

# Quantum Chemical Analysis of the Mechanism of the Solvolysis of Polyenol Ethers. PM3 Calculations on Fecapentaene-12 and Related Compounds<sup>†</sup>

Han Zuilhof, Louis B. J. Vertegaal, Arne van der Gen, and Gerrit Lodder\*

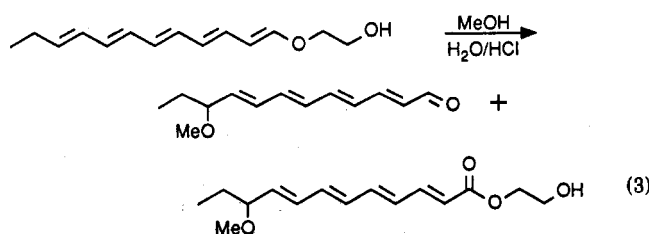
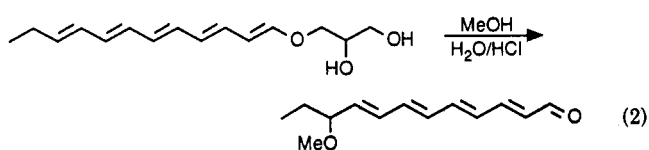
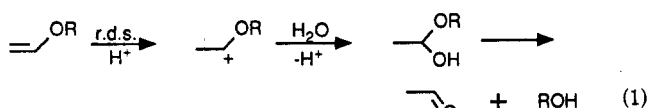
Gorlaeus Laboratories, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands

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The solvolysis pattern of polyenol ethers in protic solvents was investigated using semiempirical molecular orbital methods with the recently developed PM3 parametrization. The complex mechanisms recently proposed for these solvolyses are substantiated and refined by our calculations. Most polyenol ethers react preferably via electron transfer with dioxygen. The radicals formed in this way combine regioselectively to form a hydroperoxide zwitterion. Two limitations to this electron-transfer pathway can be formulated: (1) if the polyene chain is short (mono- and dienol compounds), the oxidation potential is too high for electron transfer to occur and enol ether hydrolysis via protonation of the conjugated chain is observed; (2) if the alkoxy chain is protonated at the C<sub>β</sub>-hydroxyl group, products resulting from a different ionic route are observed. This is the case for polyenol ethers derived from glycerol, such as fecapentaene-12, which have the possibility of intramolecular hydrogen bonding, but not for those derived from (substituted) glycol. The paper discusses in detail which of the reaction pathways are followed in each case.

## Introduction

Polyunsaturated enol ethers display an unusual chemical reactivity under acidic conditions. In contrast with the hydrolysis of vinyl ethers, which occurs exclusively via β-protonation<sup>1</sup> (eq 1), longer polyenes react via a manifold of reaction pathways. Recently two of us reported on the unusual chemical reactivity of fecapentaene-12 and related polyenol ethers of glycerol under acidic conditions.<sup>2</sup> Solvolysis of the glyceryl trienol ether (partially) and more highly conjugated enol ethers (exclusively) results in formation of unsaturated aldehydes, which are substituted by the nucleophilic solvent at the original ω-carbon atom of the polyene (eq 2). In the case of the analogous polyenol ethers of glycol, ester formation was observed in addition to aldehyde formation (eq 3).<sup>3,4</sup> This suggested that



<sup>†</sup> Dedicated to Dr. C. L. Habraken on the occasion of her 65th birthday.

(1) (a) Kresge, A. J.; Tobin, J. B. *J. Phys. Org. Chem.* 1991, 4, 587-591. (b) Keeffe, J. R.; Kresge, A. J. Kinetics and mechanisms of enolization and ketonization in *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, U.K., 1990; pp 399-480.

(2) (a) Vertegaal, L. B. J.; Van der Steeg, M.; Van der Gen, A. *Tetrahedron Lett.* 1989, 30, 5639-5642. (b) Vertegaal, L. B. J.; Van der Gen, A. *Tetrahedron* 1990, 46, 7301-7312.

different mechanisms are involved in the solvolysis of these closely related compounds.

For the formation of ω-substituted polyunsaturated aldehydes from the glyceryl polyenol ethers, the tentative mechanism shown in Scheme I was recently proposed.<sup>2a</sup> Protonation of the secondary alcohol is followed by reaction with the nucleophilic solvent at the ω-carbon of the polyene and loss of water and allyl alcohol. Experimental support for this proposal was found in the isolation of significant amounts of allyl alcohol from the reaction mixture.<sup>2a</sup>

In the proposed mechanism<sup>3,4</sup> for the formation of the ω-substituted polyunsaturated aldehydes as well as the corresponding esters from polyenol ethers of glycol, it is assumed that the electron-rich polyenol ether donates an electron to dioxygen, traces of which are always present in the reaction mixture (Scheme II). Radical combination of the radical cation of the enol ether and the dioxygen radical anion gives a zwitterion, which upon protonation on oxygen forms a resonance-stabilized cationic intermediate. Subsequently, the nucleophilic solvent reacts with this cation at the ω-carbon atom of the polyene chain, yielding a hydroperoxide.

Formation of ω-substituted esters can be envisaged as a sequence of protonation on the oxygen-bound oxygen of the peroxide, followed by loss of the elements of water.<sup>5</sup> Protonation of the peroxide intermediate at the carbon-bound oxygen atom results in the loss of hydrogen peroxide. Addition of water then yields a hemiacetal, which rapidly loses the alcohol moiety, to form an ω-substituted polyunsaturated aldehyde (Scheme II).

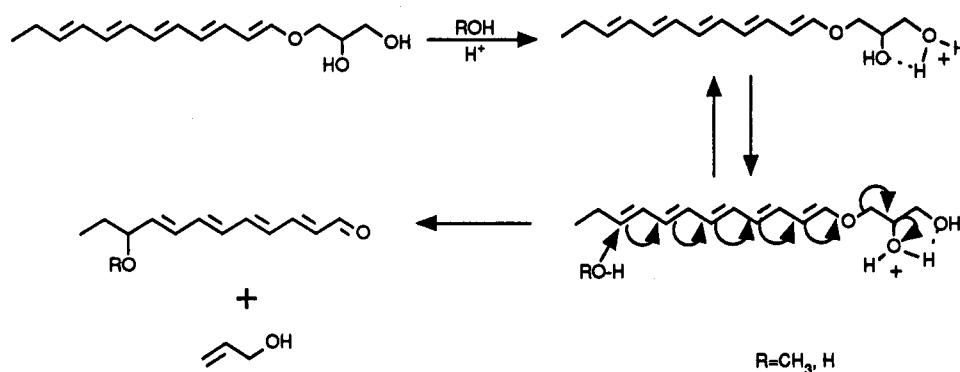
This tentative mechanism has been supported using the radical scavenger 2-*tert*-butyl-4-methylphenol.<sup>3,4</sup> The presence of 0.1 equiv of this scavenger completely suppressed the solvolysis of polyenol ethers of glycol. It was

(3) Vertegaal, L. B. J.; Nieuwenhuis, S. A. M.; De Zoete, M. C.; Van der Gen, A. Submitted for publication.

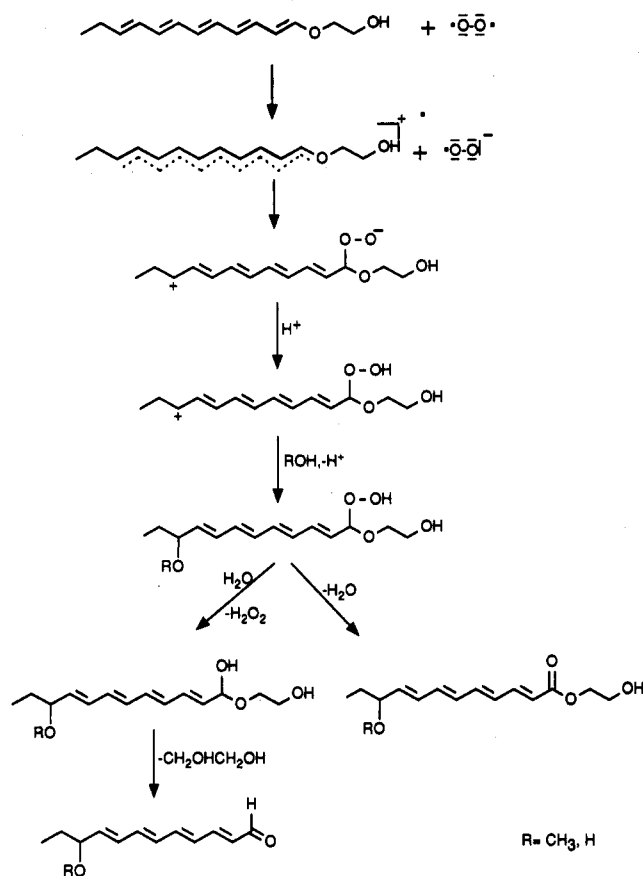
(4) Vertegaal, L. B. J. Ph.D. Thesis, Leiden University, 1991.

(5) The neutral peroxide intermediate may also decompose via a radical pathway involving the homolytic cleavage of the oxygen-oxygen bond. The formation of hydrogen peroxide and/or hydroxyl radicals from this peroxide intermediate may well be responsible for the strong mutagenic activity displayed by these polyenol ethers. Cf. Vertegaal, L. B. J.; Voogd, C. E.; Mohn, G. R.; Van der Gen, A. *Mutation Res.* 1992, 281, 93-98.

**Scheme I. Mechanism Proposed for the Ionic Solvolysis Reaction of Polyenol Ethers of Glycerol, Illustrated for Fecapentaene-12**



**Scheme II. Postulated Electron-Transfer Mechanism**



analogously shown that fecapentaene-12 also reacts partially (for about 20%) via a radical reaction mechanism.

To provide additional proof for the proposed reaction mechanisms, we have carried out semiempirical molecular orbital calculations on the enol ethers of glycerol (series 1-*N*), glycol (series 2-*N*), methylglycol (series 3-*N*), phenylglycol (series 4-*N*), and methanol (series 5-*N*), all of which have been studied experimentally.<sup>2-4</sup> The notation *M-N* is used to denote compounds with a glyceryl-, glyceryl-, or glyceryl-derived side chain *M* and a number of *N* conjugated double bonds in the polyene part (Figure 1). The enthalpy for all relevant reaction steps was calculated, as well as their dependence on the nature of the side chain *M* and the number of conjugated double bonds *N*, using the recently developed PM3 parametrization.<sup>7</sup> This approach clarifies the factors determining which of the several possible routes are chosen. Furthermore, a detailed

investigation into the rate-determining phenomena was undertaken.

**Methods of Calculation**

For each molecule a preoptimization was carried out using the program MODEL, which includes an MM2-derived optimization mode. Further reduction of the heat of formation was achieved with a restricted Hartree-Fock calculation (RHF) using the standard PM3 parameters<sup>7</sup> as implemented in the VAMP program (based on AMPAC and MOPAC) and run on a CONVEX C-120 computer. Either the Broyden-Fletcher-Goldfarb-Shanno algorithm (BFGS) or Bartels' nonlinear least squares method (NLLSQ) was used, both in combination with the keyword PRECISE.<sup>7</sup> The radical cation structures were calculated using the keyword OPEN, which results in open-shell RHF calculations.<sup>8</sup>

The reliability of the data obtained by this semiempirical approach was evaluated by analogous calculations on vinyl alcohol, its radical cation, and *C<sub>α</sub>*, *C<sub>β</sub>*, and hydroxyl protonated vinyl alcohol, for which experimental and/or ab initio data exist.<sup>9</sup> In all cases the PM3 results and the available data were in fair agreement.

**Results and Discussion**

The reactivity patterns of the species 1-1 to 5-5 are basically describable with two reaction pathways, starting with either (a) reaction with O<sub>2</sub>, leading to radical processes, or (b) reaction with solvated H<sup>+</sup>, leading to ionic solvolyses. Before discussing the details *within* paths a and b, it is important to understand which factors determine the choice between these pathways.

**Competition between Radical and Ionic Pathways.** The radical reaction is thought to start with an electron transfer between the enol ether and O<sub>2</sub>. For this process to be favorable, the one-electron oxidation potential of the enol ether should be sufficiently low. As shown in Table I the calculated heats of ionization of the simple enol ethers 5 decrease steadily as the number of double bonds increases. As expected, these heats of ionization are less than the calculated ionization potentials, since the former include relaxation of the radical cation to the

(6) (a) Stewart, J. J. P. *J. Comput. Chem.* 1989, 10, 209-220; (b) 221-245.

(7) See for a concise discussion of various optimization methods: Zerner, M. C. *Analytical Derivative Methods and Geometry Optimization in Modern Quantum Chemistry*; Szabo, A., Ostlund, N. S., Eds.; McGraw-Hill: New York, 1989; pp 437-458.

(8) (a) Hurley, A. C. *Introduction to the electron theory of small molecules*; Academic Press: New York, 1976; pp 242-253. (b) Dewar, M. J. S. *The molecular orbital theory of organic chemistry*; McGraw-Hill: New York, 1969; pp 250-277.

(9) Apeloig, Y. *Theoretical calculations in The chemistry of enols*; Rappoport, Z., Ed.; Wiley: Chichester, U.K., 1990; pp 1-74.

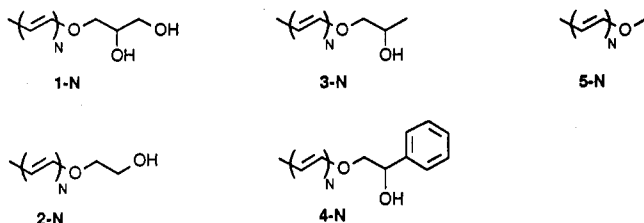


Figure 1. Notation used for the polyenol ethers studied.

Table I. Heats of Formation of the Simple Enol Ethers 5-1 to 5-5 and Their Radical Cations (in kcal/mol)

compd	$\Delta H_f$ (neutral)	$\Delta H_f$ (radical cation)	$\Delta H^\circ$ (ionization)	IP
5-1	-33.6	163.3	196.9	211.2
5-2	-19.8	164.1	183.9	193.2
5-3	-6.0	171.1	177.1	191.7
5-4	7.2	180.9	173.0	187.9
5-5	21.8	192.3	170.5	185.6

equilibrium geometry. The difference is constant at about 15 kcal/mol.

Experimentally it is indeed found that only polyenol ethers with three or more double bonds give significant yields of radical-derived products. Not all of them do, however, exhibit this type of reactivity exclusively. Poly-enol ethers with a glyceryl side chain also give significant amounts of products arising via an ionic reaction mechanism.<sup>3,4</sup> This is not caused by differences in the ionization potentials of these systems, as is borne out by calculations of this property for all five alkoxy chains with two different enol ether lengths (one and four double bonds). The ionization potential is almost independent of the side chain and dominated by the degree of unsaturation.<sup>10</sup> The deviating behavior of the glycerol series of polyenol ethers is therefore caused by another molecular property, namely, protonation of the secondary OH group. This process is favored by intramolecular hydrogen bonding. To show that this really causes the deviation, the driving forces (enthalpies) of the gas-phase addition of  $H^+$  to this hydroxyl group were calculated for the different side chains for enol ethers with four double bonds.<sup>11</sup> These are compounds which react via protonation of the OH groups rather than via protonation at carbon. Furthermore, the heat of  $H^+$  addition was calculated for the enol ethers carrying a glyceryl side chain and a varying number of conjugated double bonds to see how this affects the ease of protonation (Table II, column 3). Despite the approximate nature of this approach to the process in solution, the results are in qualitative agreement with the experimental data. That is to say: the enthalpy of protonation is significantly lower (less positive) in the case of the glyceryl ethers when hydrogen bonding is possible.

With the ethers derived from methylglycol and phenylglycol (series 3 and 4) the cation resulting from protonation of the secondary alcohol is better stabilized. This leads to significant lengthening and weakening of the C-O bond (of the protonated oxygen atom). For example, for the enol ether cation with a phenylglycol side

(10) The calculated ionization potential of the series 1-1 to 5-1 varied between 208.9 and 211.2 kcal/mol, while for the molecules with four double bonds (1-4 to 5-4) this property was calculated to be between 187.9 and 190.8 kcal/mol.

(11) It should be noted that the calculated values are off by -12.1 kcal/mol, the known deviation<sup>6b</sup> in the calculated heat of formation of  $H^+$ . Since this deviation is constant throughout the series this error does not influence the trends observable in Table II.

Table II. Heats of Protonation of the Secondary Hydroxyl Group of Several Enol Ethers (in kcal/mol) As Calculated by PM3-RHF Calculations with No Geometrical Restrictions (Column 3) and with a Fixed  $C_\beta$ -O Distance of 1.40 Å (Column 4)

compd	intramolecular H-bonding	$\Delta H^\circ$	
		(Column 3)	(Column 4)
1-2	no	191.4	195.4
1-2	yes	190.6	193.0
1-3	no	191.3	195.0
1-3	yes	190.6	192.9
1-4	no	193.0	195.7
1-4	yes	192.4	193.7
2-4		198.8	201.3
3-4		189.5	192.9
4-4		185.9	187.6

chain, the bond order of the C-O bond concerned is only 0.63, significantly lower than the C-O bond order (1.00) in the unprotonated species. Significant bond weakening, ultimately leading to dissociation, is in general not treated properly on the SCF level of MO calculations, and the energies obtained in this way are not very reliable.<sup>12</sup> Besides, in solution the dissociation is presumably not spontaneous but activated due to solvation of the protonated enol ether. Therefore, the heats of protonation of several molecules in which the C-O bond length (of the O atom carrying the two protons) was kept fixed at 1.40 Å were also calculated (Table II, column 4). Since these results are expected to give a better representation of the situation in solution, trends will be discussed on the basis of these latter calculations.

From the results in Table II two trends become clear. First, the heat of protonation of glycerol enol ethers is reduced by approximately 2 kcal/mol by the possibility of intramolecular hydrogen bonding. Second, the ease of protonation is strongly dependent on the substituent attached to C- $\beta$ . This is not surprising, since methyl, hydroxymethyl, and phenyl groups stabilize the (partial) positive charge on the adjacent carbon atom,<sup>13</sup> which is present before (complete) loss of water.

How do the results in Table II relate to the experimental findings? Due to the significantly higher heats of protonation of glyceryl enol ethers compared to those of glyceryl enol ethers, the ionic yields of the former will be substantially lower. This is caused by a large increase in the oxidation potential upon protonation—for the alcoholic oxygen-protonated form of e.g. 1-4, 70 kcal/mol—which prevents an electron-transfer reaction with triplet dioxygen.

A similar reduction in heats of protonation with respect to the glyceryl enol ethers occurs with the substituted glyceryl systems. The latter are even more easily protonated than enol ethers carrying a glyceryl side chain (Table II, entries 8 and 9). As pointed out earlier, a strongly reduced  $C_\beta$ -O

(12) Levine, I. N. *Quantum Chemistry*; Prentice-Hall: Englewood Cliffs, NJ, 1991; pp 414, 474-5.

(13) Various parameters are available from linear free energy relationships which support the resonance stabilizing nature of the hydroxymethyl, methyl, and phenyl groups (from: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* 1991, 91, 165). These data support the idea that the hydroxymethyl group stabilizes adjacent positive charge, and less than the methyl or phenyl group, in line with the slightly larger enthalpies for the hydroxymethyl substituent.

substituent	$\sigma_R$	$\sigma_R^+$	$R^+$	$\sigma_R^+$
CH <sub>2</sub> OH	-0.05	-0.04	-0.07	-0.06 (for CH <sub>2</sub> OCH <sub>3</sub> )
CH <sub>3</sub>	-0.13	-0.31	-0.32	-0.08
C <sub>6</sub> H <sub>5</sub> O	-0.08	-0.18	-0.30	-0.22

Table III. Heats of Protonation ( $\Delta H_p$ ) of the Methyl Polyenol Ether Series 5-N and the Glycerol Enol Ethers 1-4 and 1-5 for Protonation at the  $\beta$ - or  $\omega$ -Position As Calculated by PM3-RHF Calculations (in kcal/mol)

enol ether	$\Delta H_p(\beta\text{-protonation})$	$\Delta H_p(\omega\text{-protonation})$
5-1	176.6	176.6
5-2	174.2	167.2
5-3	174.6	161.0
5-4	174.2	157.0
5-5	173.9	154.3
1-4	167.5	153.7
1-5	167.3	151.6

bond order is calculated. This means that these molecules can lose water more easily than the glycerol systems. But protonation and dehydration would lead to a relatively unreactive, stabilized carbocation, in line with known parameters for resonance stabilization.<sup>13</sup> The experimental fact that no styrene is formed in the case of the enol ethers carrying a phenylglycyl side chain<sup>3,4</sup> indicates that the formation of the carbocation is reversible under the reaction conditions.

In summary, enol ethers discussed in this paper react via an electron-transfer mechanism, except when this is hampered by a high oxidation potential. In that case ionic reactions compete. Such high oxidation potentials can be caused either by the absence of a sufficient number of conjugated double bonds in the enol ether or by protonation of the  $C_{\beta}$ -hydroxyl group in the alkoxy chain.

**Protonation of Polyenol Ethers.** One of the really surprising aspects of the hydrolysis of the glycerol polyenol ethers is the fact that hydrolysis does not occur via protonation at the  $\beta$ - or  $\omega$ -carbon, which is the first step in vinyl ether hydrolysis, but via protonation of the  $C_{\beta}$ -hydroxyl group. The normal mechanism for vinyl ether hydrolysis is an oxocarbenium ion-producing reaction which occurs by rate-determining proton transfer according to eq 1.<sup>1a</sup> With longer conjugated chains, electrophilic attack at the  $\omega$ -position is normally favored, except when the  $\pi$ -system is not planar.<sup>14</sup>

To understand why for planar enol ethers like the molecules under study here no products resulting from protonation at the  $\omega$ -carbon of the  $\pi$ -system are formed, the stability of the cations resulting from protonation at the  $\beta$ - and  $\omega$ -positions of the methyl polyenol ether series 5-N and the glycerol enol ethers 1-4 and 1-5 was compared with that of their nonprotonated precursors (Table III).

The data in Table III show that the heats of  $\beta$ -protonation remain approximately constant with varying length of the conjugated chain, while the heats of  $\omega$ -protonation decrease strongly with an increase in length. This is in line with qualitative expectations based on mesomeric structures. Protonation at the  $\beta$ -carbon disrupts delocalization of the positive charge, and this effect is in a first-order approximation independent of the length of the rest of the conjugated chain. This disruption does not occur with  $\omega$ -protonation, so that the positive charge is increasingly delocalized with longer conjugated chains, leading to more stabilized cations and lower heats of protonation. The near-invariance of the heats of  $\beta$ -protonation is not dependent on the side chain used, which is understandable, since the alkoxy chain is connected to the conjugated chain via single bonds. The single C—O—C bonds do not behave as complete isolators though: the

glycerol enol ethers are about 5 kcal/mol more easily protonated than the methyl ones.

More surprisingly, in regard of the experimental data, is the result that gas-phase protonation at the  $\omega$ -carbon is more favorable than protonation at the alcoholic oxygen atom by at least 15 to 35 kcal/mol (see for comparison the data in Table II, which give a  $\Delta H_p$  for protonation of the secondary alcohol in 1-4 of more than 190 kcal/mol). Precisely for those cases in which the differences between the heats of protonation are the largest, no carbon-protonation product is found, while for those glycerol systems which show a smaller preference ( $N = 1, 2$ ) only products formed via carbon protonation are found in significant amounts (62 and 58%, respectively).<sup>3,4</sup>

One aspect of the explanation of this phenomenon might be that for the longer polyenol ethers electron transfer is so fast that it competes favorably with the ionic processes. The heat of protonation drops by 22 kcal/mol in going from the monoenol ether to the pentaenol ether, but the ionization potential drops by an even larger amount (26 kcal/mol; see Table I); that is, electron-transfer processes become relatively more important with increasing unsaturation. This is indeed found experimentally. Of all the enol ethers studied those with  $N = 1$  or 2 yield products resulting from ( $\beta$ -) protonation, while for the (modified) glycerol enol ethers with  $N > 2$ , almost only electron-transfer reactions are observed.<sup>2-4</sup>

The behavior of the glycerol series (1-N), which shows a preference for reaction starting with alcoholic oxygen-protonation for  $N > 2$ , cannot solely be explained on the basis of equilibrium data. Since species protonated at carbon have a much weaker interaction with the solvent via, e.g., hydrogen bonding than oxygen acids, an equilibrium solvation term would favor protonation on oxygen.<sup>15</sup> Even if one supposes the positive carbon atom to be completely unsolvated, and the protonated oxygen to be solvated by three strong hydrogen bonds of 5 kcal/mol each, there is still an appreciable preference for protonation at carbon. Because the actual difference in solvation between protonated oxygen and protonated carbon is likely to be less than supposed here, the thermodynamic preferential solvation of the resulting oxygen cation cannot completely explain the fact that only this type of protonation is experimentally observed. Therefore it must be assumed that the site of protonation is determined by kinetic factors as well.

Since protonation at the  $\omega$ -carbon involves a large change in resonance stabilization and solvation, this reaction will have a high intrinsic barrier relative to protonation of the alcohol.<sup>16</sup> This is especially the case for the more highly conjugated molecules. The internal reorganization energy will drop quickly with a decreasing number of conjugated double bonds in the polyenol ether—less bond length changes are taking place in the rate-determining step—and therefore the intrinsic rate for carbon protonation of small polyenol ethers is predicted to be much higher than for more highly conjugated ones. One thus expects products resulting from carbon protonation for, e.g., the glycerol enol ethers 1-1 and 1-2, in accordance with experimental data.<sup>2</sup>

(15) Pimentel, G. C.; McClellan, A. L. *The Hydrogen Bond*; W. H. Freeman and Company, San Francisco, 1960; pp 5, 197-201.

(16) (a) Bernasconi, C. F. *Pure Appl. Chem.* 1982, 54, 2335-2348. (b) Bernasconi, C. F. *Tetrahedron* 1985, 41, 3219-3234. (c) Bernasconi, C. F. *Acc. Chem. Res.* 1987, 20, 301-308; (d) 1992, 25, 9-15, and references in these papers.

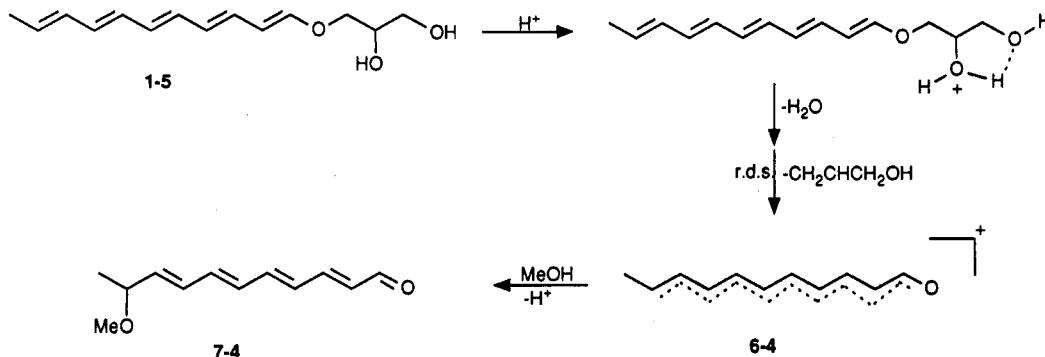
(14) Capon, B. Dienols in *The Chemistry of Enones*, Part 2; Patai, S., Rappaport, Z., Eds.; Wiley: Chichester, U.K., 1989; pp 1063-1087.

Table IV. Charges and Spin Densities on the Polyene Carbon Atoms in the Radical Cations of the Simple Enol Ethers 5-3 to 5-5<sup>a</sup>

enol ether	carbon										
	$\alpha$	$\beta$	$\gamma$	$\delta$	$\epsilon$	$\zeta$	$\eta$	$\vartheta$	$\iota$	$\kappa$	
5-3	0.212	-0.187	-0.013	0.033	-0.178	0.107					
	<i>0.165</i>	<i>0.128</i>	<i>0.144</i>	<i>0.209</i>	<i>0.060</i>	<i>0.182</i>					
5-4	0.205	-0.228	0.038	-0.056	-0.108	0.073	-0.201	0.077			
	<i>0.130</i>	<i>0.082</i>	<i>0.147</i>	<i>0.147</i>	<i>0.090</i>	<i>0.175</i>	<i>0.034</i>	<i>0.118</i>			
5-5	0.194	-0.249	0.065	-0.112	-0.056	0.007	-0.156	0.083	-0.209	0.048	
	<i>0.102</i>	<i>0.056</i>	<i>0.137</i>	<i>0.105</i>	<i>0.108</i>	<i>0.150</i>	<i>0.057</i>	<i>0.135</i>	<i>0.020</i>	<i>0.077</i>	

<sup>a</sup> Spin densities are italic.

## Scheme III. Mechanism for the Stepwise Formation of Product 7-4 from 1-5

Table V.  $\Delta H^\circ$  Values of the Overall Reaction from Protonated Enol Ether to Compounds 6-N and 7-N (in kcal/mol)

enol ether	$\Delta H^\circ(6-N)$	$\Delta H^\circ(7-N)$
1-2	99.4	-137.8
1-3	90.5	-136.6
1-4	87.4	-136.1

**Radical Reactions.** Once electron transfer from the enol ether to oxygen has occurred, the resulting radicals can combine in various ways, depending on which carbon atom the superoxide anion will attack. Experimentally, only products resulting from attack at the  $\alpha$ -carbon atom are found. To explain this phenomenon, charges and spin densities have been calculated for the radical cations of the simple enol ether 5-3 to 5-5 (Table IV).

The data in Table IV clearly show that the reaction selectivity is determined by the charge distribution in the radical cation and not by the spin density, which is highest at positions from which no products are observed. This can only be the case if the superoxide anion can move along the enol ether radical cation chain. The Coulomb attraction to the  $\alpha$ -carbon already influences its movements from a long distance, while the spin density factor can only manifest itself on close contact.

**Ionic Reactions.** Polyunsaturated glyceryl enol ethers mainly react via protonation of the secondary alcohol, followed by nucleophilic attack at the  $\omega$ -carbon of the polyene by the solvent.<sup>3,4</sup> This can either occur concerted as depicted in Scheme I, or stepwise as shown in Scheme III.

For the rate-determining step of the reaction three possibilities should be considered: (1) Nucleophilic attack by the solvent and loss of water and allyl alcohol from the enol ether take place without an intermediate energy minimum (Scheme I). (2) The protonated enol ether loses water and allyl alcohol in a rate-determining step and is subsequently attacked by the nucleophile. (3) The nucleophile-electrophile combination is rate-determining. Protonation of the alcohol is not expected to be rate-determining, since O-protonation is normally a very fast process.<sup>17</sup>

If the reaction is concerted, a correlation between the heats of formation of the protonated enol ethers and the resulting products 7-N is expected (assuming the Hammond postulate to be correct in this case). On the other

hand, if the reaction occurs stepwise, with rate-determining loss of water and allyl alcohol, a correlation between the heats of formation of the protonated enol ethers and the resulting cations 6-N should be found. This was investigated by calculating the heats of formation of the protonated enol ethers 1-2, 1-3, and 1-4, the cations (6-N) resulting from them after loss of water and allyl alcohol, and the end products (7-N) after attack at C- $\omega$  by the solvent (MeOH). From these data, the  $\Delta H^\circ$  values of the overall reaction from the protonated enol ether to compounds 6-N and 7-N were determined (Table V). Scheme III shows that cation 6-1 and product 7-1 result from 1-2, 6-2 and 7-2 from 1-3, etc.

The  $\Delta H^\circ$  data show that the driving force for product formation from the protonated enol ether is insensitive to the number of double bonds of the conjugated system. This contrasts with the marked dependence of the polyenol ether length of the driving force of water—and allyl alcohol—loss from these protonated species. Since the experimental data<sup>2b</sup> show a 15-fold difference in reaction rate between enol ether 1-2 and 1-3 and another factor of 2 between 1-3 and 1-4, the conclusion must be that loss of water and allyl alcohol is the rate-determining step in the formation of products 7-2 to 7-4. This is followed by a relatively fast nucleophile-electrophile combination.

It is not completely clear whether the loss of water and allyl alcohol proceeds in a concerted or in a stepwise fashion. The calculations indicate that water is lost easily: a geometrical restriction had to be used to prevent water from being lost spontaneously (Table II)! In the cation resulting after loss of water no trace of C-O bond breaking leading to loss of allyl alcohol is detectable, suggesting a barrier for this process. An argument against

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**Table VI. LUMO Energies (in kcal/mol) and Coefficients and Charge Distribution of the Cations 6-1 to 6-4**

compd	$E_{\text{LUMO}}$	LUMO coeff		charges	
		$\beta$ -C	$\omega$ -C	$\beta$ -C	$\omega$ -C
6-1	-178.7	0.632	0.714	0.160	0.337
6-2	-169.7	0.461	0.567	0.039	0.248
6-3	-158.8	0.350	0.464	-0.030	0.176
6-4	-155.2	0.270	0.374	-0.070	0.131

the stepwise loss of water is that no products from dehydration of the glycerol side chain were found.<sup>3</sup> From the 10-fold increase in rate of solvolysis (in THF:water [1:1]) going from 1-3 to 1-5, it follows that *if* water is lost stepwise before allyl alcohol, then this loss is not rate-determining, since the intermediate carbocations have very similar stabilities.

The calculated data presented above, in combination with the observed rates of reaction, suggest that the nucleophile-electrophile combination is not rate-determining. To understand why this is the case, the heats of formation, LUMO energies and coefficients, and the charge distribution of the cations 6-1 to 6-4 were calculated.

The results, presented in Table VI, show that both the LUMO coefficients and the charges decrease with increasing unsaturation. On top of this, the LUMO energy increases in going to more conjugated cations, thereby decreasing the energy to be gained on interaction of this orbital with the HOMO of the nucleophile. These results therefore clearly exclude the possibility that the nucleophile-electrophile combination is rate-determining. This confirms the notion that formation of the cations 6-*N* is the rate-determining step in the solvolysis of polyunsaturated enol ethers of glycerol.

Finally, the data in Table VI also explain why with polyunsaturated enol ethers reaction with the nucleophilic solvent occurs at the  $\omega$ -carbon atom of the conjugated chain. The LUMO coefficients and charges at the  $\omega$ -position are invariably more attractive for an attacking nucleophile than those at, e.g., the  $\beta$ -carbon. This preference increases upon extension of the conjugated chain, especially because of the strong decrease in charge at the  $\beta$ -carbon.

The mechanism described here for polyunsaturated enol ethers contrasts that followed by vinyl ethers, which react via rate-determining  $\beta$ -protonation (eq 1).<sup>1</sup> This shift in mechanism upon extension of the conjugated chain is effected by two factors. One is the increasing driving force

for reaction following protonation of the secondary alcohol moiety with longer conjugated chains, as discussed above. The other is probably the decreasing ease of  $\beta$ -protonation, due to a decrease in the negative charge and size of the HOMO coefficient at the  $\beta$ -carbon with extending conjugation. To confirm this, the charges and HOMO coefficients have been calculated for all glyceryl enol ethers under study. The charge at the  $\beta$ -carbon indeed drops significantly in going from 1-1 (charge = -0.28) to 1-2 (charge = -0.18),<sup>18</sup> but then stays remarkably constant, within one-hundredth of a unit charge, with further lengthening of the conjugated chain. The HOMO coefficient decreases monotonically upon chain lengthening (from 0.615 to 0.475, 0.378, 0.317, and 0.275, going from 1-1 to 1-5). Thus,  $\beta$ -protonation becomes increasingly difficult with lengthening of the chain. This diminishing ease of  $\beta$ -protonation in combination with the increasing driving force for reaction following protonation of the secondary alcohol explains why with longer conjugated chains ( $N \geq 3$ ) the ionic solvolysis mechanism depicted in Scheme III takes over from the one followed by vinyl ethers (eq 1).

### Conclusion

The solvolysis of polyenol ethers of glycerol, glycol, and substituted glycols in acidic media can be thought of as a competition between ionic and electron-transfer reaction pathways. For mono- and dienol ethers, only the ionic pathway is followed, since the oxidation potential is too high to result in electron donation to ground-state oxygen. For more highly conjugated polyenol ethers, this electron transfer occurs for the neutral species but is not feasible if the side chain is protonated on the  $\beta'$ -hydroxy group. This is the case for enol ethers of glycerol, where the protonated species is strongly stabilized by intramolecular H-bonding. Because such a type of interaction is not possible in protonated (substituted) glyceryl polyenol ethers, reaction via electron transfer is now the exclusive route.

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(18) This provides an explanation for the dramatic decrease in reaction rate going from 1-1 to 1-2,<sup>2b</sup> both compounds reacting via protonation at the  $\beta$ -carbon atom.