Retardation Effect of Jojoba Chain Length on the Chemical Reactivity of the Liquid Wax

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ABSTRACT: Jojoba wax and its derivatives are slow-reacting compounds. To elucidate the reasons for this phenomenon, we reacted jojoba mono- and bis-epoxide and *trans*-jojoba bis-epoxide (C_{38}–C_{44} long-chain esters), as well as side chain esters of three steroid skeleton mono-epoxide derivatives with NaI under acidic conditions to yield the corresponding iodohydrins, which then formed the respective bis-keto (or mono-ketone) derivatives. The kinetics, activation energies, and thermodynamic parameters of activation of nucleophilic epoxide opening and pinacol rearrangement were determined for all these compounds. The reaction rates of the jojoba derivatives were similar to those of two of the epoxides derived from the steroid skeleton compounds, and in the third case the steroid derivative reacted somewhat faster than all the rest. This pattern of rate retardation could stem either from folding of the long jojoba chain, resulting in steric hindrance around the reaction centers, or from repeated unproductive collisions along the long hydrocarbon chain of the jojoba wax (statistical effect). Our results appear to suggest that the multiple unsuccessful collisions were the dominant factor, although steric hindrance cannot be ruled out.

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KEY WORDS: Chemical reactivity, jojoba iodohydrin, jojoba mono- and bis-epoxide, mono- and bis-ketojojoba wax, pinacol rearrangement, retardation, rigid steroid skeleton vs. flexible long chain.

Jojoba liquid wax (**I**) is composed of long-chain esters (1), as follows (Scheme 1):

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

I

Chain length:	m =	7,	9,	11,	13	n =	8,	10,	12, 14
Average composition (%):		11,	71,	14,	1		1,	45,	44, 9

SCHEME 1

These esters are relatively slow-reacting molecules (2). It seems reasonable to suppose that their slowness is related to the considerable length of the ester chain, which constitutes 38–44 carbon atoms. Folding of the chain, which causes steric hindrance around the active sites along the chain (double bonds, allylic positions, and ester group), could retard reactions along the chain. Retardation might also be due to numerous unproductive collisions with the large inert portions of the hydrocarbon chain (statistical effect). Whatever the cause, the net result is that more drastic conditions, such as higher temperatures and longer reaction periods, are required to achieve the types of chemical change (2) that take place under much milder conditions within shorter times in short-chain molecules.

In a recent study, the jojoba bis-epoxides (**II**) (derived from the natural wax, which contains *cis* double bonds) and **IIa** [derived from the isomerized *trans*-jojoba (**Ia)** (3)], were reacted with NaI under acid catalysis to form an iodohydrin (**III**), which formed the bis-ketojojoba (**IV**) (Scheme 3) (4). Higher temperatures and longer periods were required for these reactions than for analogous reactions with short-chain epoxides (5). In the present paper, we describe the kinetics of these reactions for the two bis-epoxides—as well as for the mono-epoxide (**IIb**). We then discuss the kinetics of reactions with epoxides *cis*-DED (**IX**; *cis*-dihydrocholesteryl 6,7-epoxydecanoate), *trans*-DEH (**X**; *trans*-dihydrocholesteryl 3,4-epoxyhexanoate), and *cis*-EHL (**XI**; *cis*-3,4-epoxyhexyl lithocholate) (Scheme 2). These epoxides are esters derived from short-/medium-length side-chain olefins such as (*E*)-3-hexenoic acid, (*E*)-3-hexenol, or (*Z*)-6-decenoic acid (**V**) and of steroid skeleton derivatives, producing (*Z*)-dihydrocholesteryl 6-decenoate (**VI**), (*E*)-dihydrocholesteryl 3-hexenoate (**VII**), and (*Z*)-3-hexenyl lithocholate (**VIII**). The steroid skeleton is rigid and offers much less steric hindrance at the reaction site (which is on the short side chain). Still, it is a large molecule, with about 30 carbon atoms in the backbone and several atoms in the side chain. In an effort to understand the causes of reaction retardation in jojoba long-chain esters as compared with their short-chain analogs, we examined the effect of the size of the molecule (number of unproductive collisions, statistical effect), and also looked at the effect of chain length (folding and steric hindrance) on reaction rate and activation energies for both epoxide opening and pinacol rearrangement.

EXPERIMENTAL PROCEDURES

Materials. Jojoba wax (Jojoba Israel Ltd., Hatzerim, Israel) was used as the crude oil (without bleaching); an iodine number of 80.9 corresponds to a product with 94.7% of bis-unsaturated

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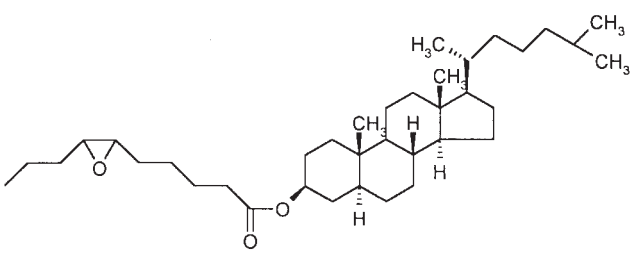
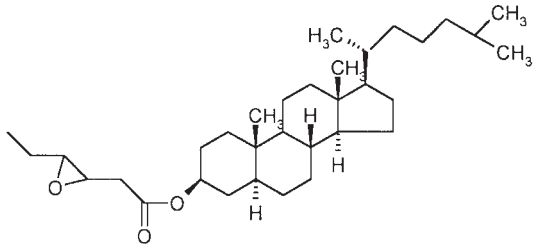
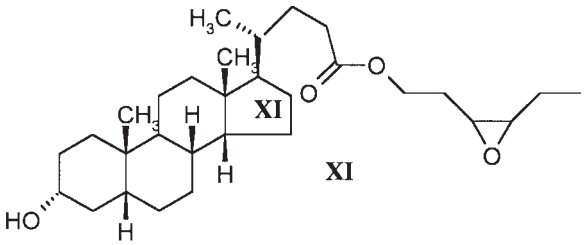


IX



X



XI

SCHEME 2

esters in the liquid wax. Silica gel 60, 70–230 mesh (Merck, Darmstadt, Germany) was used for column chromatography.

Solvents. Petroleum ether (60–80°C), CP grade (Frutarom, Haifa, Israel), was dried over $CaCl_2$ and distilled. THF, AR grade, was dried over KOH and distilled. Dimethylformamide (DMF), AR, was dried on CaH_2. Acetone, chloroform, dichloromethane, diethyl ether, ethyl acetate. and toluene, CP grade, (Aldrich, Milwaukee, WI) were used without drying.

Reagents. *m*-Chloroperbenzoic acid (85%), *n*-butanal, sodium iodide AR grade, and potassium *t*-butoxide (Fluka, Buchs, Switzerland) were used without any further purification. Triphenylphosphine, (+)-dihydrocholesterol, 6-bromohexanoic acid, lithocholic acid, (*E*)-3-hexenoic acid, (*Z*)-3-hexen-1-ol, and bromine AR (Aldrich) were used without any further purification.

Base. NaOH CP grade (Frutarom) was used.

Acids. Glacial acetic acid, HCl and H_2SO_4, AR grade (Merck, Darmstadt, Germany), were used.

Salts. $CaCl_2$, NaCl, Na_2SO_4, $MgSO_4$, $NaHSO_3$, $NaHCO_3$, Na_2CO_3, KI CP grade (Frutarom), and $AgNO_3$ (Engelhard, East Newark, NJ) were used.

General procedure. Crude products obtained after a particular chemical transformation of the jojoba wax, as well as dihydrocholesterol and lithocholic acid derivatives, were used in the subsequent step without further purification. The standard workup included pouring the reaction mixture into water, washing with $NaHCO_3$ solution (for reactions under acidic conditions) as well as with $NaHSO_3$ (after the NaI reactions), extraction with petroleum ether, washing the organic phase with a saturated solution of NaCl, drying over anhydrous Na_2SO_4 or $MgSO_4$, filtration, and evaporation of the solvent to give the crude product.

Kinetic studies. Each kinetic study on purified epoxides (after column chromatography, elution with 5–10% of ethyl acetate in petroleum ether mixtures) was run twice (except for *trans*-DEH, **X**, which was studied once), and the results are the average of the two runs. The kinetics was examined at 35, 45, and 56°C. The temperature was kept constant on all runs (±0.5°C). Samples were withdrawn at specific intervals (±1 min).

The composition of the reaction mixtures was determined by integration of the specific hydrogen atoms of the starting material (epoxide) and products (iodohydrin and keto-derivatives) in the ^{1}H NMR spectra (±5%).

IR spectra. IR spectra were obtained with a Nicolet (Madison, WI) 5ZDX FTIR spectrometer. All IR spectra (taken as neat on NaCl prisms) gave an intense carbonyl signal at 1735–1740 cm^{-1}, a signal at 1465–1466 cm^{-1}, and a broad intense signal of hydrogen–carbon bonds at 2800–3000 cm^{-1}.

^{1}H NMR spectra and analytical TLC. NMR spectra and analytical TLC were used to monitor the chemical changes occurring in each reaction. NMR (200 MHz) spectra were obtained on a Bruker WP-200SY instrument (Spectrospin AG; Sallenden, Switzerland) in $CDCl_3$ solution with Me_4Si as the internal reference. All NMR spectra of jojoba derivatives gave a terminal CH_3 as a triplet (*t*) at δ 0.92–0.94, an intense signal at 1.2–1.4 for all aliphatic hydrogen atoms, a triplet at 2.20–2.26 for CH_2COO, and a triplet at 3.96–4.00 for CH_2OCO. All other signals are described below. Integration curves were consistent with the assignment of the different hydrogen atoms, for an average of at least two experiments (±5%).

GC–MS. GC–MS analyses were performed on a Hewlett-Packard 5890 Series II gas chromatograph coupled with an AutoSpec E high-resolution mass spectrometer. The separation was performed with a 30 m × 0.32 mm × 0.25 μm DB-1 capillary column (J&W Scientific, Folsom, CA), temperature-programmed from 150 (hold 1 min) to 270°C (hold 20 min) at 10°C/min. The mass spectra were obtained using chemical ionization (CI). The reagent gas used in CI was isobutane.

All IR and ^{1}H NMR spectra fit known data of similar chemical structures (6).

*Trans-jojoba (**Ia**). Trans*-jojoba (**Ia**) was prepared according to a known procedure (3) and contained 86% *trans* double bonds and 14% *cis* double bonds, as determined by ^{1}H NMR of the epoxide derivative.

*Jojoba wax bis-epoxide (**II**) and trans-jojoba wax bis-epoxide (**IIa**).* These were prepared according to a previous procedure (4).

*Jojoba wax mono-epoxide (**IIb**).* This was prepared as

described for the bis-epoxide (4), but the amount of perbenzoic acid was cut by half.

*(Z)-6-Decenoic acid (**V**) (7).* A mixture of 22.8 g (0.05 mol) triphenyl-phosphonium salt of 6-bromohexanoic acid and 4.25 g (0.06 mol) *n*-butanal was dissolved in 100 mL of dry DMF. This solution was added within 30 min to a slurry of 11.6 g (0.102 mol) *t*-BuOK in 125 mL dry DMF at 0°C, under N_2. The reaction mixture was held at 25°C for 24 h with intensive stirring. The reaction mixture was then poured into iced water, and the triphenylphosphine oxide that formed was filtered off. The filtrate was washed with toluene (2 × 30 mL) and then acidified with 2 M HCl. The mixture was extracted with diethyl ether (4 × 25 mL), which was then washed with a saturated solution of NaCl and dried over Na_2SO_4. The crude product was chromatographed on silica gel and eluted with 30% of ethyl acetate in petroleum ether to yield 6 g of (*Z*)-6-decenoic acid (70%). IR: 3000–2500, 740 cm^{-1}. ^1H NMR δ: 11.75 (1H, –COO*H*, br, *s*), 5.37 (2H, –C*H*=C*H*–, *m*), 2.37 (2H, –CH_2COOH, *t*, *J* = 7 Hz), 2.03 (4H, –CH_2CH=CHCH_2–, *quint*, *J* = 7.5 Hz). High-resolution MS (HRMS) of MH^+ found 171.137917, calculated for $C_{10}H_{19}O_2$ 171.138505. HRMS of $[M - H]^+$ found 169.122331, calculated for $C_{10}H_{17}O_2$ 169.122855.

*(Z)-Dihydrocholesteryl 6-decenoate (**VI**).* A solution of 2 g (0.012 mol) (*Z*)-6-decenoic acid (**V**) and 4.7 g (0.012 mol) dihydrocholesterol in 100 mL of toluene and 5 drops of concentrated H_2SO_4 was refluxed for 30 min with a Dean–Stark unit for azeotropic distillation. The reaction mixture was washed with a saturated solution of Na_2CO_3 and then with NaCl, and subsequently dried over Na_2SO_4. The product was obtained as a liquid, 5.8 g (86%). IR: 2916, 2852, 1740, 1456, 1373 cm^{-1}. ^1H NMR δ: 5.37 (2H, –C*H*=C*H*–, *m*), 4.70 (1H, –OC*H*–, *m*), 2.25 (2H, –CH_2COO–, *t*, *J* = 7 Hz). HRMS of MH^+ found 541.498457, calculated for $C_{37}H_{65}O_2$ 541.502252.

(E)-Dihydrocholesteryl 3-hexenoate (**VII**) (63%) and (*Z*)-3-hexenyl lithocholate (**VIII**) (61%) were obtained by the above procedure.

*(E)-Dihydrocholesteryl 3-hexenoate (**VII**).* Melting point 57–58°C. IR: 2935, 2860, 1735, 1458, 1375 cm^{-1}. ^1H NMR 5.57 (2H, –C*H*=C*H*–, *m*), 4.70 (1H, –OC*H*–, *m*), 3.00 (2H, –CH_2COO–, *d*, *J* = 5.4 Hz). HRMS of MH^+ found 485.435334, calculated for $C_{33}H_{57}O_2$ 485.435857.

*(Z)-3-Hexenyl lithocholate (**VIII**).* Melting point 182–183°C. IR: 2983, 2860, 1735, 1458, 1375, 760 cm^{-1}. ^1H NMR 5.40 (2H, –C*H*=C*H*–, *m*), 4.06 (2H, –CH_2OCO–, *t*), 3.63 (1H, –OC*H*–, *m*), 2.35 (2H, –CH_2COO–, *t*, *J* = 7 Hz). HRMS of MH^+ found 459.610, calculated for $C_{30}H_{51}O_3$ 459.722.

*Dihydrocholesteryl 6,7-epoxydecanoate, cis-DED (**IX**).* A solution of 5.4 g (0.01 mol) **VI** and 2.6 g (0.015 mol) *m*-chloroperbenzoic acid in 50 mL chloroform was stirred for 24 h at 25°C. The product (5.5 g, 96%) was obtained as an oil. ^1H NMR 4.70 (1H, –OC*H*–, *m*), 2.92 (2H, *cis*-oxirane H, *br s*), 2.25 (2H, –CH_2COO–, *t*, *J* = 7 Hz). HRMS of MH^+ found 557.491669, calculated for $C_{37}H_{65}O_3$ 557.493372.

*Dihydrocholesteryl 3,4-epoxyhexanoate, trans-DEH (**X**).* A solid product (95%) was obtained by the same procedure as above. Melting point 105–106°C. ^1H NMR 4.74 (1H, –OC*H*–, *m*), 3.05–2.74 (2H, *trans*-oxirane H, *m*), 2.56–2.48 (2H, –CH_2COO–, *m*). HRMS of MH^+ found 501.430954, calculated for $C_{33}H_{57}O_3$ 501.430771.

*3,4-Epoxyhexyl lithocholate, cis-EHL (**XI**).* A solid product (96%) was obtained by the same procedure as above. Melting point 219–220°C. ^1H NMR 4.23 (2H, –CH_2OCO–, *t*, *J* = 6.3 Hz), 3.63 (1H, –OC*H*–, *m*), 3.01 (2H *cis*-oxirane H, *m*) 2.29 (2H, –CH_2COO–, *t*, *J* = 7 Hz). HRMS of MH^+ found 475.370604, calculated for $C_{30}H_{51}O_4$ 475.370911.

*Dihydrocholesteryl 6(7)-oxo-decanoate (**XII**).* To a solution of 8.9 g (0.016 mol) **IX** in 60 mL of THF and 20 mL of acetone, 4 mL of glacial acetic acid, 0.5 mL of water, and 3.75 g NaI (0.025 mol) were added. The reaction was conducted at reflux for 48 h under N_2. After workup, 0.39 g (44%) of the product was obtained. IR: 2961, 2870, 1745, 1691 cm^{-1}. ^1H NMR 4.70 (1H, –OC*H*–, *m*), 2.37 (4H, –CH_2COCH_2–, *t*, *J* = 7 Hz), 2.27 (2H, –CH_2COO–, *t*, *J* = 7 Hz). HRMS of MH^+ found 557.491639, calculated for $C_{37}H_{65}O_3$ 557.493372.

*3(4)-Oxohexyl lithocholate (**XIII**).* The keto derivative was obtained by the same procedure as above from the epoxide **XI** (40%). IR: 2937, 2864, 2846, 1737, 1714 cm^{-1}. ^1H NMR 3.63 (1H, –OC*H*–, *m*), 2.46 (–CH_2COCH_2–, *t*, *J* = 7 Hz), 2.30 (2H, –CH_2COO–, *t*, *J* = 7 Hz). HRMS of MH^+ found 475.382490, calculated for $C_{30}H_{51}O_4$ 475.378736.

Kinetics of rearrangement. A mixture of 1 g (1.6 mmol) of jojoba bis-epoxide (**II**) (either *cis*- or *trans*-jojoba), or 0.98 g (1.6 mmol) of jojoba mono-epoxide (**IIb**), or 0.89 g (1.6 mmol) of dihydrocholesteryl 6,7-epoxydecanoate (**IX**), or 0.81 g (1.7 mmol) of dihydrocholesteryl 3,4-epoxyhexanoate (**X**), or 1.1 g (2.3 mmol) of 3,4-epoxyhexyl lithocholate (**XI**), in 60 mL of THF, 20 mL of acetone, 4 mL of glacial acetic acid, 0.5 mL of H_2O, and 7.5 g (0.05 mol for bis-epoxides and **XI**) or 3.75 g (0.025 mol for mono-epoxides) of NaI was stirred at different temperatures (35, 45, and 56°C) under N_2 for 48 h. The pH was kept constant at 3 by adding drops of acetic acid when needed. Aliquots were taken at specific times for TLC and NMR analyses. After rearrangement of epoxide **X**, only three products (**XIV, XVI**, and **XVII**) were identified in the reaction mixture. The concentration percentage shows the relative amount in the mixture.

*Dihydrocholesteryl 3-hydroxy-4-iodohexanoate (**XIV**).* ^1H NMR: 4.17–4.04 (1H, H_4, *m*), 3.57 (1H, H_3, *m*), 2.70–2.50 (2H, H_1 and H_2, *m*). Concentration: 85% of the mixture.

*(E)-Dihydrocholesteryl 4-hydroxy-hex-2-enoate (**XVI**).* ^1H NMR: 6.83 (1H, H_3, *dd*, *J* (H_3H_2) = 16 Hz, *J* (H_3H_4) = 5 Hz), 6.00 (1H, H_2, *dd*, *J* (H_2H_3) = 16 Hz, *J* (H_2H_4) = 2 Hz), 3.74 (1H, H_4, *m*). Concentration: 10% of the mixture.

*(E)-Dihydrocholesteryl 2-hydroxy-hex-4-enoate (**XVII**).* ^1H NMR: 5.80–5.40 (2H, H_5 and H_4, *m*), 4.40 (1H, H_3, *m*), 2.70–2.50 (2H, H_1 and H_2, *m*). Concentration: 5% of the mixture.

RESULTS AND DISCUSSION

Epoxide opening and pinacol rearrangement. The two-step chemical transformation of jojoba derivatives is shown in

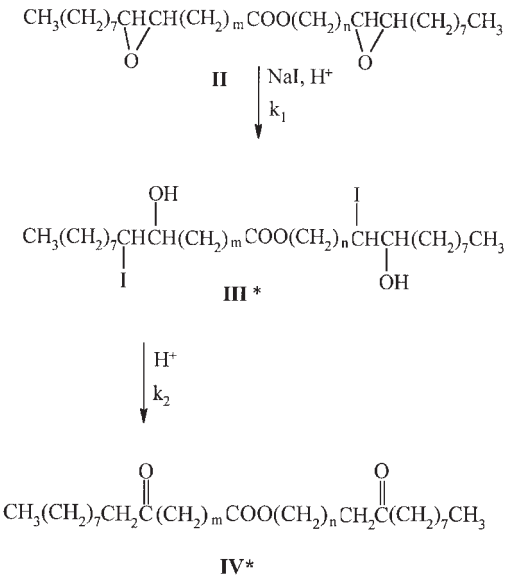
Scheme 3. The steroid skeleton derivatives follow the same pathway, giving the corresponding ketone products.

Kinetics. In the 35–56°C range, under slightly acidic conditions, a temperature dependence is evident in the reactions of the iodide ion with epoxides derived from natural jojoba (*cis* double bonds) [bis-epoxide (**II**) and mono-epoxide (**IIb**)], with *trans*-jojoba bis-epoxide (**IIa**), and with epoxides **IX**, **X**, and **XI** derived from (*Z*)-dihydrocholesteryl 6-decenoate (**VI**), (*E*)-dihydrocholesteryl 3-hexenoate (**VII**), and (*Z*)-3-hexenyl lithocholate (**VIII**), respectively: The higher the temperature, the faster the reaction. There were, however, some differences in reaction rates between the compounds. At 35°C, the reaction with natural jojoba proceeded slowly, taking 60 min to achieve 55% conversion, whereas that with *trans*-jojoba was even slower, close to 2 h being required to reach the same conversion level. The mono-epoxide of jojoba reacted yet more slowly, conversion after 2 h amounting to a mere 45%. The steroid skeleton compounds displayed two different patterns of behavior: either the same reaction rates as for the jojoba epoxides—as in the case of the dihydrocholesteryl derivatives DED (**IX**) and DEH (**X**)—or a faster rate, as for the lithocholic acid derivative EHL (**XI**), which yielded 80% conversion after 60 min at 35°C. Even at the highest temperature tested, 56°C, the reactions with natural jojoba (*cis*) and the *trans*-isomer proceeded at different rates. At that temperature, 55% conversion was achieved after 10 min in the case of *cis*-jojoba vs. 45 min in the case of *trans*-jojoba, whereas for jojoba mono-epoxide the same level of conversion was recorded only after 30 min. The dihydrocholesteryl derivatives behaved similarly to the jojoba epoxides, although the shorter chain of **X** reacted slightly more rapidly than **IX**: After 10 min there was 45% conversion of **IX** and 60% of **X**. The fastest of all the six epoxides was the lithocholic acid derivative, which showed 75% conversion after 10 min. The results showing faster reaction in the case of the lithocholic acid derivative should be viewed with caution, as its starting molar concentration was higher (2.3 mmol) than that of all the others (1.6 mmol). If a higher concentration was indeed the reason for the faster rate observed, then we should conclude that this compound behaves like the other two dihydrocholesteryl derivatives and is therefore distinctly similar to the jojoba derivatives. This means that the size of the molecule and the many unproductive collisions are main factors responsible for the chemical tardiness of jojoba wax.

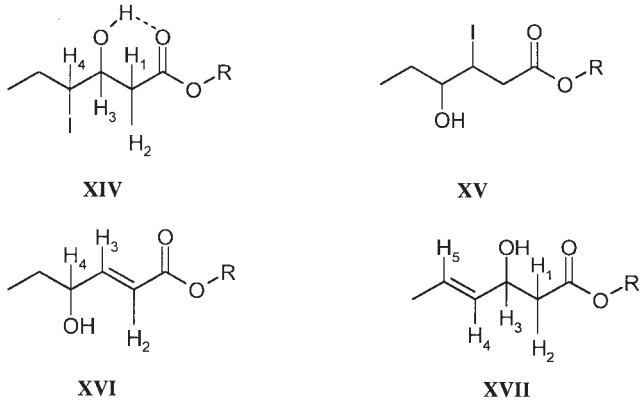
The transformation of the iodohydrins formed in the first step to the keto derivatives was also temperature dependent. Formation of bis-ketojojoba proceeded slowly, with a lag time of almost 3 h after onset of the reaction at 35°C and of 10–25 min at 45 and 56°C. The yield of ketojojoba derivatives at the end of the reaction (48 h) was low in all instances, ranging from 3 to 5% at 35°C (the lower limit of detection of hydrogen atoms α next to the carbonyl) to 25–60% at 56°C.

While the reactivity pattern of the dihydrocholesteryl decanoate system (**IX**) followed that of the jojoba derivatives (ketone production 3–5% at 35°C and 10% at 56°C), there was no rearrangement of the dihydrocholesteryl hexanoate system (**X**), and the iodohydrin formed remained almost unchanged after 48 h of reaction. The reason for this probably lies in the fact that the major iodohydrin formed (**XIV**, 85% of the reaction mixture) is stabilized by a strong intramolecular hydrogen bond. The other isomer (**XV**) was not detected, but its elimination product, **XVI**, was found to be 10% of the mixture. The elimination product **XVII** (product of **XIV**) was detected in 5% of the mixture (see Scheme 4). No ketone product was found.

The reaction of the lithocholic acid derivative (**XI**) was difficult to decipher, as the NMR signals of the hydrogen atoms adjacent to the carbonyl overlapped those of the ester, but a qualitative evaluation is possible. This reaction was much faster than the others. Formation of iodohydrin reached a maximum within a short time (50% after 2 h at 35°C and 60% after 60 min at 56°C) and was accompanied by rearrangement to the ketone



SCHEME 3



SCHEME 4

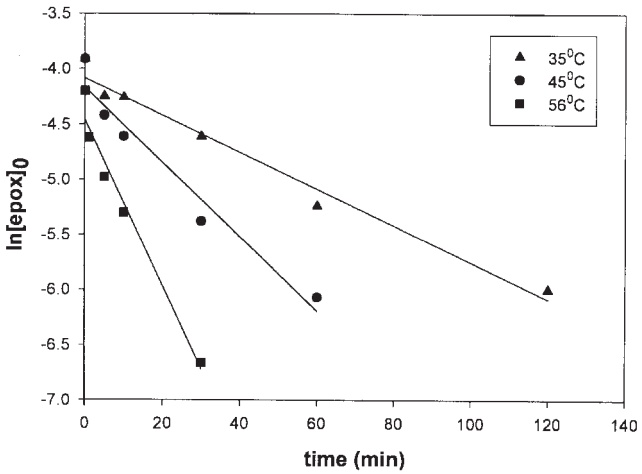


FIG. 1. Plot of ln[epoxide] as function of time for the epoxide ring opening of 3,4-epoxyhexyl lithocholate (**XI**).

XIII. The yield of **XIII** could not be calculated due to overlapping of peaks in the NMR spectra**,** but much less of the iodohydrin was left in the reaction mixture after 4 h (25%) as compared with the other compounds (55% of **II**, 60% of **IIa**, 35% of **IIb**, and 75% of **IX**). The iodohydrin presumably began to transform into the keto derivative as soon as it was formed, thereby keeping its concentration in the reaction mixture low.

Rate constants and activation energies for ring opening. The kinetics of ring opening was studied by following the conversion of epoxide to iodohydrin as a function of time in the presence of excess NaI. When ln[epoxide] was plotted vs. time, linear curves resulted, indicating that the reaction was pseudo-first order in [epoxide]. A representative example is presented in Figure 1 (lithocholic acid derivative **XI**).

$$V_1 = -d[\text{epoxide}]/dt = k_1' [\text{epoxide}] \quad [1]$$

where $k_1' = k_1[\text{NaI}]$, or

$$\ln[\text{epoxide}] = \ln[\text{epoxide}]_0 - k_1' t \quad [2]$$

The reaction mixture, which was composed of THF, acetone, acetic acid, and a small amount of water, dissolved both the organic molecules and the NaI. Thus, there was no problem of two-phase reaction.

The rate constants for ring opening at different temperatures were calculated for all six of the epoxides under investigation and are presented in Table 1 alongside the activation energies (based on graphs such as Fig. 2). The slightly higher rate found for *cis*-jojoba bis-epoxide compared with *trans*-jojoba bis-epoxide may be related to the greater accessibility of the epoxide to the iodide ion in the *cis*-configuration, which is less crowded on one side. The low rate for the jojoba mono-epoxide as compared with the bis-epoxide may be due to a greater number of unproductive collisions, for the same chain length, in the case of the single epoxide ring.

The rates for the two jojoba bis-epoxides were similar to those for the two dihydrocholesteryl derivatives **IX** and **X**, indicating that the size of the molecule is the major factor retarding the reactivity of the jojoba long-chain ester. On the other hand, the relatively fast ring opening found for the lithocholic acid derivative **XI** suggests that steric hindrance may also play a role, although the effect of differences in starting molar concentration should not be ignored (see preceding discussion). The reaction site on the side chain is somewhat farther from the rigid steroid skeleton and is therefore more exposed to the attacking nucleophile, but the number of unproductive collisions is the same.

Another factor that may affect the reaction rate is the somewhat higher polarity of the steroid skeleton molecules and particularly of the lithocholic acid derivative, owing to the free hydroxyl group present in the latter. If higher polarity is indeed a significant factor, then it follows that, as in the other compounds, the size of the molecule (and thus the number of unproductive collisions) plays a more important role than steric hindrance. The proximity of the ester functional group in **XI** seems to have had only a negligible enhancing effect, since **X** is also characterized by such proximity yet displayed only weak enhancement as compared with the jojoba derivatives or with **IX**.

The activation energies listed in Table 1 reveal the same pattern of similarities and trends. The longer side chain of the steroid skeleton, **IX**, had a higher E_a than the shorter one, **X**. The lithocholic acid derivative **XI** had the lowest E_a in the series. As short chains react even at 5°C but the jojoba epoxide does not react at all at that low temperature (4), the differences

TABLE 1
Rate Constants k_1 (M^{-1} s^{-1}) and Activation Energies (E_a) for Epoxide Ring Opening[a]

Compound	Temperature 35°C	45°C	56°C	ln *A*	E_a (kcal mol^{-1})
cis-Jojoba (mono-epoxide)	2.42E-03	3.58E-03	3.02E-02	33.0	23.8 ± 0.6
trans-Jojoba	2.40E-03	5.56E-03	3.00E-02	32.8	23.7 ± 0.5
cis-Jojoba	3.64E-03	5.45E-03	4.21E-02	32.0	23.2 ± 0.1
cis-DED	5.20E-03	2.15E-02	5.75E-02	27.4	22.8 ± 2.1
trans-DEH	5.08E-03	1.15E-02	3.78E-02	25.7	19.1
cis-EHL	1.52E-02	3.68E-02	6.93E-02	19.3	14.4 ± 0.2

[a]*cis*-DED, dihydrocholesteryl 6,7-epoxydecanoate; *trans*-DEH, dihydrocholesteryl 3,4-epoxyhexanoate; *cis*-EHL, 3,4-epoxyhexyl lithocholate.

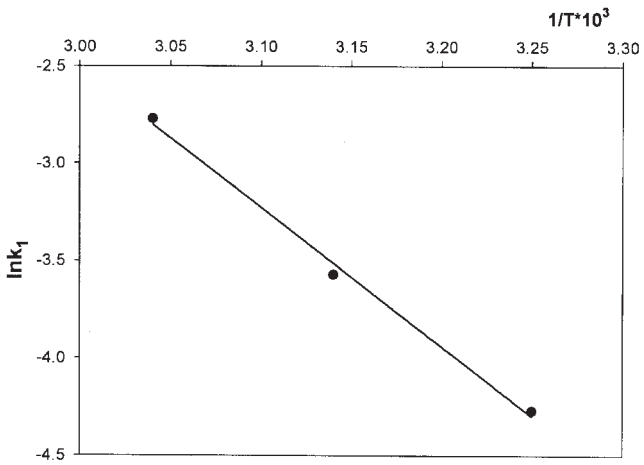


FIG. 2. Plot of ln k_1 vs. 1/*T* for the epoxide ring opening of 3,4-epoxyhexyl lithocholate (**XI**).

in reactivity between the two are particularly striking. These differences were corroborated by the differences in E_a.

Rate constants and activation energies for pinacol rearrangement. The formation of the keto product was followed over time. As is evident from the rate constants (Tables 1 and 2), ring opening proceeded much more rapidly than rearrangement, indicating that transformation of the jojoba iodohydrin started after a certain lag period. The concentration of iodohydrin was in excess and thus seems to be constant. For a more accurate calculation, however, the actual amount of iodohydrin present must be taken into consideration.

$$V_2 = \frac{d[\text{ketone}]}{dt} = k_2[\text{iodohydrin}] \quad [3]$$

$$[\text{iodohydrin}]_{\max} = [\text{epoxide}]_0 \left(\frac{k_2}{k_1'} \right)^{k_2/(k_1' - k_2)} \quad [4]$$

$$\ln[\text{iodohydrin}]_{\max} = \ln[\text{epoxide}]_0 \ \frac{k_2}{k_1' - k_2} (\ln k_2 - \ln k_1') \quad [5]$$

Rate constants [as calculated with Mathematica 2.2 (8)] and E_a for the pinacol rearrangement of the five molecules are summarized in Table 2. Once again, the behavior of the dihydrocholesteryl derivative recalls that of the jojoba derivatives, demonstrating the role of molecular size in reactivity retardation. On the other hand, rearrangement was 2–3 times faster for the lithocholic acid derivative, while the E_a was much lower (see preceding discussion of molar concentration). The difference in polarity among the compounds in this reaction is less pronounced, as all now have both hydroxyl and iodide groups in their structure.

Thermodynamic parameters of activation for epoxide opening and pinacol rearrangement. The E_a is derived from the Arrhenius equation (Eq. 6). A plot of ln *k* vs. 1/*T* gives the slope of E_a/R (Fig. 2), from which one can find the activation energy:

$$K = A^* e^{(-E_a/RT)}\ ;\ \ln k = \ln A - (E_a/R)(1/T) \quad [6]$$

The dependence of the reaction rate on temperature, based on the transition theory (9), is given by Equation 7:

$$K = (K_B T/h) \exp(\Delta S^{\ddagger}/R) \exp(\Delta H^{\ddagger}/RT) \quad [7]$$

$$\ln (k/T) = \ln (K_B/h) + (\Delta S^{\ddagger}/R) - (\Delta H^{\ddagger}/RT) \quad [8]$$

where K_B is the Boltzmann constant; *h*, Planck's constant; $\Delta S^{\ddagger}$, the entropy of activation, and $\Delta H^{\ddagger}$, the enthalpy of activation. A plot of ln(*k*/*T*) vs. 1/*T* gives the slope, which is $\Delta H^{\ddagger}/R$, to yield the enthalpy of activation. The intersection of the line with the *y* axis gives $\ln(K_B/h) + (\Delta S^{\ddagger}/R)$. Assuming that $\ln(K_B/h) = 23.76$ (10), one may calculate the entropy of activation.

Gibbs' free energy of activation is found using Equation 9:

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger} \quad [9]$$

The parameters of activation for epoxide ring opening and pinacol rearrangement are listed in Tables 3 and 4, respectively. We see that as the reaction rates increase, the enthalpy and free energy decrease. However, the decrease in the free energy values is very slight. This is because the entropy of activation becomes more and more negative (see Eq. 9). The more negative it is, the more ordered are the transition states of both the S_N2 epoxide opening and the acid-catalyzed pinacol rearrangement of the iodohydrin.

TABLE 2
Rate Constants k_2 ($M^{-1}s^{-1}$) and E_a for Pinacol Rearrangement[a]

Compound	Temperature 35°C	45°C	56°C	ln *A*	E_a (kcal mol^{-1})
cis-Jojoba (mono-epoxide)	2.08E-05	4.29E-05	3.10E-04	31.0	25.5 ± 0.8
trans-Jojoba	2.19E-05	8.28E-05	2.74E-04	28.3	24.0 ± 1.5
cis-Jojoba	4.00E-05	6.05E-05	4.73E-04	30.7	23.9 ± 2.1
cis-DED	4.03E-05	1.04E-04	4.68E-04	27.6	23.0 ± 0.3
cis-EHL	1.82E-04	2.95E-04	6.50E-04	18.8	16.9 ± 0.2

[a]For abbreviations see Table 1.

TABLE 3
Thermodynamic Parameters of Activation of Epoxide Ring Opening[a]

Compounds	E_a (kcal mol^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})
cis-Jojoba (mono-epoxide)	23.8 ± 0.6	23.1 ± 0.6	3.3 ± 1.8	22.0 ± 0.2
trans-Jojoba	23.7 ± 0.5	23.0 ± 0.5	3.1 ± 2.3	22.0 ± 0.3
cis-Jojoba	23.2 ± 0.1	22.5 ± 0.0	3.3 ± 0.4	21.5 ± 0.1
cis-DED	22.8 ± 2.1	22.2 ± 2.0	2.6 ± 7.8	21.3 ± 0.1
trans-DEH	19.1	18.3	-10.2	21.5
cis-EHL	14.4 ± 0.2	13.8 ± 0.4	-22.5±0.9	20.9 ± 0.1

[a]For abbreviations see Table 1.

TABLE 4
Thermodynamic Parameters of Activation of Pinacol Rearrangement

Compound	E_a (kcal mol^{-1})	$\Delta H^{\ddagger}$ Δ(kcal mol^{-1})	$\Delta S^{\ddagger}$ Δ(cal mol^{-1} K^{-1})	$\Delta G^{\ddagger}$ (kcal mol^{-1})
cis-Jojoba (mono-epoxide)	25.5 ± 0.8	24.9 ± 1.6	0.1 ± 4.5	24.9 ± 0.3
trans-Jojoba	24.0 ± 1.5	23.3 ± 1.5	−4.6 ± 4.4	24.8 ± 0.0
cis-Jojoba	23.9 ± 2.1	23.3 ± 2.1	−4.4 ± 6.0	24.6 ± 0.2
cis-DED	23.0 ± 0.3	22.5 ± 0.9	−6.4 ± 3.0	24.5 ± 0.1
cis-EHL	16.9 ± 0.2	16.3 ± 4.3	−21.8 ± 5.8	23.2 ± 0.6

[a]For abbreviations see Table 1.

In homologous series of reacting chemicals, a relationship may be expected between the enthalpy and the entropy of activation. If the line is linear, as in Figure 3, a single mechanism must be operating in each reaction (10). This implies that there is a temperature—the isokinetic temperature—at which all compounds in the series would have the same rate of reaction. The isokinetic temperatures are as follows: epoxide ring opening, 80°C (353 K); pinacol rearrangement, 140°C (413 K). As expected, these temperatures are higher for pinacol rearrangement than for epoxide ring opening.

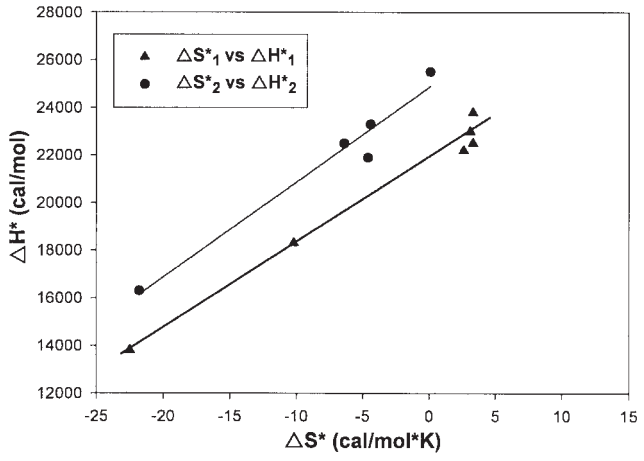


FIG. 3. Plot of enthalpy of activation vs. entropy of activation for the epoxide ring opening ($\Delta H^{\ddagger}_1$, $\Delta S^{\ddagger}_1$) and pinacol rearrangement ($\Delta H^{\ddagger}_2$, $\Delta S^{\ddagger}_2$) of jojoba and steroid skeleton derivatives.

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