Hydroxymethylation of Jojoba Oil by Lewis Acid-Catalyzed Ene Reaction with Formaldehyde

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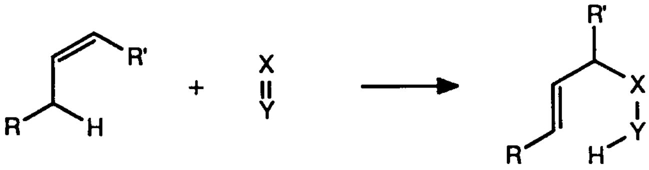
Formaldehyde undergoes ethylaluminum dichloride-catalyzed ene reaction with jojoba oil to afford a mixture of 1:1 and 1:2 adducts. The hydroxymethyl products were identified by comparison with model adducts prepared from methyl oleate and oleyl acetate.

KEY WORDS: **Ene addition, hydroxymethylation, jojoba oil, methyl oleate, oleyl acetate.**

Ene reactions, which involve addition of an alkene having an allylic hydrogen (the "ene") to an unsaturated compound (enophile, X = Y) to form a new bond with migration of the ene double bond and 1,5-hydrogen shift, find widespread use in organic synthesis (1). In contrast, although the reaction of maleic anhydride with unsaturated fatty acids ("maleinization") is well documented (2), the use of ene additions for the functionalization of lipid alkenes has received little attention (3,4) (Scheme 1).



SCHEME 1

We now report that Lewis acid-catalyzed ene reactions of formaldehyde can be used to introduce hydroxymethyl substituents into jojoba oil (I), which is a liquid wax largely composed of esters of monounsaturated fatty acids (C_{18}–C_{24}) and monounsaturated alcohols (C_{18}–C_{24}), and which is attracting considerable interest (5–7) as a replacement for sperm whale oil.

$$(Z,Z)\text{-}CH_3(CH_2)_7CH{=}CH(CH_2)_mCO_2(CH_2)_nCH{=}CH(CH_2)_7CH_3$$

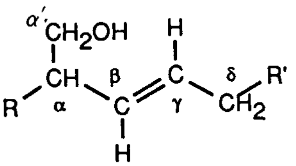
I; $m = 7,9,11,13$; $n = 8,10,12,14$

EXPERIMENTAL PROCEDURES

Reaction of fatty acid esters with formaldehyde. Ethylaluminum dichloride (5.50 mmol, 5.5 mL of 1.0 M solution in hexanes; Aldrich Chemical Company, Ltd., Milwaukee, WI) was added slowly by means of a syringe to a solution of the olefinic fatty acid ester (2.50 mmol) and paraformaldehyde (2.75 mmol) in dry dichloromethane (15 mL) at 0°C in a flame-dried flask under nitrogen, and the mixture was stirred for 1 h. The reaction was quenched by addition of diethyl ether (20 mL), followed by water (10 mL). After the precipitated solids had dissolved, the organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The products were isolated by dry flash chromatography (Fluka GF_{254} silica, eluted with 1:1 hexane/Et_2O; Fluka, Buchs, Switzerland).

RESULTS AND DISCUSSION

Before using jojoba oil as a substrate, two simple fatty acid esters—methyl oleate and oleyl acetate—were examined to establish the reactivity of such unsaturated lipids and also to provide model ene adducts to facilitate structural identification of the modified jojoba oil. Formaldehyde itself is not sufficiently reactive as an enophile toward unactivated alkenes. However, such additions can readily be accomplished with Lewis acid catalysis (8). Methyl oleate, which was chosen as a model for the carboxylate fragment of jojoba oil, was reacted with formaldehyde in the presence of ethylaluminum dichloride by the procedure described by Snider and Phillips (8), and from the reaction mixture a regioisomeric mixture of 1:1 ene adducts (**IIa**) and (**IIb**) in a combined yield of 63% was isolated. The products were readily identified from their spectroscopic properties. In addition to characteristic infrared peaks at 3440 cm^{-1} (OH) and 1742 cm^{-1} (C=O), the ^1H nuclear magnetic resonance (NMR) spectrum shows distinctive absorptions for the hydroxymethyl substituent, the new alkene unit and the adjacent allylic positions (see Table 1). H(β) appears as a multiplet (*ddt*) at 5.10 ppm and H(γ) also as a multiplet (*d+d*) at higher frequency (5.50 ppm). The 15.3 Hz coupling between these protons confirms the assignment of *trans*-geometry for the alkene moiety; there was no evidence for the presence of *cis*-alkenes. There are also characteristic peaks for the hydroxymethylene group [H(α') 3.49 and 3.30 ppm, C(α') 65.74 ppm], the allylic CH [H(α) 2.11 ppm, C(α) 45.63 ppm] and the allylic methylene [H(δ) 2.00 ppm, C(δ) 32.43 and 32.31 ppm]. The doubling of some peaks in the ^{13}C NMR spectrum is consistent with the formation of both regioisomers (**IIa**) and (**IIb**) in similar amounts.



SCHEME 2

IIa R = $(CH_2)_7CH_3$, R′ = $(CH_2)_5CO_2Me$
IIb R = $(CH_2)_7CO_2Me$, R′ = $(CH_2)_5CH_3$
IIIa R = $(CH_2)_7CH_3$, R′ = $(CH_2)_6OAc$
IIIb R = $(CH_2)_8OAc$, R′ = $(CH_2)_5CH_3$

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TABLE 1

Selected Nuclear Magnetic Resonance Data[a] for Lipid–Formaldehyde Ene Adducts

	Compound	(IIa, IIb)	(IIIa, IIIb)	(IV)[b]	(V)
δ_H/ppm	H(α)	2.11 (*m*)	2.07 (*m*)	2.11 (*m*)	2.11 (*m*)
	H(β)	5.10 (*ddt*)	5.08 (*ddt*)	5.10 (*br.dd*)	5.10 (*br.dd*)
	H(γ)	5.50 (*dtd*)	5.45 (*dtd*)	5.50 (*br.dt*)	5.50 (*br.dt*)
	H(δ)	2.00 (*m*)	1.95 (*m*)	≈2.0[c]	2.00 (*q*)
	H(α′)	3.49 (*ddd*)	3.44 (*ddd*)	3.48 (*dd*)	3.48 (*dd*)
		3.30 (*ddd*)	3.28 (*dd*)	3.30 (*dd*)	3.30 (*dd*)
J/Hz	H(β)-H(γ)	15.3	15.3	15.3	15.3
δ_C/ppm	C(α)	45.63	45.64	45.73	45.79
	C(β)	131.30	131.24	131.13	131.12
		131.03	131.05		
	C(γ)	133.50	133.49	133.65	133.85
		133.14	133.24		
	C(δ)	32.43	32.42	32.48	32.52
		32.31	32.37		
	C(α′)	65.74	65.74	65.81	65.82

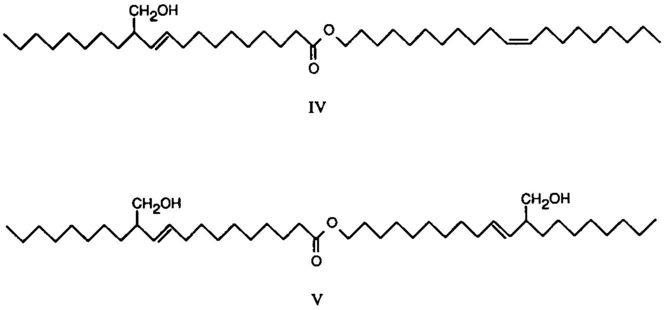
[a] Recorded in $CDCl_3$ at 360 MHz (^1H) and 50 MHz (^{13}C).

[b] Peaks for unreacted lipid alkene at: δ_H 5.31 (*t*) (=CH), 1.97–2.02 (*m*) (allylic CH_2); δ_C 129.69 (=CH), 27.00 (allylic CH_2).

[c] Overlapping allylic signals of unreacted alkenes.

Oleyl acetate was examined as a model for the unsaturation present in the alcohol portion of jojoba oil. Reaction with formaldehyde under similar conditions yielded a *ca.* 1:1 mixture of regioisomeric ene adducts (**IIIa**) and (**IIIb**) in 82% yield. As anticipated, the NMR data for the hydroxymethyl, alkene and associated allylic groups of these products were indistinguishable from those of the methyl oleate analogues (see Table 1 and Scheme 2).

Having established that hydroxymethyl adducts could be prepared from typical monounsaturated lipids, the corresponding reaction with jojoba oil was investigated. Ethylaluminum dichloride-catalyzed addition of formaldehyde to a solution of jojoba oil (HCHO/jojoba, 1.1:1) in dichloromethane afforded, after removal of the solvent, a yellow oil. The ^1H NMR spectrum of the product mixture showed the presence of both ene-adducts and unreacted lipid alkenes. The signals for the carbons of the adduct alkene unit and the attached protons (see Table 1) were similar to those of model compounds (**II**) and (**III**). By comparing the intensities of the ester OCH_2 and allylic hydroxymethyl signals, it was estimated that 21% of the double bonds had reacted. Chromatography of the reaction mixture (silica, hexane/Et_2O) afforded, in order of elution, unreacted jojoba oil (54%), a fraction composed of 1:1 adducts (30%) and, finally, a mixture of 2:1 products (8%). Compounds (**IV**) and (**V**) are representative examples of the 1:1 and 2:1 adducts (Scheme 3). A greater degree of modification was achieved by using an excess of the enophile; using a 2.2:1 molar ratio of formaldehyde to jojoba oil, the degree of double bond modification rose to 70%, and from the reaction mixture unreacted jojoba oil (10%), 1:1 adducts (32%) and 2:1 adducts (52%) were isolated. In conclusion, Lewis acid-catalyzed addition of formaldehyde to jojoba oil provides ready access to hydroxymethyl-substituted analogues suitable for conversion to a range of derivatives. As many common vegetable oils contain similar unsaturation, this type of modification could find wider application.



SCHEME 3

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