Thermal Reactions of Fatty Acids with Diethylene Triamine

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ABSTRACT: The relative reactivities of the primary and secondary amino groups of diethylene triamine with fatty acids depend on the thermal reaction conditions. Without solvents, the primary amines are more reactive than the secondary amine for steric reasons, and the reaction results mainly in the 1,3-diamide. However, in dilute solution, the secondary amine shows higher reactivity than the primary amines, and the reaction proceeds probably by way of the 1,2-diamide, which forms imidazolines under much milder conditions than from the 1,3-diamide. The hydrolysis of imidazoline to the 1,2-diamide as the major product confirmed the higher reactivity of the secondary amine.
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KEY WORDS: Decanoic acid, 1,2- and 1,3-diamide, diethylene triamine, ^{1}H NMR, IR, MS and HPLC analysis, palmitic acid, thermal reaction.

SCHEME 1

Fatty imidazolines and fatty amides are used widely or are precursors for surface-active compounds (1,2). Industrially, imidazolines are prepared in a thermal reaction between diethylene triamine (DETA) with fatty acids, triglycerides, or methyl esters of fatty acids (3,4). However, the literature of this fatty acid–DETA reaction is contradictory. It is claimed that DETA reacts with fatty acids to form fatty acid monoamides **3** (Scheme 1), which can cyclize to imidazoline compounds **4** that contain a free primary amine group (5). Even though no structural evidence is given, the preparation of compounds **3** and **4** is still claimed in recent patents (6,7). Other researchers have reported that the reaction of DETA with fatty acids does not take place in a 1:1 molar ratio; hence fatty acid monoamides **3** and the related imidazoline derivatives **4** are unlikely (3,4,8). Additionally, discrepancies exist in the literature over the mechanism of the reaction, in particular the relative reactivities of the primary and secondary amines (3,4,8,9). To clarify the mechanism of this important thermal acylation reaction and to prepare fatty amides or imidazoline compounds that contain a free primary amine group, we have studied the reaction of fatty acids **1** and DETA **2,** and report here the results of our studies.

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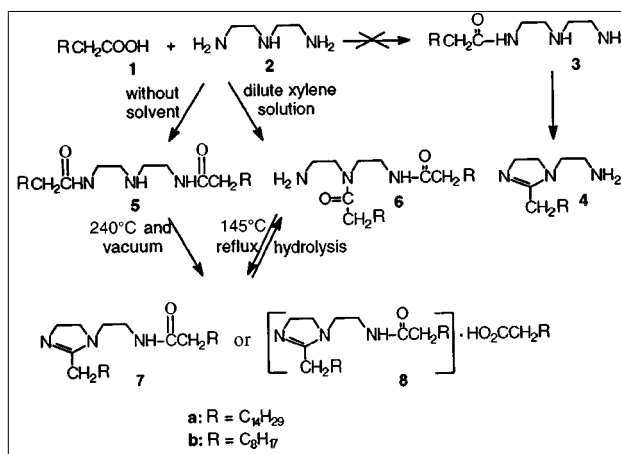
MATERIALS AND METHODS

Materials and instrumentation. Melting points were measured with an Electrothermal IA9300 digital apparatus. Infrared (IR) spectra were recorded on a (CO_2-free, dry air-purged) Digilab FTS-7 Fourier transform infrared (FTIR) spectrophotometer (Biorad, Cambridge, MA). [1]H nuclear magnetic resonance (NMR) (300 MHz) spectra ($CDCl_3$) were obtained with a Bruker AC-300 instrument (Bruker, Germany) (Me_4Si as reference). Mass spectra were measured in a Varian VG70-250S double-focusing magnetic-sector instrument (VG Analytical, Manchester, England) at 15 ev. A model 8452A diode-array spectrophotometer (Hewlett-Packard, Palo Alto, CA) was used for quantitative analysis of the Schiff base-forming reactions. The analysis procedure was as follows: 20–60 mg of fatty amine compound was dissolved in 2 mL $CHCl_3$ in a 10-mL volumetric flask. Glacial acetic acid (0.35 mL) and salicylaldehyde (0.60 mL) were added, and the flask was placed in a water bath at 30°C. After 1 h, the solution was made up to 10.0 mL with $CHCl_3$, and the absorption at 410 nm was measured. A molar absorptivity of 200 for all fatty amine compounds was used for all subsequent calculations (10). Analytical high-performance liquid chromatography (HPLC) was conducted with a Waters 600E pump (Millipore Corporation, Milford, MA), equipped with a Hewlett-Packard model 1050 ultraviolet (UV) detector and an RSIL-NH_2 column (Alltech Associates, Deerfield, IL)

(250 × 4.6 mm). Analytical-grade decanoic and palmitic acids (98%) and DETA (98%) (Riedel-de Haen, Germany) were used without further purification.

Thermal reactions with xylene as solvent. Reaction mixtures were refluxed in xylene (145°C) in a flask fitted with a Dean-Stark-type water trap. Temperature was measured directly with a thermometer immersed in the reaction mixtures. A solution of fatty acid (0.02 mol) in xylene (50 mL) was added dropwise by syringe to a solution of DETA (2.06 g, 0.02 mol) in xylene (25 mL) under reflux. After addition was complete (1 h), the reaction mixture was refluxed for 4 h. After removing the solvent, the residue was recrystallized from ethyl acetate to give the imidazoline–acid complex **8a** or **8b** (Scheme 1) as white crystals. For product **8a**: (4.15 g, 76%), m.p. 85–87°C; m/z 563 (MH$^+$, 100%), 282 (10%); υ_{max}/cm^{-1} 3424 (NH), 1648 (CO), 1607 (C=N), 1554 (complex NH); δ_H (300 MHz, CDCl$_3$) 0.88 (9 H, t, 3 CH$_3$), 2.15–2.25 (4 H, overlapping triplet, CH$_2$CO and CH$_2$R), 2.31 (2 H, t, CH$_2$CO), 3.33–3.58 (6 H, m, CH$_2$ · N · CH$_2$CH$_2$), 3.78 (2 H, t, CH$_2$ · N=C). For product **8b**: (2.68 g, 71%), m.p. 60–62°C; m/z 394 (MH$^+$, 100%), 198 (15%); υ_{max}/cm^{-1} 3300 (NH), 1646 (CO), 1609 (C=N), 1556 (complex NH); δ_H (300 MHz, CDCl$_3$) 0.88 (9H, t, 3 CH$_3$), 2.15–2.23 (4 H, overlapping triplet, CH$_2$CO and CH$_2$R), 2.38 (2 H, t, CH$_2$CO), 3.41–3.72 (6 H, m, CH$_2$ · N · CH$_2$CH$_2$), 3.82 (2 H, t, CH$_2$ · N=C).

Thermal reactions without solvent. DETA **2** (Scheme 1) (10.32 g, 0.1 mol) was heated to 150°C in a 50-mL round-bottom flask. Fatty acid **1a** (0.2 mol) or **1b** (0.1 mol) was added to the flask in small portions over 2 h. The reaction mixture was stirred at 150°C for 5 h. After cooling, the hard, waxy material was recrystallized from acetone/toluene (1:1) to give 1,3-diamide compound **5a** or **5b** (Scheme 1) as white crystals. For product **5a**: (17.85 g, 62%), m.p. 117–119°C; m/z 581 (MH$^+$, 100%), 282 (35%); υ_{max}/cm^{-1} 3287 (NH), 1636 (CO); δ_H (300 MHz, CDCl$_3$) 0.88 (6 H, t, 2 CH$_3$), 2.18 (4 H, t, 2 CH$_2$CO), 2.75 (4 H, t, CH$_2$ · N · CH$_2$), 3.33 (4 H, q, 2 CH$_2$ · NHCO). For product **5b**: (9.62 g, 78%), m.p. 109–110°C; m/z 412 (MH$^+$, 100%), 198 (40%); υ_{max}/cm^{-1} 3310 (NH), 1637 (CO); δ_H (300 MHz, CDCl$_3$) 0.87 (6 H, t, 2 CH$_3$), 2.19 (4 H, t, 2 CH$_2$CO), 2.75 (4 H, t, CH$_2$ · N · CH$_2$), 3.33 (4 H, q, 2 CH$_2$ · NHCO).

The 1,3-diamide **5a** (4.76 g, 8.20 mmol) or **5b** (1 g, 2.43 mmol) was placed into a 50-mL round-bottom flask and heated at 240°C under reduced pressure (30 mm Hg) for 0.5 h. The residue was crystallized from hexane to give imidazoline **7a** or **7b** (Scheme 1) as fine white crystals. For product **7a**: (4.33 g, 94%), m.p. 80–82°C; m/z 563 (MH$^+$, 100%), 282 (12%); υ_{max}/cm^{-1} 3321 (NH), 1643 (CO) 1609 (C=N); δ_H (300 MHz, CDCl$_3$) 0.88 (6H, t, 2 CH$_3$), 2.12–2.20 (4 H, q, CH$_2$CO and CH$_2$R), 3.19 (2 H, t, N · CH$_2$), 3.27 (2 H, t, CH$_2$ · N), 3.39 (2 H, q, CH$_2$ · NHCO), 3.69 (2 H, t, CH$_2$ · N=C). For product **7b**: (0.88 g, 92%), m.p. 54–55°C; m/z 394 (MH$^+$, 100%), 198 (10%); υ_{max}/cm^{-1} 3285 (NH), 1646 (CO), 1607 (C=N); δ_H (300 MHz, CDCl$_3$) 0.88 (6 H, t, 2 CH$_3$), 2.12–2.20 (4 H, q, CH$_2$CO and CH$_2$R), 3.19 (2 H, t,

N · CH$_2$), 3.27 (2 H, t, CH$_2$ · N), 3.38 (2 H, q, CH$_2$ · NHCO), 3.68 (2 H, t, CH$_2$ · N=C). Analysis of compounds **5** and **7** by Schiff base showed that both contained no primary amine.

*Hydrolysis of imidazoline **7**.* Imidazoline **7a** or **7b** (1 g each) was added separately to 20 mL of EtOH/H$_2$O (1:1), and the reaction mixture was refluxed for 3 h. After removing the solvent under reduced pressure, the crude product was recrystallized twice from EtOH to give white crystals. For product **6a**: (0.8 g, 78%). ^{1}H NMR analysis of the product revealed that it consisted of 60% compound **6a** (Scheme 1), 25% compound **5a**, and 15% of starting material **7a**. The analytical sample of **6a** was obtained as white crystals by repeated recrystallization from ethanol: m.p. 104–106°C (decompose); m/z 581 (MH$^+$, 75%), 564 (32%), 282 (100%); υ_{max}/cm^{-1} 3283 (NH), 1621 (CO); δ_H (300 MHz, CDCl$_3$) 0.88 (6 H, t, 2 CH$_3$), 2.13 (2 H, t, CH$_2$CO), 2.36 (2 H, t, CH$_2$CO), 2.95 (2 H, t, CH$_2$ · NH$_2$), 3.34–3.44 (4 H, m, CON · CH$_2$CH$_2$ · NCO), 3.54 (2 H, t, CON · CH$_2$). For product **6b**: the IR analysis of residue showed no imidazoline **7b** present. After removing 1,3-diamide **5b** (0.35 g, 33%) by repeating recrystallization from ethyl acetate first, the analytical sample of **6b** (0.66 g, 63%) was obtained as white crystals by repeated recrystallization of residue from ether: m.p. 75–76°C (decompose); m/z 412 (MH$^+$, 95%), 395 (40%), 198 (100%); υ_{max}/cm^{-1} 3283 (NH), 1621 (CO); δ_H (300 MHz, CDCl$_3$) 0.88 (6 H, t, 2 CH$_3$), 2.16 (2 H, t, CH$_2$CO), 2.36 (2 H, t, CH$_2$CO), 2.94 (2 H, t, CH$_2$ · NH$_2$), 3.33–3.44 (4 H, m, CON · CH$_2$CH$_2$ · NCO), 3.54 (2 H, t, CON · CH$_2$). The Schiff base reaction of compounds **6** showed that both **6a** and **6b** contained primary amino groups.

HPLC analysis. The diamide compounds **5a** and **6a** (10–15 mg) were dissolved separately in 1 mL of mobile phase (cyclohexane/CH$_3$OH/CHCl$_3$, 4:3:3), and 5 µL of the resulting solutions was injected onto an RSIL-NH$_2$ column for analysis (isocratic for 15 min; flow rate: 0.5 mL/min; detection at 230 nm). Retention times given later in Figure 2 are quoted ±σ, based on 3–4 replicate determinations.

RESULTS AND DISCUSSION

Thermal reaction of palmitic acid with DETA. The reaction of fatty acids with DETA involves two main sequential steps (diamide and imidazoline), which proceed as the temperature is raised. The products and intermediates vary, depending on the reaction conditions used (Scheme 1). When equimolar quantities of palmitic acid **1a** or two molar equivalent of decanoic acid **1b** and DETA **2** are heated at 150°C for 7 h without solvent, the 1,3-diamides **5a** and **5b** are formed in 62 and 78% yield, respectively. After separation and purification, two 1,3-diamides **5** are separately cyclized to the relative imidazolines **7** in 94 or 92% yield by heating at 240°C under vacuum (30 mmHg) for 0.5 h. On the other hand, when an equimolar amount of fatty acid **1a** or **1b** was slowly added to a dilute solution of DETA **2** in xylene and refluxed at 145°C for 5 h, high yields of imidazoline-acid complexes **8** (76% for **8a** and 68% for **8b**) were obtained.

Although in general, the secondary amine of polyamine compounds has greater nucleophilicity with most electrophilic reagents, the primary amine function is more reactive for steric reasons (11). Hence, the reaction pathway of fatty acids with DETA strongly depends on the concentration of reactants. Without solvent, the relative reactivities of the primary and secondary amino groups appear to be governed by steric interactions. Thus, the primary amine is more reactive than the secondary amine in that the 1,3-diamides **5** are the main reaction products. Traditionally, formation of imidazoline compounds **7** from the 1,3-diamides **5** requires severe reaction conditions (high temperature and vacuum or long reaction times) (3,8,9). In the present work, when a highly dilute solution of **1** and **2** was used, amide formation took place with the more reactive secondary amine position, and the reaction proceeded probably by way of 1,2-diamides **6** (Scheme 1), which led to the imidazoline compounds **8** in good yield under mild reaction conditions. The imidazoline–acid complexes **8** can be used directly in most cases, or they can be dissociated to the imidazolines **7** under alkaline conditions (8).

The hydrolysis of imidazoline **7a** or **7b** in refluxing EtOH/H$_2$O (1:1) gave the 1,2-diamide **6a** (60%) or **6b** (65%) as the major kinetic product (12), not the 1,3-diamides **5,** which have been incorrectly reported in the literature (9). This result confirmed the higher reactivity of the secondary amino group. This result is also in agreement with a previous report (3) that the secondary amine group of DETA is more reactive than the primary amino group under thermal acylation conditions, but no structural assignments were given. Also, in that work, the pure 1,2-diamides were only isolated from the hydrolysis of imidazoline compounds under conditions similar to those used in the present work. In the present work, the 1,2-diamides **6** were the major kinetic products of hydrolysis (12), but the relative reactivity of the primary and secondary amines in the forward thermal acylation depends on the conditions employed.

The previously reported primary monoamide compounds **3** and their imidazoline derivatives **4** (Scheme 1) were not encountered by us, even when equimolar amount of fatty acids were slowly added to the DETA (with or without solvent). Hence, it was not possible to control conditions to obtain the primary monoamides **3** by a simple thermal reaction. The selective acylation of two primary amines by active ester (13) is probably the best approach to make the fatty primary monoamide compounds **3.**

Structure determinations and HPLC analysis. The structures of all diamides **5, 6** and imidazoline compounds **7, 8** shown in Scheme 1 were established from their IR, ^{1}H NMR, mass spectra, and by HPLC analysis. The selective Schiff base-forming reaction between salicylaldehyde and primary amines in the presence of acetic acid, which can be monitored easily by UV at 410 nm, was also helpful in structural assignments (10). The diamides **5** and **6** and imidazolines **7** and **8** showed C=O stretching at 1620 and 1640 cm^{-1} or C=N bands at 1605–1610 cm^{-1}, respectively. ^{1}H NMR spectra (the Materials and Methods section) were consistent with the assigned

structures. Major differences among the diamide compounds **5a, 6a** and imidazoline **7a** were shown in their ^{1}H NMR spectra (Fig. 1). Compounds **5** and **7** failed to form a colored Schiff base with salicylaldehyde, indicating the absence of a primary amine group in these compounds. However, compounds **6** had an absorbance that corresponded to the presence of 1 molar equivalent primary amine. This technique proved useful in distinguishing between the 1,3-diamides **5** and 1,2-diamides **6.** Mass spectra of the diamides **5** and **6** showed molecular ion peaks *m/e* 581 and 412 for the different fatty diamides, and the imidazolines **7** and **8** showed molecular ion peaks *m/e* 563 and 394, respectively. A peak at *m/e* of 282 or 198 corresponded to the fragment (C$_{15}$H$_{31}$CON-HCH$_2$CH$_2$)$^+$ or (C$_9$H$_{19}$CONHCH$_2$CH$_2$)$^+$, formed by γ-cleavage of all diamide compounds. However, for the 1,2-diamide derivatives **6,** a second γ-cleavage was observed at *m/e* 564 or 395 (M − NH$_2$)$^+$, which also indicated a free primary amine group present in compound **6a** or **6b** and helped to distinguish between the 1,2-diamides **6** and the 1,3-diamides **5.** Differences between imidazoline compounds **7** and their acid–com-
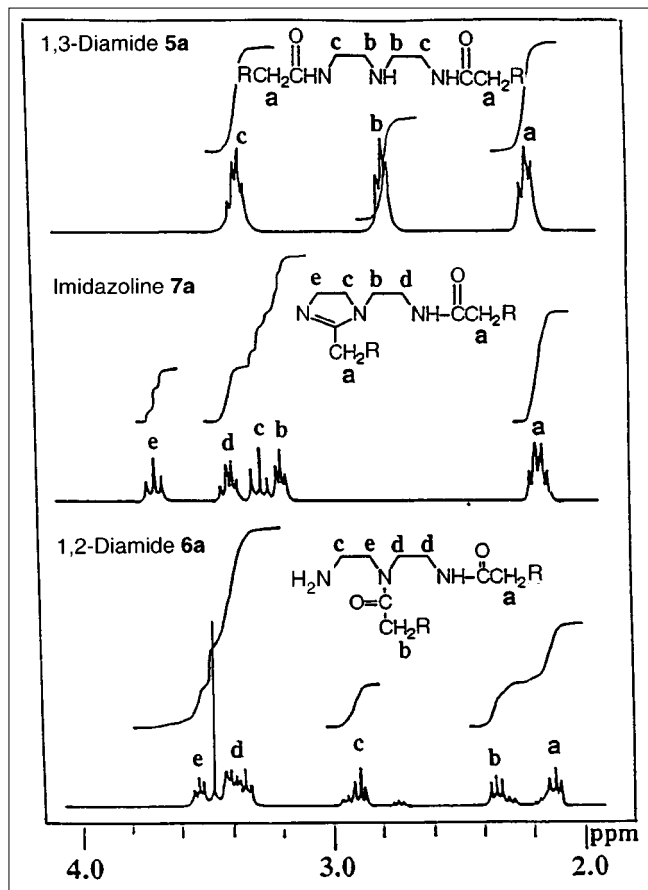

FIG. 1. Parts of the ^{1}H nuclear magnetic resonance (NMR) spectra of 1,3-diamide **5a,** 1,2-diamide **6a,** and imidazoline **7a** that show the major differences in proton chemical shifts among them. The same ^{1}H NMR chemical shifts were observed for compounds **5b, 6b,** and **7b** in the ranges of 2 to 4 ppm.
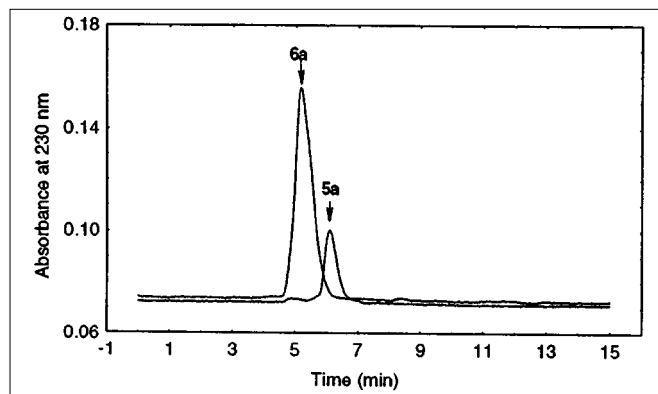
FIG. 2. High-performance liquid chromatograms of 1,3-diamide **5a** (6.10 min) and 1,2-diamide **6a** (5.15 min) (retention time, ±0.01 min).

plexes **8** were noted in their ^{1}H NMR spectra. The molar ratio of fatty acids to DETA is 2:1 for compounds **7,** while for compounds **8** it is 3:1. However, the nature of these imidazoline complexes **8** is not clear (14).

Structural differences between the 1,3-diamide **5a** and 1,2-diamide **6a** were established further by HPLC analysis (Fig. 2). Because the fatty amide compounds have low UV absorption maxima (230 nm) and low solubility in most solvents, previous HPLC analyses were made with refractive index detectors and large injection volumes (15,16). The solvent system, cyclohexane/CH_3OH/$CHCl_3$ (4:3:3), used in the present work allowed for UV detection at 230 nm. The relatively high solubility of the fatty amides in this mobile phase enabled high concentration solutions to be prepared, and hence, a small injection volume (5 µL) to be used.

ACKNOWLEDGMENT

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