaction is carried out in the presence of surfactants which can take up the substrates and provide a reaction environment which is less polar than water.[18]

Added silver oxide can act as an electrophilic catalyst, and it increases the amount of elimination from neryl chloride (Table III) probably because reaction occurs in a basic medium at the surface of a particle. However, the various adducts do not markedly change the nature of the substitution products (Tables I–IV).

Added lithium perchlorate also tends to favor elimination (Tables I–IV). The lithium ion is strongly hydrated so that the effective water content of the solvent is reduced, and perchlorate ion interacts with preformed carbocations in water;[19] such an interaction could hinder nucleophilic addition but interfere less with loss of a β-hydrogen.

Methanolysis. The patterns of the products of methanolysis of neryl and geranyl chloride are similar to those found in aqueous acetone (Table V), but more open chain and more primary substitution products are formed than in hydrolysis. For example, the ratio of linalyl (**3**) to geranyl (**2**) products is much less in MeOH than in the aqueous solvents, especially in the presence of the basic Ag_2O and NaOMe. These observations could be explained in terms of concurrent S_N1 and S_N2 reactions, but S_N2' reactions seem to be relatively unimportant, because they would give linalyl methyl ethers. An alternative formulation involves bimolecular attack by lyate ion upon an intimate ion pair, cf. ref 20. However, it is difficult to draw a distinction between an S_N2 reaction in which there is considerable bond breaking in the transition state and rate limiting bimolecular attack upon an ion pair, unless the ion pair can be trapped or otherwise detected. The ratio of elimination to substitution is much less sensitive to added solutes for methanolysis than for hydrolysis. But perchlorates favor the formation of terpinyl (**4**) products in the methanolysis of neryl chloride and linalyl as compared with geranyl products in the methanolysis of geranyl chloride (Table V).

Hydrolysis of the Phosphates and Pyrophosphates. The products of hydrolysis of the phosphates and pyrophosphates have already been studied,[3-6] and our experiments were largely on the effects of inert solutes or those of frozen solutions which change the product composition (Tables VI and VII).

When neryl phosphate or pyrophosphate is hydrolyzed in ice, the amount of elimination increases. Reaction in frozen solutions occurs in the aqueous interstices where the electrolytes are concentrated,[21] and as in reactions of the chlorides, $LiClO_4$ increases elimination (Table VI). In the hope of forcing capture of the carbocation by an alkene, we hydrolyzed neryl pyrophosphate in ice, under the conditions shown in Table VI, but with half an equivalent of limonene. We observed ca. 5% of an unidentified alcohol by GLC analysis, but it had the retention time expected for a C_{10} alcohol, and it was not one of the common bicyclic terpenoids (cf. ref 9 and 22).

Hydrolyses of neryl phosphate were also made in the presence of NaLS and CTABr with and without 0.2 M isoprene. Micellized NaLS increased the ratio of α-terpineol to linalool (Table VI) but it and CTABr had no other marked effect and we detected no C_{15} products when isoprene was added. The increased formation of α-terpineol was probably due to subsequent acid-catalyzed conversion of linalool into α-terpineol which should be strongly assisted by anionic micelles.[14] Similar interconversions[3] could be occurring in hydrolysis of geranyl phosphate and pyrophosphate in the presence of NaLS (Table VII).

Our results for the hydrolysis of geranyl phosphate at pH 1.5 and 25 °C are very similar to those on the pyrophosphates,[3,4] and micellized surfactants favored formation of cyclic products (Table VII). Elimination is relatively unimportant when the phosphates and pyrophosphates react in aqueous solution (Tables VI and VII and ref 3–5 and 23).

Analysis of the Product Composition. Despite marked differences in the nature of the leaving groups (Cl,

(17) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, New York, 1969, Chapter 9.

(18) Elimination is favored relative to substitution by a decrease in solvent polarity,[17] and the micellar surface is less polar than water.[14]

(19) M. J. Postle and P. A. H. Wyatt, *J. Chem. Soc., Perkin Trans. 2*, 474 (1972); C. A. Bunton and S. K. Huang, *J. Am. Chem. Soc.*, **94**, 3436 (1972); C. A. Bunton, S. K. Huang, and C. H. Paik, *ibid.*, **97**, 6262 (1975).

(20) R. A. Sneen, *Acc. Chem. Res.*, **6**, 46 (1973).

(21) R. E. Pincock, *Acc. Chem. Res.*, **2**, 97 (1969).

(22) J. C. Fairlie, G. L. Hodgson, and T. Money, *J. Chem. Soc., Chem. Commun.*, 1196 (1969).

(23) When geranyl and neryl pyrophosphates are solvolyzed in the presence of excess Mn^{2+}, considerable amounts of hydrocarbon are generated, whereas alcohols are the predominant products in solvolysis in water or in the presence of Mg^{2+}.[24]

(24) (a) D. N. Brems and H. C. Rilling, *J. Am. Chem. Soc.*, **99**, 8351 (1977); (b) unpublished results of L. Chayet, M. C. Rojas, G. Portilla, and O. Cori.

Table V. Methanolysis of Neryl and Geranyl Chloride[a]

	MeOH[b]		3 M $LiClO_4$		0.1 M $AgClO_4$		Ag_2O		0.2 M NaOMe	
	NCl	GCl	NCl	GCl	NCl	GCl	NCl	GCl	NCl	GCl
acyclic alkenes	0.6	1.8	0.3	1.6	0.8	0.2	0.7	1.2	0.6	0.4
limonene	13.6	0.3	9.7	0.6	8.0	0.1	10.4	1.7	14.4	0.2
terpinolene	3.2	0.5	1.0	1.0	2.9	0.2	5.3	1.2	4.4	0.4
α-terpinene	0.3	0.3	0.2	0.4	0.6	0.1	0.6	0.5	0.8	0.2
3, OMe	27.9	54.3	15.5	63.2	24.4	58.7	1.5	3.2	20.2	26.0
1, OMe	14.3	trace	5.1	0.2	13.4	7.2	11.7	15.6	26.7	8.4
2, OMe	1.7	42.2	0.9	28.0	2.8	33.0	9.1	52.4	1.8	64.0
4, OMe	39.8	0.3	65.4	4.6	46.2	0.4	59.1	23.4	30.1	0.4
alkenes, %	18	3	11	4	12	1	17	5	20	1

[a] At 25.0 °C. [b] Contains 2,6-lutidine to neutralize acid formed.

Table VI. Hydrolysis of Neryl Phosphate (NP) and Pyrophosphate (NPP)[a]

	conditions						
	H_2O[b]		3 M $LiClO_4$	ice[c]		NaLS[d]	$CTABr^d$
product	NP	NPP	NPP	NP	NPP	NP	NP
acyclic alkenes	trace		0.5	0.6	0.6	trace	
limonene	1.9	1.5	5.1	6.6	8.9	3.0	2.2
terpinolene	1.4	1.2	3.6	2.1	5.8		1.9
linalool	24.9	26.5	18.4	22.6	23.6	2.6	26.7
nerol	2.9	trace	1.0	2.0	2.0	0.4	3.8
geraniol	trace				trace		
α-terpineol	69.0	70.2	70.5	64.8	53.3	89.1	65.3

[a] At 25.0 °C and pH 2 with HCl, except where specified. [b] Reference 6. [c] At −25 °C. [d] 0.02 M.

Table VII. Hydrolysis of Geranyl Phosphate and Pyrophosphate[a]

	added solute		
products		$CTABr^b$	NaLS[b]
acyclic alkenes	1.5	2.4 (trace)	0.9 (trace)
cyclic alkenes		trace (trace)	trace (trace)
linalool	88.1	82.7 (74.3)	79.3 (75.5)
nerol		(0.2)	0.1 (trace)
geraniol	9.8	9.0 (23.1)	9.2 (17.9)
α-terpineol	0.6	5.9 (2.4)	10.5 (6.5)

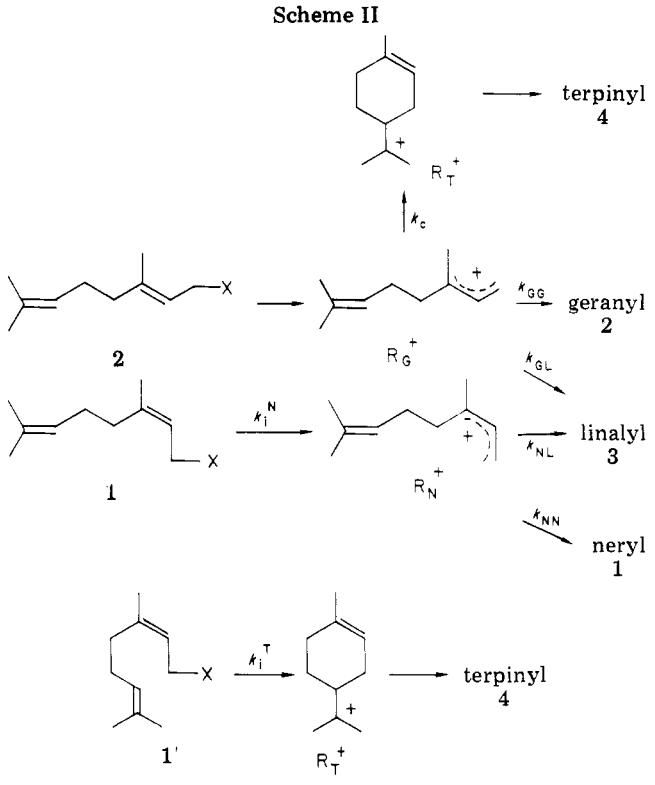
[a] At 25.0 °C, pH 1.5 with HCl; the values in parentheses are for geranyl pyrophosphate. [b] 0.02 M.

$H_2PO_4^-$, and $H_3P_4O_7^-$), neryl substrates give extensive amounts of monocyclic products (4), and geranyl substrates give largely acyclic products; the major differences in product composition seem to be in elimination to substitution ratios, which are close to those found in other similar S_N1 solvolyses.[17] However, even in water, the product distribution in deamination is different from that in hydrolysis, especially as regards the formation of rearranged products.[6]

The reaction products can be rationalized in terms of Scheme II. A geranyl substrate (2) forms the allylic cation, R_G^+, which reacts to give the tertiary, linalyl (3), or the primary, geranyl (2), products or may undergo rotation followed by cyclization to give monocyclic products (4) via the cation R_T^+. A neryl substrate (1) can ionize to the allylic cation R_N^+, which would give the acyclic linalyl (3) or neryl (1) products, but it can also ionize, with π participation, to give a cyclic terpinyl cation R_T^+. However, the beneficial effect of π participation is offset by the unfavorable gauche interactions which stem from the *syn*-butane-like conformation of the transition state.[8]

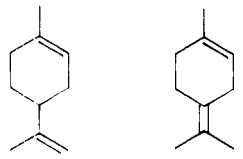
In Scheme II we assume that R_G^+ can generate the terpinyl-like cation, R_T^+, which should be the lower in free energy, but we do not take into account interconversion of R_G^+ and R_N^+. Generally only small amounts of neryl or geranyl products are found in solvolyses of the other substrate (Tables I and III–VII and ref 3–6). It is difficult to exclude the possibility of slight cross-contamination in the preparation of these and similar allylic derivatives.[25]

Scheme II



Partitioning of the Carbocations. Because of the diversity of the products in the solvolysis of neryl and geranyl compounds, we analyze the partitioning of the carbocations in terms of Scheme II, assuming that the cyclic alkenes, limonene (7) and terpinolene (8), are derived from R_T^+ and the acyclic alkenes, myrcene (9) and ocimene, shown in the trans form, 10, are derived from the open chain cation R_G^+.

(25) L. Chayet, R. Pont-Lezica, C. George Nacimento, and O. Cori, *Phytochemistry*, 12, 95 (1973).



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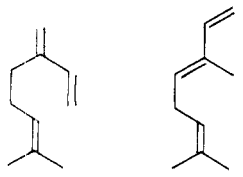

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The reactions shown in Scheme II lead to eq 1–6, where the product concentrations are expressed as mole fractions, n,[26] and the subscripts and superscripts T, N, L, and G denote respectively terpinyl, neryl, linalyl, and geranyl compounds.

For reactions of neryl substrates (1)

$$n_T = k_i^T/(k_i^N + k_i^T) \equiv k_i^T(\text{rel}) \quad (1)$$

$$n_N = k_i^N k_{NN}/(k_i^N + k_i^T)(k_{NN} + k_{NL}) \quad (2)$$

$$n_L = k_i^N k_{NL}/(k_i^N + k_i^T)(k_{NN} + k_{NL}) \quad (3)$$

For reactions of geranyl substrates (2)

$$n_T = k_c/(k_c + k_{GL} + k_{GG}) \equiv k_c(\text{rel}) \quad (4)$$

$$n_G = k_{GG}/(k_c + k_{GL} + k_{GG}) \quad (5)$$

$$n_L = k_{GL}/(k_c + k_{GL} + k_{GG}) \quad (6)$$

These equations allow us to estimate rate ratios for partitioning of the open chain cations R_G^+ and R_N^+, including k_c(rel), which is the partitioning of R_G^+ between cyclic and acyclic products, and the relative amount, k_i^T(rel), of the ionization of a neryl substrate which gives the cyclic cation R_T^+ (Scheme II).

The relative rates of partitioning of the cations are given in Tables VIII and IX. The values for the chlorides are calculated from the data in Tables I, III, and IV. We did not use the data for reaction in strongly basic solutions because of possible incursion by bimolecular reactions. The values for the phosphates and pyrophosphates are calculated from published data, and the results are in Tables VI and VII. These data are from three different laboratories[3-6] and were obtained at different temperatures and acidities. The experiments of Valenzuela and Cori[3] were at 37 °C, and the others were at 25 °C[6] or ambient temperature.[4] In addition, Valenzuela and Cori did not analyze alkenes formed (in relatively low concentration) during hydrolysis. The relative rates shown in Tables VIII and IX are similar despite differences in experimental conditions used by the various investigators. These differences could be important in hydrolyses of the phosphates and pyrophosphates where acid dissociation of the substrates depends upon pH and the presence of such inert solutes as electrolytes and surfactants. In addition, although changes in water content have major effects on the ratio of elimination to substitution, in reactions of the chlorides they do not affect the partitioning parameters in Table VIII.

(26) In formulating Scheme II, we assume that the structures of the cations are independent of the precursors, so that the treatment may be inadequate for reactions involving ion paired intermediates, cf. ref 8 and 13.

Table VIII. Partitioning of the Intermediates in the Solvolyses of the Chlorides

	neryl		geranyl	
substrate conditions	k_i^T(rel)	k_{NN}/k_{NL}	k_{GG}/k_{GL}	k_c(rel)
MeOH	0.57	0.5	1.3	0.01
MeOH–$AgClO_4$	0.58	0.56	1.4	0.08
MeOH–$LiClO_4$	0.76	0.32	0.44	0.07
95% H_2O–Me_2CO	0.78	0.1	0.12	0.07
H_2O–Me_2CO[a]	0.81	0.11	0.14	0.05
H_2O–Me_2CO–$LiClO_4$	0.87	v.s.[b]		
H_2O–NaLS	0.81	v.s.[b]		

[a] Mean values over the range of solvent composition. [b] Very small.

Table IX. Partitioning of the Intermediates in the Hydrolysis of Phosphates and Pyrophosphates[a]

	neryl		geranyl	
substrate conditions	k_i^T(rel)	k_{NN}/k_{NL}	k_{GG}/k_{GL}	k_c(rel)
RP–0.085 M H_2SO_4[b]	0.67	0.21	0.24	0.017
RPP–0.085 M H_2SO_4[b]	0.72	0.17	0.22	0.027
RPP–0.05 M HCl[c]	0.69	0.23	0.13	0.02
RPP, pH 1.75[c]	0.69	0.23	0.13	0.02
RP–dil. HCl[d]	0.72	0.12	0.11	0.01
RPP–dil. HCl[d]	0.73	v.s.[e]		
RPP–dil. HCl + 3 M $LiClO_4$	0.79	0.06		
RP–CTABr			0.11	0.06
RPP–CTABr			0.34	0.02

[a] RP denotes a phosphate and RPP a pyrophosphate. [b] Reference 4. [c] Reference 3. [d] Reference 6. [e] Very small.

Scheme II does not include ion pair return, although it is important in hydrolysis of linalyl p-nitrobenzoate in aqueous acetone[13] and has been postulated in some acetolyses.[8] It appears to be unimportant in hydrolysis of the phosphates in water,[4,5] the acid heterolyses of the alcohols,[3] and in hydrolysis of neryl chloride in aqueous acetone. Internal return in the hydrolysis of neryl chloride should generate at least some of the less reactive α-terpinyl chloride, but this hydrolysis is clearly first order,[7] so that internal return is playing no major role in this system. We see no evidence for ion pair return, but the products could be derived from attack on an ion pair of the carbocation with the leaving anion or with an added anion, e.g., perchlorate, which in water pairs readily with carbocations.[19]

Factors Governing Partitioning of the Carbocations. We see differences in the partitioning of the carbocations (Tables VIII and IX) which depend upon the medium rather than on the leaving group (but not upon the water content in aqueous acetone). For example, in solvolyses of neryl compounds, the values of k_i^T(rel) are consistently smaller and those of k_{NN}/k_{NL} larger in methanol than in the aqueous solvents. For solvolyses of geranyl compounds, k_{GG}/k_{GL} is also consistently larger in methanol than in the aqueous solvents, i.e., solvolysis in methanol favors formation of primary relative to tertiary products, but addition of lithium perchlorate to methanol decreases k_{GG}/k_{GL}, i.e., it favors formation of tertiary products. Methanol is more nucleophilic than water, and therefore the lifetime of a carbocation, or its ion pair, could be shorter in it than in water. But added perchlorate ions should pair with the cation and protect it from the solvent,[19] and partitioning of the carbocations in MeOH/$LiClO_4$ is similar to that in water. These observations suggest that the product composition depends in part upon the time available for a carbocation or its ion pair to attain its most stable conformation.

Although we see differences between the partitioning of the cations in methanol and aqueous acetone, there is little dependence on the water content of the aqueous acetone, except as regards the elimination–substitution ratio, and methanol, the more nucleophilic solvent, favors attack upon the primary center, which carries less positive charge in an allylic cation.

Structures of the Carbocationic Intermediates. The inclusion of three carbocationic intermediates in Scheme II rationalizes the products and the secondary kinetic hydrogen isotope effects.[7]

A major question is that of rotation about the delocalized allylic double bond, for example in R_G^+.[2] Geranyl phosphate or pyrophosphate are biological precursors of cyclic terpenoids, by a process which involves a bond rotation.[27,28] Assuming that the biological reactions involve carbocation-like intermediates, we can envisage rotation about a delocalized allylic double bond, akin to that in the step $R_G^+ \rightarrow R_T^+$ in the purely chemical reactions (Scheme II). Alternatively, the geranyl substrate could rearrange to an intermediate linalyl compound, e.g., a pyrophosphate, which could readily attain the conformation required for cyclization.

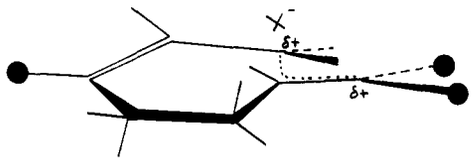
Free-energy barriers for rotational isomerization of allylic carbocations are in many cases large,[29] e.g., 16–20 kcal mol^{-1}, but they should be smaller in the present case where the allylic cation is a tertiary–primary resonance hybrid,[29b] whose structure should be very similar to that of a hypothetical classical linalyl cation. That part of the barrier to rotation which depends upon orbital overlap should be similar to the free-energy difference between a hypothetical classical linalyl cation and the delocalized cation, R_G^+ (Scheme II).

In our chemical system it seems safe to assume that covalent linalyl compounds are not reaction intermediates. For example, Cramer and Rittersdorf have evidence against internal return, although it is important in hydrolysis of linalyl *p*-nitrobenzoate,[13] but the *p*-nitrobenzoate ion should be more nucleophilic than the phosphate ion, and *p*-nitrobenzoates are good substrates for observing ion pair return.

Thus, even though linalyl pyrophosphate, **3b**, is a reasonable intermediate in the biological formation of cyclic terpenoids from geranly precursors, evidence from these chemical model systems suggests that there are other reasonable reaction paths. Although we must be cautious in drawing analogies between chemical and biological transformations, we note that cyclic terpenes are formed from geranyl pyrophosphate (the *E* isomer) with no $E \rightarrow Z$ rearrangement of the substrate, and the interconversion of enzyme bound carbocations was postulated.[28]

In a number of solvolyses, the neryl and geranyl substrates have similar reactivities,[3,7,8] although the secondary hydrogen isotope effect shows that there is at least some π participation in the solvolysis of neryl chloride,[7] and neryl is approximately three times as reactive as geranyl chloride in hydrolysis.[7b] We believe this relatively small difference in reaction rates to be the result of fortuitous free-energy compensations. Allylic delocalization in the ionization of either a neryl or geranyl substrate is less conformationally demanding than π participation (Scheme II). But π participation imposes considerable conformational restraints upon the transition state, which are costly both entropically, because of loss of rotational entropy, and enthalpically, because transition state formation involves partial gauche-like butane interactions. In a transition state with π participation (**11**), there is an interaction between the reaction center and the π system of the isopropylidene group so that the incipient positive charge will be delocalized between the primary and tertiary centers.

It is difficult to assess the importance of these *syn*-butane-like interactions in the transition state (**11**) for

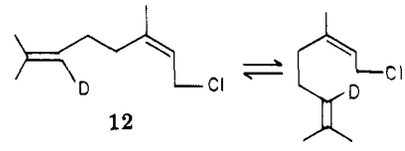


11

formation of the cyclic carbocation, R_T^+, because for π participation the forming six-membered ring will be puckered, which will minimize the gauche interactions, cf. ref 8. Inspection of **11** also shows that lack of coplanarity between the carbocation at the reaction center and the allylic substituents means that allylic delocalization should be relatively unimportant in the transition state for formation of R_T^+ with π participation. Astin and Whiting give a very careful analysis of the free energy difference between the initial state conformations **1** and **1′** of neryl derivatives, which places **1′** at a much higher free energy than **1**,[8] although some of the unfavorable interactions in **1′** will be relieved in forming the transition state (**11**).

The opposing effects of allylic delocalization, π participation, and *syn*-butane eclipsing rationalize the similar reactivities of geranyl and neryl substrates in S_N1 reactions,[3,7,8] without invoking the necessity of ion pair return in reactions in polar hydroxylic solvents. In addition, considerable amounts of open chain (linalyl) products are formed in reactions of neryl substrates via an acyclic transition state (Scheme II) with no unfavorable *syn*-butane interactions.

The observed isotope effect, $k_H/k_D = 0.92$, in the hydrolysis of the neryl derivative **12** is consistent with these



12 **12′**

explanations, because it is smaller than the value of $k_H/k_D \sim 0.8$ which would be expected if all the reaction proceeded through a transition state having sp^3 hybridization at the carbon bearing the isotopic substituent.[30] It is reasonable to assume that there is no isotope effect on that part of the reaction which gives acyclic products, formally via **12**, whereas π participation, in ionization of **12′**, will show the usual secondary isotope effect in going from sp^2 to sp^3 hybridization.[30]

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Registry No. **1a**, 16751-01-2; **1b**, 16751-02-3; **1c**, 20536-36-1; **1** (X = OH), 106-25-2; **1** (X = OMe), 2565-83-5; **2a**, 16750-99-5; **2b**, 763-10-0; **2c**, 5389-87-7; **2** (X = OH), 106-24-1; **2** (X = OMe), 2565-82-4; **3** (X = OH), 78-70-6; **3** (X = OMe), 60763-44-2; **4c**, 39864-10-3; **4** (X = OH), 98-55-5; **4** (X = OMe), 14576-08-0; **7**, 138-86-3; **8**, 586-62-9; **9**, 123-35-3; **10**, 3779-61-1; β-terpinyl chloride, 70682-36-9.

Molecular Rearrangements. 14. Photolysis and Thermolysis of Phenylpropionanilides

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Photolysis and thermolysis of phenylpropionanilide and (*o*-methylphenyl)- and (*p*-methylphenyl)propionanilides gave the corresponding arylamine, 1,4-diphenylbutane, together with ortho and para (α-phenethyl)arylamine. The first step in such a process is the homolysis of the acyl–N bond into arylamino and phenylpropionyl free radicals. The latter undergo decarbonylation into β-phenethyl radicals which rearrange to their α isomers. Photolysis was found to be an intramolecular process, while thermolysis was found to be mainly intermolecular as shown by cross-over experiments. On the other hand, alkyl derivatives of the solvent were isolated when the anilides were pyrolyzed in the presence of β-naphthol or isoquinoline as aromatic solvents.

Acetanilide, propionanilide, butyranilide, and benzanilide were reported[1-3] to rearrange on irradiation forming the corresponding *o*- and *p*-aminophenyl alkyl ketones through an intramolecular mechanism where the acyl–N bond undergoes cleavage. Partial transfer of the acyl group from acetanilide to a foreign molecule was also observed.[2]

Recently,[4] photolysis of benzanilide in ethanol as a solvent was found to produce a mixture of *o*- and *p*-aminobenzophenones together with ethyl benzoate, benzamide, azobenzene, and phenanthridone suggesting a free-radical intermolecular mechanism. Far less is known about the behavior of anilides on thermolysis.

The present work describes a study on the rearrangement pathway of β-phenylpropionanilide, (*o*-methyl-β-phenyl)propionanilide, and (*p*-methyl-β-phenyl)propionanilide on photolysis and thermolysis. The acetone-initiated ultraviolet irradiation of β-phenylpropionanilide for 30 h at room temperature (25 °C) gave rise to ethylbenzene, 1,4-diphenylbutane, and 2,3-diphenylbutane as neutral products together with aniline and a mixture of *o*- and *p*-(α-phenethyl)aniline.

Similar results were also obtained on photolysis of (*o*-methyl-β-phenyl)propionanilide under the same conditions whereby the above-mentioned neutral products were obtained in addition to *o*-toluidine and 4-(α-phenethyl)-*o*-toluidine as amine products. Also, the photolysis of (*p*-methyl-β-phenyl)propionanilide gave rise to *p*-toluidine and 2-(α-phenethyl)-*p*-toluidine in addition to the above-mentioned neutral products as shown in Table I.

Thermolysis of β-phenylpropionanilide either by reflux or by heating in a sealed tube at about 350 °C for 7 days gave rise to aniline, ethylbenzene, 2,3-diphenylbutane, and a mixture of *o*- and *p*-(α-phenethyl)aniline in addition to evolution of carbon monoxide.

In isoquinoline as a solvent, the same products were obtained together with 1-(α-phenethyl)isoquinoline.

In β-naphthol as a solvent, the previous products were formed in addition to 2,2′-dinaphthol and a nitrogenous byproduct, mp 112 °C, which was not further identified.

Table I. Percentage Composition of β-Phenylpropionanilide Photolysates

	β-phenyl-propion-anilide	(*o*-methyl-β-phenyl)-propion-anilide	(*p*-methyl-β-phenyl)-propion-anilide
ethyl-benzene	14.6	14.70	2.1
1,4-diphenyl-butane	11.9	22.40	3.3
2,3-diphenyl-butane	3.8	2.45	0.6
arylamine	9.5[a]	6.25[b]	20.5[c]
alkylaryl-amine	40.4[d]	32.25[e]	4.2[f]
unchanged anilide	14.9	20.75	69.0

[a] Aniline. [b] *o*-Toluidine. [c] *p*-Toluidine. [d] *o*-(α-Phenethyl)aniline and its para isomer in the ratio 1:5. [e] 4-(α-Phenethyl)-*o*-toluidine. [f] 2-(α-Phenethyl)-*p*-toluidine.

Similar results were also obtained from thermolysis of (*o*-methyl-β-phenyl)propionanilide and its para isomer where *o*- or *p*-toluidine were obtained in addition to substitution products of the α-phenethyl group on the corresponding toluidine moiety as shown in Table II.

The photorearrangement of such anilides was found to be an intra- rather than intermolecular process since irradiation of a mixture of α-phenylacetanilide and (*o*-methyl-β-phenyl)propionanilide in acetone solution gave products indicating that each anilide rearranges independently. Thus the amine products identified were only aniline, *N*-benzylaniline, (*o*-aminophenyl)phenylmethane, (*p*-aminophenyl)phenylmethane, *o*-toluidine, and 4-(α-phenethyl)-*o*-toluidine. No substitution of the alkyl group into the ring of the other compound took place. Had the rearrangement proceeded through an intermolecular pathway, cross-bred products such as *o*- and *p*-(α-phenethyl)aniline or (4-amino-3-methylphenyl)phenylmethane should be obtained, yet they are not detected among the products by GLC or TLC analyses of the amine products as compared with reference samples. Hence, it can be

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