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REMARKABLE ELECTROPHILIC PROPERTIES OF THE PENTAENOL ETHER SYSTEM OF FECAPENTAENE-12.[1]

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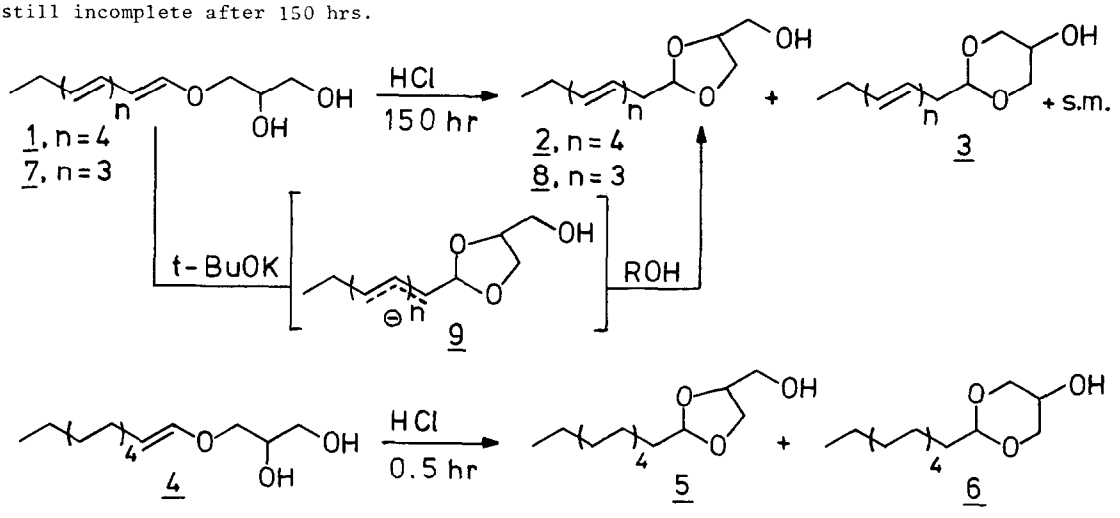
Summary: Polyenol ethers display an unexpected reactivity towards nucleophiles under basic conditions. This reactivity increases with increasing number of double bonds, as does the mutagenic activity of these compounds. The first addition product of an external nucleophile to fecapentaene-12 is described.

Fecapentaene-12 (1) is a major representative of a group of structurally closely related strongly mutagenic compounds, isolated from human feces[2,3]. Natural fecapentaene-12 has the *S*-configuration and presumably occurs as a mixture of *E*- and *Z*-isomers around the enol ether double bond. The mechanism by which 1 interacts with critical bio(macro)molecules is unknown at the present time. It has been suggested that the fecapentaenes need prior activation by an electrophile, *e.g.* a proton, to become reactive towards nucleophilic cell constituents[4,5]. Syntheses for 1 have recently been described by us[6,7] and by others[8,9,10], thus making this unique polyunsaturated glyceryl enol ether available for further study. We have investigated the reactivity of 1 and other, less unsaturated, glyceryl enol ethers towards nucleophiles, both under acidic and basic conditions, and compared the results with the mutagenicity data[11].

Synthetic 1[6], when treated with 1 equiv of dry hydrochloric acid in DMSO solution at room temperature, reacted only sluggishly. Conversion into the tetraene acetals 2 and 3[12,13] was still incomplete after 150 hrs.

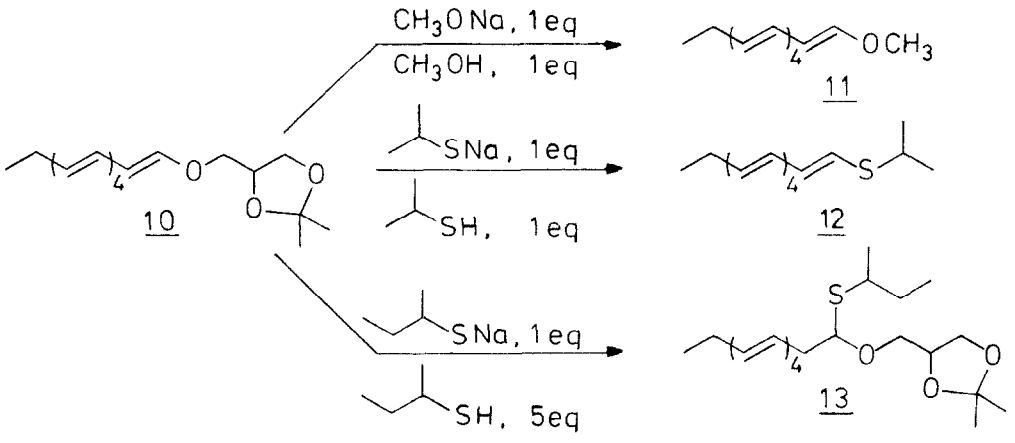


Under the same conditions, enol ether 4, possessing no additional unsaturation, was completely converted into the cyclic acetals 5 and 6[12,13] within 0.5 hr. It thus appears that the rate of acid-catalyzed nucleophilic addition to enol ethers actually decreases with increasing unsaturation and therefore a mechanism as proposed[4,5] cannot properly explain the mutagenic properties displayed by the natural fecapentaenes.

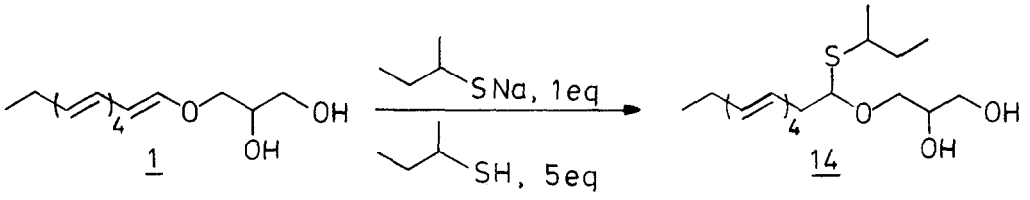
We want to report here the remarkable reactivity displayed by polyenol ethers under basic conditions. In its simplest form, this reactivity is exemplified by the rapid ring closure that 1 undergoes upon treatment with 0.2 equiv of potassium *t*-butoxide in DMSO solution. The reaction is complete within 5 min at room temperature and affords the dioxolane 2, as a 1 to 8 mixture of *cis*- and *trans*-isomers, as the sole product (isolated yield 76%). This propensity to undergo base-catalyzed intramolecular nucleophilic addition rapidly decreases with decreasing unsaturation. Ringclosure of the tetraenol ether 7 to the corresponding dioxolane 8 took 3 hrs and less unsaturated enol ethers were not reactive at all under these conditions.

Nucleophilic addition of alcohols to unactivated double bonds is a rare phenomenon and has, to the best of our knowledge, only been observed in strained systems, in which the hydroxyl group is forced in close proximity to the double bond[14,15]. From our results it is clear that in polyenol ethers this kind of reaction is greatly facilitated. The experiments carried out so far, support the intermediacy of a delocalized carbanionic species as depicted in 9, which becomes protonated at C2 to give the dioxolane.

We then turned our attention to the addition of external nucleophiles. In order to avoid intramolecular ring closure, initial reactions were carried out with the acetonide 10. Upon treatment with sodium methoxide (1 equiv) and methanol (1 equiv) in DMSO at room temperature, the starting material had completely reacted in 3 hrs. From the reaction mixture, the methyl pentaenol ether 11 was isolated by flash column chromatography, albeit in modest yield (54%)[13], thus showing that addition to the enol ether double bond had indeed occurred.



Reaction with a sulfur nucleophile (1 equiv of sodium 2-propanethiolate and 1 equiv of 2-propanethiol) in DMSO similarly afforded the thio enol ether 12[13]. In the expectation that, by increasing the amount of thiol, protonation of an intermediate carbanion would be promoted and elimination of the glyceryl-acetonide would be suppressed, we reacted 10 with 1 equiv of sodium 2-butanethiolate and 5 equiv of 2-butanethiol in DMSO. The reaction was complete after 16 hrs and afforded, upon flash column chromatography, the pure adduct 13 in 47% yield[13]. Because, under these conditions, deprotonation of aliphatic hydroxyl groups will occur only to a very limited extent (δ $pK_a \sim 5$), the unprotected pentaenol ether 1 was subjected to the same reaction conditions. The reaction was discontinued after 20 hrs at room temperature. After separation by flash column chromatography, there was obtained, apart from unconverted starting material and a small amount of dioxolane 2, a 32% yield of the monothioacetal 14, the first addition product of an external nucleophile to fecapentaene-12 to be described[13].



Thus it appears that polyunsaturated compounds such as the pentaenol ether 1 possess an unpredicted reactivity towards nucleophiles under basic conditions, a reactivity that may well be related to the strong mutagenic properties displayed by these compounds.

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11. The pentaenol ether moiety is essential for the direct mutagenic activity that is observed in bacterial test systems. Tetraenol ethers only display mutagenic activity at much higher concentrations and less unsaturated enol ethers are not active at all (S.V. Govindan, D.G.I. Kingston, A.A.L. Gunatilaka, R.L. Van Tassell, T.D. Wilkins, P.P. de Wit, M. van der Steeg, and A. van der Gen, J. Nat. Prod., in press and ref. 4).
12. The cyclic acetals 2, 3, 5, and 6, obtained under acidic conditions, were mixtures of about equal amounts of *cis*- and *trans*-isomers.
13. Selected spectroscopic data (^{1}H-NMR spectra were recorded at 200 MHz in $CDCl_3$):
    2 *c/t*: ^{1}H-NMR δ 4.94 (t, J=4.6 Hz) and 5.04 (t, J=4.8 Hz) 1H, OCHO.
    3 *c/t*: ^{1}H-NMR δ 4.44 (t, J=5.1 Hz) and 4.59 (t, J=5.1 Hz) 1H, OCHO.
    5 *c/t*: ^{1}H-NMR δ 4.89 (t, J=4.8 Hz) and 4.99 (t, J=4.8 Hz) 1H, OCHO.
    6 *c/t*: ^{1}H-NMR δ 4.39 (t, J=5.1 Hz) and 4.55 (t, J=5.1 Hz) 1H, OCHO.
    11: ^{1}H-NMR δ 3.61 (s, 3H, OCH_3); 5.60 (dd, J=10.3 and 12.5 Hz, 1H, CH=CHO); 5.73 (dt, J=6.8 and 13.9 Hz, 1H, CH_2-CH=); 6.63 (d, J=12.5 Hz, 1H, CHO).
    12: ^{1}H-NMR δ 1.32 (d, J=6.6 Hz, 6H, $CH(CH_3)_2$; 3.15 (hep, J=6.6 Hz, 1H, $CH(CH_3)_2$; 5.6-5.8 (m, 2H, =CH) and 6.0-6.5 (m, 8H, =CH).
    13: ^{1}H-NMR δ 4.65, 4.67, 4.68, 4.70 [4x(t, J=6.8 Hz)], 1H, SCHO, 4 diastereomeric pairs. UV: λ_{max} (EtOH) 288, 302, 316. MS: m/e 380.2407 (M^+), $C_{22}H_{36}O_3S$ requires 380.2385.
    14: ^{1}H-NMR δ 4.61, 4.63, 4.65, 4.67 [4x(t, J=6.7 Hz)], 1H, SCHO, 4 diastereomeric pairs. UV: λ_{max} (EtOH) 288, 302, 316. MS: m/e 340.2069 (M^+), $C_{19}H_{32}O_3S$ requires 340.2072.
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