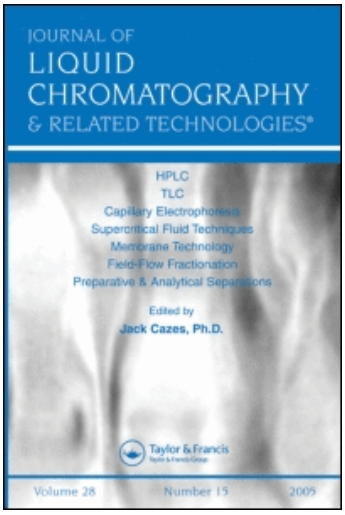

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Albert A. Ben-bassat[a]; Tamar Wasserman[a]; Avraham Basch[a]
[a] Israel Fiber Institute, Jerusalem, Israel

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QUANTITATIVE MONITORING OF STEARIC ACID MONOALKANOLAMIDE SYNTHESES BY HPLC

Albert A. Ben-Bassat*, Tamar Wasserman, and Avraham Basch

Israel Fiber Institute
P. O. Box 8001
Jerusalem 91 080 Israel

ABSTRACT

The application of a reversed-phase high performance liquid chromatographic method for the quantitative determination of various stearoyl monoalkanolamides is described. The base catalyzed amidation of methyl stearate with different monoalkanolamines, during two hours at 100°C, is examined. In each case the amount of the monoalkanolamide formed is determined directly in the crude reaction product by isocratic elution with a ternary solvent system of tetrahydrofuran-acetonitrile-water at pH 2.6 (37.5:37.5:25v/v) followed by detection with a differential refractometer. The quantitative results indicate that under the present experimental conditions the monoalkanolamines used react with methyl stearate at different rates without significant formation of byproducts.

*Author to whom correspondence should be addressed.

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INTRODUCTION

Fatty alkanolamides are known as a class of essentially nonionic surfactants which have a wide spectrum of uses and economic importance. Certain alkanolamides are popular as foam boosters and stabilizers in liquid detergents. Alkanolamides produced from higher fatty acids find wide use as essential components in commercial products: detergents, shampoos, thickening agents, emulsifying and wetting agents, plasticizers, germicides and industrial cleaners (1-6). The fatty alkanolamides are products of condensation between an alkanolamine and a fatty acid or its derivative (methyl ester, triglyceride). Alkoxide catalysis had been used extensively by the industry to accelerate the aminolysis of fatty acid methyl esters and of triglycerides to mono-and diethanolamides (3,7,8,9). The reaction with a monoalkanolamine is more simple and rapid compared to that with a dialkanolamine because of the presence of one hydroxyl group and the higher reactivity of the primary amine function. In certain cases, in addition to the major product, monoalkanolamide, the ester of the starting monoalkanolamine can be obtained as byproduct. The composition of the reaction product depends on the conditions employed. Some tedious methods for quantitative determination of the alkanolamide formed are based on systematic separation and purification treatments of the crude reaction product (2) or on isolation and calculation of the unreacted fatty acid methyl ester (10,11). Homologous series of fatty acid alkanolamides have been separated by gas chromatography

(12). This method, however, requires their conversion into volatile derivatives before analysis. Few studies on qualitative HPLC separation of homologous series of fatty acid mono-and diethanolamides were carried out (13-15).

The purpose of the present work was to develop an HPLC method which enables simple and rapid quantitative separation, elution and determination of stearoyl monoalkanolamides directly in the crude reaction product without preliminary treatments. These studies are a further advance of our previous work on HPLC separation of homologous soybean fatty acid ethanolamides as well as their byproducts (16). The preparation of four structurally different monoalkanolamides of stearic acid was examined. They were synthesized according to reported methods (7,8,9,17) with certain modifications: the reactions were carried out at atmospheric pressure with a constant flow of nitrogen to expel the produced methanol. For each synthesis, the course of the reaction was followed by HPLC analysis of aliquots withdrawn periodically. In each case, the ratio of stearic-palmitic monoalkanolamides was, within experimental error, the same as that in the starting methyl ester (26:1). We therefore defined each detected derivative as stearoyl derivative.

The chromatographic results showed that the used monoalkanolamines react at different rates with methyl stearate. The stearoyl monoalkanolamides were obtained in high yields without measurable amounts of byproducts. Sometimes small amounts of the unreacted methyl stearate were eluted and

detected. The relatively low reaction temperature (100°C) possibly assures the synthesis of the monoalkanolamides without significant formation of byproducts.

The optimum eluent composition and flow rate as well as the column packing material were experimentally determined. The final reaction products were crystallized and repeated HPLC measurements confirmed their purification from impurities or unreacted methyl ester.

The crystallized "stearoyl monoalkanolamides" were characterized by m.p. determination, ir and nmr measurements and also by elemental microanalysis.

EXPERIMENTAL

Chemicals

The chemicals were used as received. Tetrahydrofuran, perchloric acid and ethanol (analytical grade) were obtained from Frutarom, Laboratory Chemicals Ltd., Haifa, Israel. Acetonitrile (HPLC grade) was purchased from Bio-Lab., Ltd., Jerusalem, Israel. Deionized water was twice distillated, first in the presence of potassium permanganate. Perchloric acid was used to adjust the pH of the water to 2.6. Methyl stearate (Edenor ME C18) was obtained from Henkel KGaA, Dusseldorf, West Germany. HPLC analysis of this material showed a purity of 96.3%. The minor component (3.7%) which first eluted was detected as methyl palmitate (see Figure 1). This analysis was verified by gas chromatographic measurements. Sodium methoxide (purified) was purchased from Fisher Scientific Company, New Jersey, U.S.A. The al-

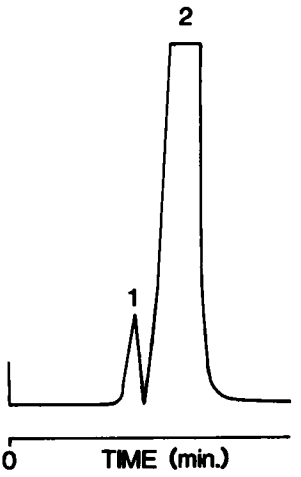

FIGURE 1: Reversed-phase HPLC chromatogram of the methyl stearate (Henkel). Peaks: 1 = methyl palmitate (RT = 6.97 min); 2 = methyl stearate (RT = 10.1 min).

kanolamines: 1-Amino-2-propanol, 3-Amino-1-propanol, 2-(Methylamino) ethanol and 2-Amino-2-methyl-1-propanol were of over 99% purity and obtained from Aldrich Chemical Company, Milwaukee, Wisconsin, U.S.A.

Instrumentation

Melting points were taken on a "Thermopan" microscope equipped with the Kofler Hot Stage, Reichert, Austria. The values of the m.ps were confirmed by measurements on a Mettler TA 3000 Thermal Analyzer/DSC, Mettler Instruments A.G., Greifensee, Switzerland. IR spectra were obtained on a Perkin-Elmer 257 Grating Infrared Spectrophotometer using a neat melt or film from chloroform solution. Nmr spectra were taken on a Varian FT-80A spectrophotometer at normal

operating temperature (25°C) for approximately 15% solution in deuterochloroform (Aldrich Chemical Company). The elemental analyses were provided by the microanalytical laboratory of the Hebrew University, Jerusalem.

The HPLC determinations were run on a Varian 5030 HPLC system. Differential Refractometer-R401 Waters Associates was used to detect the separated and eluted compounds. A reverse-phase type RP-9 Merck steel column (11.5 cm x 0.4 cm I.D.) packed with Ultrasphere Octyl F was used. The column was operated at ambient temperature. The detector was connected to a Hewlett-Packard 3390A integrator to record retention times, peak areas and percentage amounts.

HPLC Procedure

The compounds were eluted isocratically at a pressure of about 160 psis using an eluent composition of tetrahydrofuran-acetonitrile-water at pH 2.6 (37.5:37.5:25v/v). The eluent flow rate was 1 ml/min. The examined samples were dissolved in the eluent (4% w/v) by gentle warming as necessary. 20µl of the solution were injected via loop injector. To assure that the elution of the components is complete, the HPLC measurements were carried out up to 30 minutes.

Typical Amidation Procedure

Throughout this investigation, the molar ratio of amine to methyl stearate was 1.1:1.0.

To a four necked round bottom flask (500ml) were connected: a) a condenser with a receiving flask followed by a trap containing silicon oil to detect the leaving nitrogen; b) a ground-glass adapter to pass nitrogen through the reaction mixture. The adapter was connected via a trap (with silicon oil) to a cylinder of pure nitrogen; c) a glass stirrer; d) a thermometer.

0.4% (w/total weight of reactants) of sodium methoxide were introduced in the reaction vessel followed by 0.33 mole of the corresponding alkanolamine. Using constant agitation and gradual heating, a solution was obtained (approx. 80°C). Then 89.55 g. (0.3 mole) of methyl stearate were added. Passing a constant flow of nitrogen through the reaction medium, the temperature was elevated to 100°C and the reaction continued up to 2 hours. At the end of the reaction, the temperature was reduced to 90°C and 1.5ml of distilled water was added. After short, vigorous agitation, the product was transferred to a porcelain dish.

For m.p. determination, spectroscopic measurements and elemental microanalysis, portion of the final crude product was crystallized from hot ethanol (90%) solution and dried over silica gel under reduced pressure. Repeated HPLC analysis confirmed the absence of peaks from impurities or unreacted ester.

RESULTS AND DISCUSSION

Four structurally different monoalkanolamides were prepared:

A. Stearoyl-NH(2-hydroxy-propyl) amide.

$C_{17}H_{35}CONHCH_2CH(OH)CH_3$

B. Stearoyl-NH(3-hydroxy-propyl)amide.

$C_{17}H_{35}CONHCH_2CH_2CH_2OH$

C. Stearoyl-N(methyl), ethanolamide.

$C_{17}H_{35}CON(CH_3)CH_2CH_2OH$

D. Stearoyl-NH(1-methyl, 1-hydroxymethyl-ethyl) amide.

$C_{17}H_{35}CONHC(CF_3, CH_2OH)CH_3$

Certain properties of these monoalkanolamides are compiled in Table I.

TABLE I

Physical Properties of the Synthesized Monoalkanolamides of Stearic Acid.

Compound	Physical appearance	Mp*, °C	Formula***
A	white solid	85**	$C_{21}H_{43}NO_2$
B	white solid	96.9	$C_{21}H_{43}NO_2$
C	white solid	53-54	$C_{21}H_{43}NO_2$
D	white solid	68.1	$C_{22}H_{45}NO_2$

*After crystallization from hot 90% ethanol.

**86.1°C (18).

***All compounds were analyzed for C, H and N; the results were within ± 0.9% of the theoretical values.

HPLC Study

The course of the synthesis of each stearoyl monoalkanolamide was followed by HPLC analysis of aliquots withdrawn from the reaction mixture at definite periods. Each analysis was performed in duplicate. The replicate measurements showed a deviation of ± 0.04 min for the retention time and 1.2% for the values of percentage amount. HPLC chromatograms of the synthesized products contain two peaks for monoalkanolamides: at lower retention time from the palmitoyl monoalkanolamide followed by the peak from the major stearoyl monoalkanolamide. Figure 2 represents the HPLC chromatogram of product B (Table II; 100% monoalkanolamide). The chromatograms of the four synthesized derivatives showed that, in each case, the ratio of the percentage amounts of the two homologous monoalkanolamides remained the same (within experimental error) as that of the starting methyl esters (see Figure 1). As previously stated, starting material and products were calculated and are reported as stearic derivatives. Figure 3 represents the extent of formation of each type of monoalkanolamide against various reaction times.

HPLC analyses of prepared mixtures of methyl stearate and product B showed that sensitivity of the differential refractometer detector was almost equal for both components and that, for the purposes of this study, correction factors would be insignificant. Consequently, such correction factors were not applied.

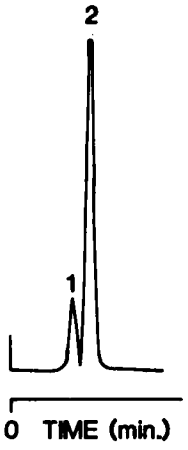

FIGURE 2: Reversed-phase HPLC chromatogram of compound B (see Table II); Peaks: 1 = the palmitoyl component (RT = 3.27 min); 2 = the stearoyl component (RT = 4.05 min).

TABLE II

HPLC Analysis Data for Four Synthesized Stearoyl Monoalkanolamides.*

Compound	Monoalkanolamide** percentage amount
A	88.6
B	100.0
C	100.0
D	92.9

*Reaction conditions: 2 hours at 100°C.

**Mean value of repeated experiments. The data relate to HPLC analysis of the crude final reaction product.

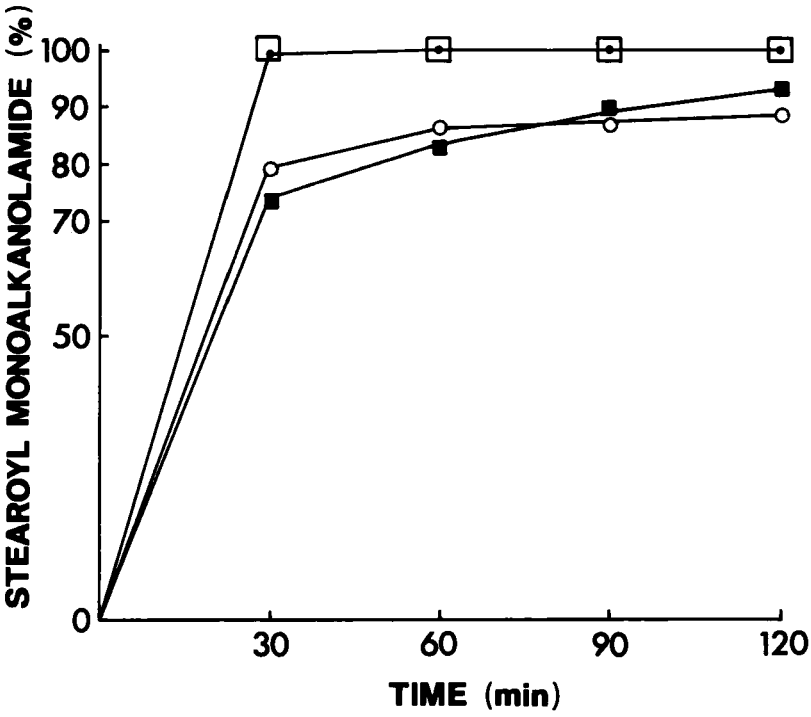

FIGURE 3: Rate of formation of the four stearoyl monoalkanolamides (reversed-phase HPLC analysis); o Compound A; ● Compound B; □ Compound C; ■ Compound D.

We wish to emphasize that the HPLC technique developed in our laboratory (16) enabled us to perform kinetic studies accurately and reproducibly. According to Figure 3, it may be concluded that up to 60 minutes the velocity of formation of compounds A and D is much slower. A possible explanation can be a steric effect on the reactivity of the corresponding monoalkanolamines. On the other hand, the synthesis of the compounds B and C was almost complete after 30 minutes. The percentage amount of each mono-

alkanolamide in the final crude product is presented in Table II.

Spectroscopic Studies

As additional characterization, the ir and nmr spectra of the compounds A-D were also run. The ir spectra showed characteristic bands at: 3320-3380 cm^{-1} for νNH and OH; 1634-1640 cm^{-1} for νC=O, amide; 1550 cm^{-1} for νN-H bending (this band was absent in the spectrum of compound C); 1053 cm^{-1} for νOH primary (this band was absent in the spectrum of compound A); 1100 cm^{-1} for νOH secondary (only in the spectrum of compound A); weak band at 720 cm^{-1} which belongs to the long normal alkyl residue. The ester carbonyl stretch at 1720 cm^{-1} was not observed in the case of compounds B and C and was quite weak in the spectrum of A and D.

The H-nmr spectra of compounds A, B and D showed one proton broad signal around 6.0 ppm for the N-H amidic. In the case of compound C, the three protons singlet at 3.06 ppm of $N-CH_3$ was observed. The spectrum of compound D showed the singlet at 1.42 ppm of the two $C-CH_3$ groups. The triplet (at 3.53-3.55 ppm) of the methylene group in the alkanol chain and bonded to the amidic nitrogen was observed in the spectrum of compounds B and C. The spectra of the four monoalkanolamides showed a three protons triplet at 1.25 ppm of the methyl group of the fatty chain.

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