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HYDROLYSES OF TERPENOID DIPHOSPHATES. EFFECTS OF AZIDE ION ON PRODUCTS OF HYDROLYSIS

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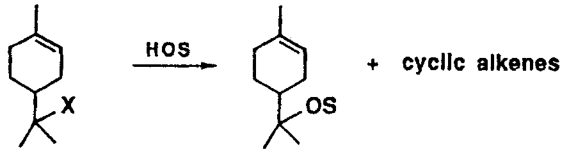
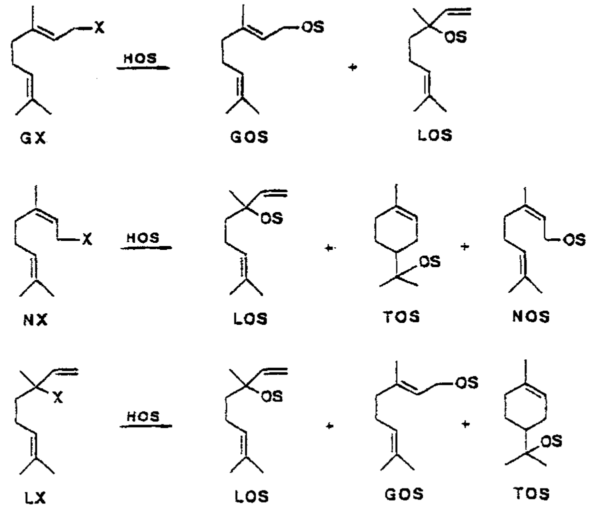
Hydrolysis of geranyl diphosphate (GPP) at pH 7 in water gives largely linalool (LOH) + geraniol (GOH) in the ratio of 3:1. Added N_3^- generates mixed acylic allylic azides and increases the LOH GOH ratio to 15:1 in 2 M NaN_3, but does not speed up the overall reaction. Hydrolysis of neryl diphosphate (NPP) gives largely α-terpineol (TOH) + LOH, but their ratio is not very sensitive to NaN_3 concentration although acyclic azide and small amounts of α-terpinyl azide (TN_3) are formed. Hydrolysis of α-terpinyl diphosphate (TPP) gives large amounts of the cyclic alkenes, limonene and terpinolene. Added N_3^- does not change the amount of elimination, but increases the ratio of limonene to terpinolene, and diverts some substitution product to TN_3. Trapping of carbocationic species from GPP by N_3^- is sharply increased by addition of Mn^{2+}, which also catalyzes the overall reaction. Products of reaction of GPP are derived from acyclic intermediates and of NPP from acyclic and cyclic intermediates, and ionizations of the three substrates do not generate common carbocationic species.

INTRODUCTION

Solvolyses of geranyl, neryl and linalyl derivatives (GX, NX and LX, respectively) give products derived from carbocationic intermediates. The substitution products are shown in Scheme 1 for reaction in a hydroxylic solvent, HOS, where the leaving group X is halide, carboxylate, phosphate or pyrophosphate.[1–7] Elimination is very important in non-nucleophilic solvents,[6] but substitution products dominate in reactions of the open-chain substrates in polar, nucleophilic solvents. Cyclic products form in reactions of neryl and linalyl derivatives because the carbocations can cyclize to give a terpinyl cation (T^+), which gives cyclic products.[1–7] α-Terpinyl derivatives (TX) are solvolyzed without ring





X = halide, carboxylate, phosphate, diphosphate

Scheme 1

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opening. Cyclization is relatively unimportant in solvolyses of geranyl derivatives because it involves rotation of an allylic carbocation. The chemical reactions have been studied extensively because biosynthetic reactions of prenyl diphosphates and similar compounds involve carbocationoid intermediates.[7–11]

Products of S_N1 reactions can be derived from free carbocations or from ion pairs, depending on the solvent, leaving group and substituents at the reactive center.[12] Azide ion traps labile carbocations at diffusion-controlled rates, so competition between N_3^- and other nucleophiles or bases measures rates of other competitive reactions of carbocations.[13,14] Azide ion is a much more effective nucleophile than expected from its relatively low basicity.[15]

Reactions were followed in water and the substrates were geranyl diphosphate (GPP), neryl di- and triphosphate (NPP and NPPP) and α-terpinyl diphosphate (TPP) (we follow precedent[1–7] in denoting the diphosphate residue as PP). Spontaneous and metal ion-catalyzed hydrolyses of most of these and similar substrates have been studied kinetically and the products have been examined.[1,2,7,16–18] The kinetics of these reactions are consistent with their following a general S_N1 mechanism, but the products are so different that they must be generated by a variety of carbocationic species.

Azide ion trapping has been examined extensively for reactions of neutral substrates that ionize to a pair of univalent ions,[12–14,19] but our phosphate esters have multivalent leaving groups,[7] which may influence product formation. In addition, the formation of acyclic and cyclic products from linalyl and neryl derivatives imposes conformational requirements that may influence the competition between water and azide ion for carbocationic intermediates. Although neryl and linalyl substrates generate cyclic products, differences in product compositions suggest that the reactions do not involve a common terpinyl carbocation.[1–4,7] Participation by the 6,7-double bond is important, at the rate or product stage, in reactions of neryl and linalyl substrates,[1–7,18] and chiral linalyl esters give optically active terpinyl products,[1] but the timing of the participation is uncertain and may depend on the reaction conditions.

We made most experiments at pH 7, where N_3^- is not protonated. Most experiments on hydrolyses of the phosphates and diphosphates have been made in aqueous acid where reaction probably involves undissociated phosphate or diphosphate esters.[1,2a,4] Our reaction conditions were those used earlier in studying metal ion catalysis.[7,16,17]

RESULTS AND DISCUSSION

Rate constants

Reactivities of the various phosphate esters are as expected from earlier work,[1–3,5,20] in that GPP and NPP have similar reactivities, NPPP is more reactive than NPP and TPP is the least reactive substrate. Most experiments were at pH 7 and based on $pK_a = 6.6$[7] for deprotonation of GPP^{2-} and from the overall first-order rate constants, k_ψ, at pH 7 and 8 (Table 1) we estimate approximate first-order rate constants for the disappearance of substrate of $2{\cdot}3 \times 10^{-6}$ and $0{\cdot}19 \times 10^{-6}$ s^{-1} for hydrolyses of GPP^{2-} and GPP^{3-} at 40·0 °C. Therefore, at pH 7 most of the reaction involves the dianion. The higher overall rate constant at pH 6 is due to incursion of reaction of the monoanion but the concentration of this species is so low that we do not estimate a rate constant for its reaction. This separation of reactivities neglects buffer effects which should be small for spontaneous hydrolyses in water.

Added NaN_3 does not increase the overall rates of reaction within the limit of 10% for reaction of GPP with 1.5 M added NaN_3, so there is no nucleophilic interaction with substrate. This result shows that the return of carbocationic species to substrate is kinetically unimportant or is unaffected by their trapping by N_3^-. There is no evidence for isomerization of terpenoid substrates during solvolyses in polar solvents of high water content.

The reaction of GPP is catalyzed by Mn^{2+} and the rate constants reach plateau values that correspond to reaction of a bismetallic complex.[7,16,17] The rate of Mn^{2+}-catalyzed hydrolysis is unaffected by added NaN_3 (Figure 1).

Reaction products

In the absence of N_3^-, the products are as found earlier. Geranyl diphosphate gives largely geraniol + linalool and little cyclization and elimination (Table 2). Cyclization is important in hydrolyses of NPP and NPPP (Tables 3 and 4). These results are consistent with the geometries of geranyl and neryl derivatives (*E* and *Z*, respectively) and the ability of carbocations with a *Z*-conformation to give either acyclic products by

Table 1. Overall first-order rate constants of substrate hydrolysis[a]

Substrate	$10^7 k_\psi (s^{-1})$
GPP	2·9;[b] 9·0; 35[c]
NPP	12
NPPP	90
TPP	5·0
LPP[d]	1200

[a] At 40·0 °C, pH 7, 0·1 M TES, unless specified.

[b] pH 8, 0·1 M Tris.

[c] pH 6, 0·1 M succinate.

[d] At 30·0 °C, Ref. 7.

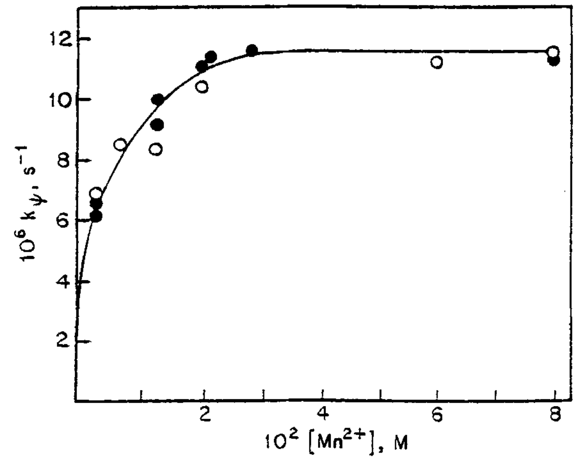


Figure 1. Effect of Mn^{2+} on the reaction of GPP (●) without and (○) with 0·1 M NaN_3. Conditions as specified in Table 1

Table 2. Effect of azide ion on the products (mol%) of overall reaction of GPP[a]

$[NaN_3]$ (M)	LOH	GOH	α-TOH	RN_3^b	LOH/GOH	k_N/k_w
—	74[c]	23[c]	3		3·2	
0·08	61	17	1·5	21	3·7	49
0·5	54	16	1	29	3·4	46
1·0	50	9		51	5·6	48
1·3	36	4		60	9·0	64
1·5	27	2·5		70·5	10·8	88
2·0	24	1·5		74·5	15	81

[a] In water, pH 7, 0·1 M TES at 40 °C.
[b] Denotes mixture of allylic azides.
[c] These values were given incorrectly (reversed) in Ref. 17.

attack on an allylic cation or cyclic products by interaction of the 6,7-double bond with an allylic cation.[1-7,20] Neryl di- and triphosphate give similar products, including alkenes, but in different proportions (Tables 3 and 4). There was extensive elimination from TPP (Table 5). Hydrolysis of LPP at pH 7 gives LOH + TOH in almost equal amounts and little GOH and NOH and *ca* 21% of alkenes, which are largely acyclic.[7] Azide ion trapping was not examined.

The value of LOH/GOH = 3.2 for hydrolysis of GPP at pH 7 is lower than those for the acid hydrolysis of GPP or hydrolyses of the chloride or acetate in aqueous acetone of high water content,[1,2,4] probably owing to the difference in charge of the leaving groups.

Azide ion trapping

Azide ion traps carbocationic intermediates from all the substrates. Allylic acyclic azides rapidly equilibrate[19,21] and we could not distinguish between them, but α-terpinyl azide is stable and we could distinguish between it and the mixture of allylic azides by gas–liquid chromatography (Experimental).

If water and N_3^- trap a common carbocationic intermediate, the relative second-order rate constants, k_N and k_W, are given by[12-14]

$$\frac{k_N}{k_W}=\frac{55\cdot5\,[RN_3]}{[ROH]\,[N_3^-]} \qquad (1)$$

We explicitly include the molarity of water in equation (1), so that k_N/k_W is dimensionless, although k_W can be written as a first-order rate constant and the dimensions of k_N/k_W are then l mol^{-1}.

For the reaction of GPP, but not the other substrates, the values of k_N/k_W increase with increasing $[NaN_3]$, which suggests that ROH and RN_3 are not derived from a common intermediate (Table 2). For

Table 3. Effect of azide ion on the products (mol%) of overall reaction of NPP[a]

$[NaN_3]$ (M)	α-TOH	LOH	NOH	Alkene	α-TN_3	RN_3	k_N/k_w
—	71	16	5	7[b]			
0·25	57	21	6	7	2	7	24
0·5	56	16	5	7	4	12	23
1.25	54	15		5	5	21	17

[a] Conditions as in Table 2; values with no NaN_3 are from Ref. 17.
[b] Limonene/terpinolene = 5:2.

Table 4. Effect of azide ion on the products (mol%) of overall reaction of NPPP[a]

$[NaN_3]$ (M)	α-TOH	LOH	NOH	Alkene	α-TN_3	RN_3	k_N/k_w
—	63	24	6	7			
0·84	45	16		3	8	28	36

[a] Conditions as in Table 2.

Table 5. Effect of azide ion on the products (mol%) of overall reaction of α-TPP[a]

$[NaN_3]$ (M)	α-TOH	α-TN_3	Limonene	Terpinolene	k_N/k_w[b]
—	37		41	22	
	39		41	20	
1·1	26	12	54	9	23
	28	11	53	8	20
1.7	24	16	52	8	20

[a] Conditions as in Table 2.
[b] Based on TN_3/TOH.

Table 6. Reaction of GPP in the presence of Mn^{2+}[a]

$[Mn^{2+}]$ (M)	LOH	GOH	RN_3	LOH/GOH	k_N/k_w
0·003	61	18	21	3·4	150
0·007	69	16	16	4·3	110
0·01	61	21	18	2·9	120
0·02	66	15	19	4·4	130

[a] At 40 °C, pH 7, 0·1 M TES and 0·1 M NaN_3. Products in mol%.

reactions of NPP and TPP there are alkene products and we do not include them in the calculation, and for both compounds $k_N/k_W \approx 20$ for nucleophilic attack of N_3^- and H_2O (Tables 3–5). Values of k_N/k_W for TPP will be lower by factors of 2–3 if we include alkene formation in the calculation. These values of k_N/k_W are lower than those for hydrolyses of a variety of alkyl and allyl halides in 80% aqueous acetone,[12–14,19] in part owing to differences in water content and viscosity of the two media, because trapping of short-lived carbocations is diffusion controlled.[13,14]

The dependence of k_N/k_W on $[NaN_3]$ for reactions of GPP (Table 2) is not due to a salt effect because added $LiClO_4$ does not markedly affect k_N/k_W (see Experimental) and for NPP it does not depend on $[NaN_3]$. Hydrolysis of GPP is catalyzed by Mn^{2+}, which also increases k_N/k_W. These results are discussed later.

There should be significant differences between anionic and non-ionic substrates regarding relative rates of trapping by H_2O and N_3^-, because there will be strong coulombic repulsions between N_3^- and the anionic diphosphates, especially with high $[NaN_3]$. For example, in 1 M electrolyte the average interionic distance is *ca* 9.4 Å, and the coulombic energy is not small relative to thermal energy, even in water.[22] Coulombic interactions will cause N_3^- to be, on average, as distant as possible from the diphosphate leaving group. Movement of N_3^- toward carbocationic centers will therefore probably not follow a random-walk path, but will be influenced by coulombic forces.

In addition, a non-ionic substrate has a monoanionic leaving group, but our substrates react largely as dianions at pH 7 and a trianionic leaving group will affect nucleophilic attack upon a forming carbocation before the partners have fully separated.

Mechanism of reaction of azide ion

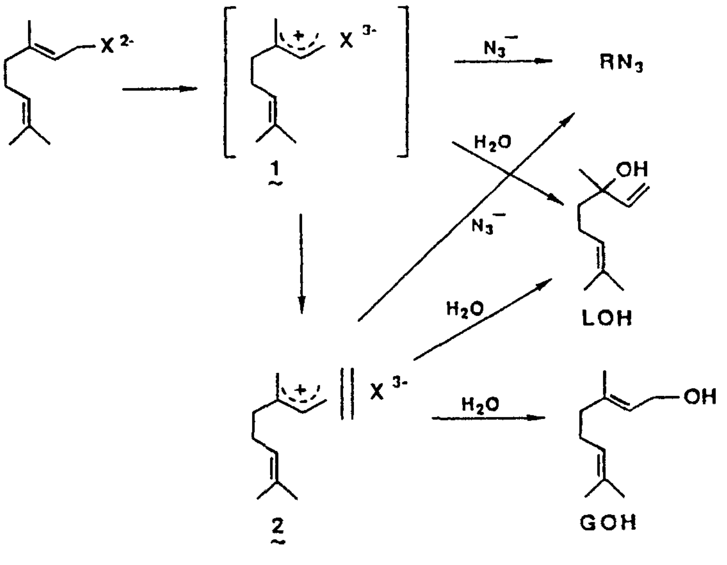
There is a marked dependence of k_N/k_W on $[NaN_3]$ for reaction of GPP and unexpectedly addition of NaN_3 markedly changes the product ratios for the formation of isomeric alcohols and, with TPP, of alkenes. In particular, in the reaction of GPP addition of N_3^- not only generates allyl azides, but also sharply decreases the formation of the primary alcohol, GOH, and has a much smaller effect on the formation of the tertiary alcohol, LOH (Table 2). These results cannot be explained on the assumption that all the products of reaction of a given substrate are derived from the same carbocationic intermediate (Tables 2–5). We therefore postulate that carbocationic species only partially interconvert and that N_3^- affects interconversion and we consider possible explanations of these effects. Carbocationic intermediates can differ in several ways. They can be free, or ion paired, and both tight ion pairs within a solvent cage and solvent-separated ion pairs are believed to exist.[12–14,19,23] Carbocations can differ conformationally, depending on rotations about single bonds and the formation of α-terpinyl products involves cisoid carbocations.[1–7] Geranyl substrates give largely acyclic products because rotation of allylic carbocations is relatively slow.[24]

Free and ion-paired carbocations often give different solvolysis products,[12–14,19,23] but ion pairs are typically formed in low-polarity media and not in as good an ionizing solvent as water. However, the leaving diphosphate trianion should interact coulombically with a carbocation, even in water,[22] so ionization probably generates ion pairs that may react with nucleophiles or bases, or dissociate to free carbocations. Any of these intermediates may react with H_2O and N_3^- and their relative reactivities will probably be different toward ion pairs and free carbocations. In addition, ion pairs may change conformations before they dissociate or react.

Distinctions are often drawn between ion pairs within a solvent cage and solvent-separated ion pairs. Sneen and co-workers[19] suggested that the leaving group in an intimate ion pair is close to the α-carbon, and we use this concept in discussing our data. Therefore, in an intimate ion pair formed from GPP the anion will be close to the primary center even though positive charge is delocalized on to the tertiary center.

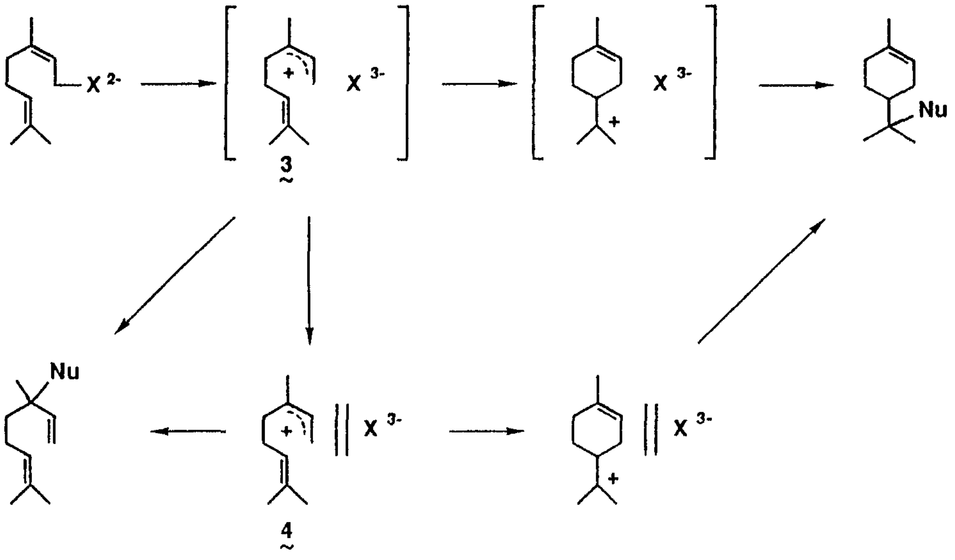
The key feature in the hydrolysis of GPP is the marked suppression of formation of the primary alcohol, GOH, by N_3^- (Table 2), showing that LOH and GOH are derived from different species. We suggest that a first-formed species that gives LOH can be trapped before it forms a second species that gives GOH. A possible reaction path is shown in Scheme 2. Ionization generates an ion pair (**1**), probably in a solvent cage, that can be attacked at the tertiary center by solvent water or N_3^- to give LOH and LN_3, respectively, although the latter readily isomerizes to an equilibrium mixture of allylic azides (RN_3). Attack at the primary center by an external reagent is hindered by the leaving diphosphate trianion, in part because of its high negative charge. As the ion pair dissociates, water that separates the ions (**2**) can attack the primary center giving GOH. Such a water molecule should be activated nucleophilically by hydrogen bonding to the basic diphosphate trianion, and its lone-pair electrons will be directed towards the carbocation. Further dissociation of **2** generates a free carbocation with its charge largely on the tertiary center, and it could rotate to a cisoid conformation and cyclize to give TOH in addition to forming acyclic linalyl products. Cyclization is a minor reaction,[1-4] and is suppressed by N_3^-. On this model attack of N_3^- on the first-formed species (**1**) (Scheme 2) reduces the extent of its dissociation to form other carbocationic species (**2**) that react with water to give GOH. In this and other schemes RN_3 denotes a mixture of equilibrating allylic azides, [ ] ion pairs within a solvent cage and || pairs separated by solvent molecule(s).

The situation is different for hydrolysis of NPP (Scheme 3), where trapping by N_3^- is never a dominant reaction and does not have a dramatic effect on the reaction products (Table 3). The 6,7-double bond can interact at the reaction center at various stages of the overall reaction to give TOH and TN_3. We assume that ionization generates a pair within a solvent cage (**3**). This species may be trapped by solvent water at the tertiary allylic center to give LOH or by N_3^- to give allylic



$X^{2-} \equiv P_2O_7^{2-}$

Scheme 2



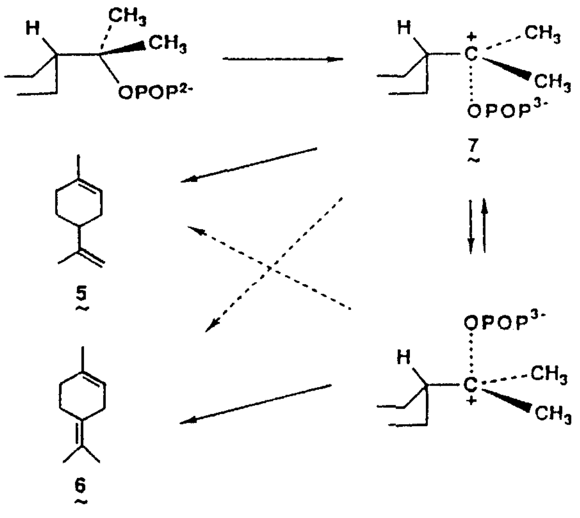
$X^{2-} \equiv P_2O_7H^{2-}$; Nu $\equiv$ N_3, OH

Scheme 3

azides (RN_3), but if it has a cisoid conformation interaction with the 6,7-double bond generates a species that gives TOH or TN_3. If the ions break through the cage to give **4**, attack on tertiary centers can give terpinyl products after cyclization or LOH plus RN_3. Nerol and alkenes are minor products (Table 3) and we do not show them in Scheme 3, but nerol is probably formed from a solvent-separated pair (**4**).

In this system π-participation, which requires a cisoid conformation, competes with attack by external nucleophiles. The effect of N_3^- on product composition is therefore less marked than in reactions of GPP (Scheme 2 and Table 2). We noted earlier that the trianionic leaving group could hinder attack on the primary center of an intimate ion pair by external nucleophiles, but it should have less effect on interaction with the 6,7-double bond. The behavior of NPPP is qualitatively similar to that of NPP (Tables 3 and 4) and the products can be explained in terms of reactions similar to those shown in Scheme 3.

α-Terpinyl diphoshate differs from the other substrates in that reaction gives only cyclic products, and there is extensive elimination. Postulated reactions are shown in Scheme 4. The cyclohexene residue hinders nucleophilic substitution. Elimination gives limonene (**5**) and terpinolene (**6**) in the approximate ratio of 2:1 in the absence of N_3^- (Table 5). Statistically the ratio should be 6:1, but the formation of terpinolene, the most alkylated alkene, fits the Saytzeff rule.[25] However, the formation of limonene is favored by N_3^- and the limonene/terpinolene ratio then becomes close to 6:1. The ratio of substitution to elimination, i.e. TOH + TN_3 to total alkene, is only slightly changed by NaN_3 (Table 5). The Saytzeff rule is typically obeyed in



Scheme 4

*E*1 reactions that involve fully formed carbocations.[25] Bentley and Carter[26] suggested that nucleophilic participation is kinetically important in solvolyses of *tert*-butyl chloride in nucelphilic solvents, and on this view nucleophiles could participate in reactions of α-terpinyl compounds, although not necessarily during the formation of the transition state. Azide ion could interact nucleophilically with a forming carbocationic center and also abstract a proton. If abstraction is random limonene (**5**) should be formed in large excess over terpinolene (**6**). Intervention of N_3^- shortens the lifetime of the carbocationic intermediates so they have less time in which to become 'free' of the leaving group so that the Saytzeff rule does not apply.

Another possibility is that the basic trianionic leaving group helps to abstract the proton. The initial conformation of the reaction center of TPP is probably that shown in Scheme 4. The forming carbocation (**7**) may rearrange conformationally so that the leaving trianion can abstract the proton in a *syn*-elimination, but if addition of N_3^- shortens the lifetime of the carbocationic species a proton will be lost statistically, which favors formation of limonene (**5**). It appears, therefore, that substitution and elimination products of TPP are derived from carbocationic species that differ, at least conformationally.

Ratios of TOH to TN_3 are very different for reactions of TPP, NPP and NPPP (Tables 3–5). Therefore, cyclizations of neryl, and also linalyl,[7] derivatives do not involve carbocationic species identical with those formed in reactions of TPP.

We discuss product formation from carbocationic species on the assumption that the counter ion is $P_2O_7H^{3-}$. At pH 7 the reaction largely involves dianionic substrate and the lifetimes of the intermediates in water are probably too short for diffusion-controlled protonation, or deprotonation,[27] involving H_3O^+, or OH^-, to change the charge on the leaving group.

Conformational effects

The discussion thus far has not explicitly considered conformations of acyclic substrates or carbocationic intermediates, although the formation of cyclic products requires their precursors to adopt cisoid conformations that have *gauche* interactions. Astin and Whiting[3] pointed out that *syn*-butane interactions, which could arise in cyclization, are energetically costly, but two additional factors have to be considered. First, cyclization does not require strict eclipsing,[20] and second, in a structured solvent such as water, unfavorable alkane–water interactions in an extended structure will decrease as the alkane chain coils. These hydrophobic interactions[28] should offset unfavorable eclipsing strains. Solvophobic interactions should be unimportant in acetic acid, the solvent used by Astin and Whiting.[3]

Added sodium azide should not affect the conformations of the substrates, but trapping of carbocations or ion pairs by N_3^- shortens their average lifetimes and therefore could inhibit conformational changes in these intermediates. Conformational changes should be relatively unimportant in reactions of GPP, which generate largely acyclic products.[1–6]

The situation is different for reactions of linalyl and neryl derivatives. Solvolyses of chiral linalyl substrates give optically active α-terpinyl products,[1,29] and acid-catalyzed oxygen exchange of linalool is faster than its racemizaton.[20] Therefore, π-participation by the 6,7-double bond is controlling the conformation and configuration of the carbocationic intermediate(s) in these reactions.

There is also extensive π-interaction in solvolyses of neryl substrates to give cyclic products and it will inhibit conformational equilibrium by rotation of single bonds in carbocationic intermediates. These results do not require π-participation in the rate-limiting step of ionization of linalyl and neryl substrates, although it has been postulated in some conditions.[1,18]

We did not obtain large amounts of azide products in the hydrolysis of NPP, in part because interaction of the 6,7-double bond with the forming carbocationic center generates TOH rather than TN_3 and, in addition, π-participation competes with nucleophilic attack at the allylic centers (Table 3). The isopropylidene residue of a neryl substrate is sheathed in a cage of water molecules which will not be fully hydrogen bonded and they should be more reactive than bulk water, and will react rapidly with a forming tertiary cationic center. Thus, H_2O and N_3^- probably have different relative reactivities adjacent to, and distant from, the initial reaction center.

Rate increases due to neighboring-group participation are largest in apolar solvents that do not effectively solvate forming ionic centers and in the absence of strongly electron-donating substituents at the reaction center.[5,12,30,31] Participation has entropically unfavorable conformational requirements. Water effectively solvates trianionic leaving groups and allylic delocalization stabilizes forming carbocations, so the 6,7-double bond may participate after ionizaton of neryl and linalyl diphosphates. However, it has a significant role in product formaton, so the situation is different from that for hydrolysis of GPP where there is little interaction of the 6,7-double bond and N_3^- markedly changes the relative rates of formation of the acyclic alcohols LOH and GOH. Although large amounts of LOH are formed in this reaction they do not come from a tertiary 'linalyl' cation that has time to adopt a cisoid conformation and cyclize.

Our results indicate that products are not derived from a common, free, allylic carbocation, but rather from pairs either within a solvent cage or separated by water or, in limiting situations, from free carbocations.

There will be strong coulombic interactions between partners within a solvent cage, but these species will not be true intermediates if their dissociation, and escape from the cage, does not involve a free energy barrier. In the same way interaction of the 6,7-double bond may occur either during ionization or in an ion pair within a solvent cage or subsequent to escape from the cage. However, π-participation does not significantly increase the rates of overall reaction, based on comparison of the reactivities of geranyl and neryl compounds, possibly because it is offset by loss of rotational entropy in a cisoid conformation.

Carbocation lifetimes

If water and N_3^- attack a common carbocationic intermediate, the product composition gives the relative rate constants of substitution by N_3^- and H_2O and the spontaneous formation of alkenes by deprotonation. The absolute rate constants can then be calculated from the diffusion-controlled rate constant for reaction of N_3^-.[13,14] We cannot use this straightforward approach for reactions in which products are derived from different carbocationic species which may not even be true intermediates, i.e. be in energy minima with respect to all degrees of freedom. To this extent our values of k_N/k_W (Tables 2–5) gives estimates of k_w which are only qualitative. This situation applies even to reaction of TPP (Table 5), because the composition of alkenes depends on N_3^-, suggesting that H_2O and N_3^- are attacking carbocationic species that differ conformationally or in the extent of ionic dissociation.

The ratio of LOH to GOH in hydrolyses of geranyl substrates is sensitive to the charge on the leaving group even in highly aqueous media, as shown by comparison of the value of LOH/GOH (Table 2) with other data. For hydrolyses of GPP in dilute aqueous acid, LOH/GOH is in the range 5–6[1,2a] and is *ca* 8 for hydrolysis of geranyl chloride in 95% water–acetone and decreases modestly with decrease in the water content of the solvent.[4] Ionization of non-ionic substrates generates a pair of univalent ions and their coulombic interactions will be weaker than in reactions of dianionic phosphates that involve departure of a trianion. Thus, in reactions of non-ionic substrates in polar solvents, H_2O and N_3^- compete for carbocations that are relatively free of the leaving group. Many descriptions of S_N1 reactions involve ion pairs[12,19,23] with the implication that they are in free-energy minima. The products of hydrolyses of prenyl disphosphates seem to be derived from a range of species which differ in solvation and conformation and may not be fully relaxed before trapping. These questions were raised in early explanations of partial inversion of configuration in terms of shielding by the leaving group,[32] whereas attack on ion-paired intermediates was subsequently postulated.[33] These explanations become equivalent if the 'ion-pair' is trapped before it is fully relaxed, and this situation may apply to product formation in heterolyses of monterpenoid derivatives. If we are to consider 'ion pairs' and 'free' carbocations as discrete chemical intermediates and calculate absolute or relative rate constants of their trapping reactions, we must assume that relaxations of these species are not affecting the kinetics of trapping. This assumption may not always be justified.

The use of diffusion-controlled trapping by N_3^- as the clock for measuring rates of capture of carbocations by other reagents requires the competing reactions to involve a common intermediate.[13,14] This condition is not fulfilled in our reactions, and if there are strong coulombic interactions between the diphosphate leaving group and N_3^- movement of the latter may not follow a random walk. In that even, even if trapping by N_3^- is an encounter process its rate constant may not be that characteristic of a diffusion-controlled reaction between non-interacting species.

Substrate ionization requires a conformation that permits stabilization of the forming carbocation by electronic delocalization from adjacent groups. We show the substrates in cisoid conformations about the 4,5-single bond and, although this representation is conventionally used, there will be equilibria between conformers that interconvert by rotation about single bonds.[1-7] These conformational changes are part of the energy barrier to reaction. Formation of cyclic as compared with acyclic products, subsequent to the rate-limiting step, may require conformational changes in remote groups and the rates of these changes may be similar to those of ion-pair dissociation or encounter formation of products. The product changes that we observe are therefore sensitive to interactions of substrate and carbocationic species with their environment, because solvent relaxation is involved in all the steps that govern rates and products.

Effects of manganese ion

Metal dications catalyze hydrolyses of prenyl diphosphates by forming bismetallic complexes.[7,16,17] The first-order rate constants of hydrolysis of GPP increase monotonically to a constant value with increasing $[Mn^{2+}]$ (Fig. 1 and Ref. 17), and dilute NaN_3 (0·1 M) does not increase the rate. The carbocationic species formed in the Mn^{2+}-catalyzed reaction (Table 6) are trapped effectively by N_3^-, probably because the bismetallic complex of GPP has a positive charge which attracts N_3^-, and increases the probability of N_3^- being adjacent to the reaction center(s). In this system the probability of capture of carbocationic species by N_3^- should be higher than expected in terms of a random-walk process. However, Mn^{2+} does not significantly affect the value of LOH/GOH, although it affects the formation of minor products, including alkenes.[17]

EXPERIMENTAL

Materials. The substrates were prepared from tritiated alcohols by the standard phosphorylation procedure of Cramer as described earlier,[1,7,17] and mono- and diphosphates were separated by ion exchange as described. We also isolated neryl triphosphate (NPPP) by ion exchange. α-Terpinyl diphosphate (TPP) was prepared from tritium-labelled α-terpineol isolated from the hydrolysis of mixed [1-^{3}H]neryl phosphates. Substrates were characterized by thin-layer and gas–liquid chromatography (GLC) after enzymic hydrolysis.[7,17] A mixture of allylic monoterpenoid azides was prepared by reaction of NaN_3 with geranyl or neryl *p*-nitrobenzoate in dimethylformamide. The mixture appeared to contain linalyl, gernayl and neryl azides based on the ^{1}H NMR spectrum of the mixture at 300 and 500 MHz, but we could not separate them by GLC and they equilibrate readily.[21] The preparation and properties of this mixture will be described elsewhere. α-Terpinyl azide was prepared in low yield by reaction of the chloride with NaN_3 and was isolated by GLC. Its ^{1}H NMR spectrum is similar to that of α-TOH. It does not equilibrate with the other azides and is stable at room temperature.

Determination of rates and products. Reactions were followed, unless specified otherwise, at 40 °C in aqueous 0.1 M *N*-tris(hydroxyethyl)-2-aminoethanesulfonic acid (TES) buffer (pH 7) with 20–200 μM tritiated substrate, as described.[7,17] TES does not interact strongly with Mn^{2+} and we used it in earlier work.[17] We used 0·1 M succinate at pH 6·0 and 0·1 M Tris at pH 8·0. Samples were removed, cooled in ice and organic products were extracted into hexane. Tritium activities were determined by scintillation counting.[7,17] Reactions were followed for $< 10\%$. Salt effects of NaN_3 and $LiClO_4$ were $< 10\%$ for up to 1·5 M salt at pH 7 and the initial rates varied linearly within ±10% with substrate up to 200 μM. Added $LiClO_4$ did not affect the formation of azides from GPP.

Products were separated by GLC on a 10 ft × 0·25 in. i.d. 3% SE-30 on Chromosorb column and were identified by their retention times and co-injection. Alcohols were the dominant products in most reactions and alkenes were not always separated, but they had been identified in earlier work.[1–7,17] Amounts of products were determined by radioactive counting.[7,17] Retention times of most of the products has been determined, but those of the mixed allylic azides and of α-TN_3 were 2·4 and 2·74, respectively, relative to that of LOH.

Minor products are usually easily detected by GLC[1–7] but it is difficult to quantify them, especially if their retention times are similar to those of major products. Terpinyl compounds have longer retention times than their acyclic isomers so uncertainties in product composition are larger for ratios of acyclic alcohols.

Although 0·1 M NaN_3 does not increase rates of the Mn^{2+}-catalyzed reactions, there is a rate increase with 0·3 M NaN_3 and the rates depend on Mn^{2+}, probably because N_3^- is then affecting the equilibrium of GPP with Mn^{2+}. We did not examine the products under these conditions.

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