Kinetic Study on the Esterification of Hexanoic Acid with *N,N*-Dialkylamino Alcohols: Evidence for an Activation by Hydrogen Bonding

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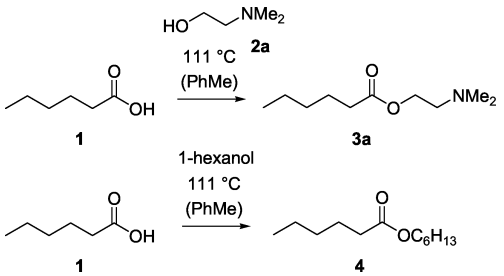
The pseudo-first order rate constant for the esterification of hexanoic acid (**1**) and five different *N*,*N*-dialkylamino alcohols (**2**) was determined in comparison to 1-hexanol ($k = 0.67 \cdot 10^{-5}$ s^{-1}). The values range from $0.60 \cdot 10^{-5}$ s^{-1} to $9.3 \cdot 10^{-5}$ s^{-1}. The data suggest a differing reactivity for structurally related compounds, which is directly correlated to the ability of the corresponding amino alcohol to activate the carboxylic acid by hydrogen bonding. A seven-membered transition state $\mathbf{C}^{\neq}$ is postulated for reactions of 2-amino alcohols. The fastest reaction was observed for *trans*-2-(*N*,*N*-dimethylamino)cyclohexanol (**2e**), in which the amino and the hydroxyl groups are in an almost perfect synperiplanar 1,2-position. Attempts to further enhance the rate of the esterification by the addition of potential catalysts failed. Only $Cu(OTf)_2$ (2.5 mol-%) allowed for a moderate rate increase from $7.5 \cdot 10^{-5}$ s^{-1} (uncatalyzed) to $14.8 \cdot 10^{-5}$ s^{-1} (catalyzed) in the esterification of hexanoic acid (**1**) with 2-(*N*,*N*-dimethylamino)ethanol (**2a**).

Key words: Acylation, Amino Alcohols, Hydrogen Bonds, Kinetics, Transition States

Introduction

The esterification of an alcohol with a carboxylic acid is one of the best known and probably one of the oldest chemical reactions [1]. It proceeds most commonly by a nucleophilic attack of the alcohol at the carboxylic group of the ester ($A_{Ac}2$ mechanism) [2]. While plenty of data has been amassed over the decades on this reaction, some mechanistic details still remain unravelled. We became interested in the reaction of the title compounds with carboxylic acids in connection with the industrially important cross-linking of polycarboxylic acids and triethanolamine [3]. This process is routinely carried out at 180 – 200 °C and it was our goal to elucidate the mechanism of this reaction more closely and to evaluate possible catalysts. The test reaction which we established is depicted in Scheme 1. Hexanoic acid (**1**) and 2-(*N*,*N*-dimethylamino)ethanol (**2a**) were converted into the corresponding ester **3a**. For comparison, the kinetics of the esterification of hexanoic acid with 1-hexanol were also recorded. Remarkably, it turned out that the former reaction proceeds at 111 °C (refluxing toluene) in the absence of a catalyst ten times faster than the latter reaction. It was shown by varying the amino alcohol that the rate of the esterification is heavily dependent on its ability to activate the carboxylic acid by intermolecular hydrogen bonding. In this paper we provide full details of our work in this area and discuss the mechanism of the process. The rate of the esterification of amino alcohol **2a** was shown to be *not* significantly influenced by acidic catalysts.



Scheme 1. Esterification of hexanoic acid (**1**) with amino alcohol **2a** and 1-hexanol.

Results

Kinetic studies

The alcohol **2a** (or 1-hexanol) ($c = 0.125$ M) was converted into the corresponding ester **3a** (or **4**) under

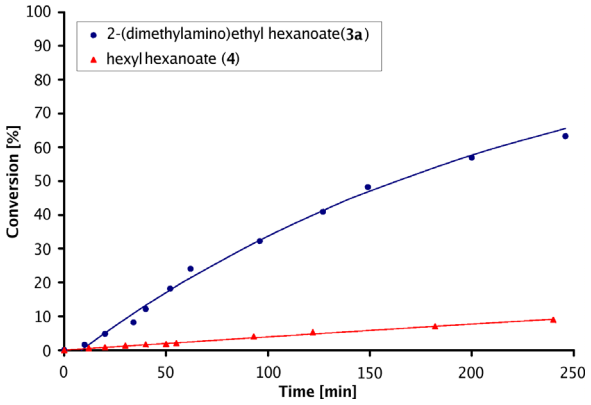


Fig. 1. Uncatalyzed conversion of 1-hexanol and 2-(*N*,*N*-dimethylamino)ethanol (**2a**) to the corresponding hexanoates **3a** and **4**.

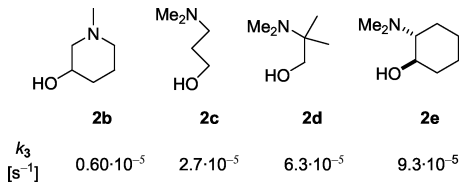
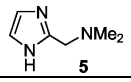


Fig. 2. Pseudo-first order rate constants for the esterification of hexanoic acid with amino alcohols **2b** – **2e** in toluene at 111 °C to the corresponding esters **3b** – **3e**.

pseudo-first order reaction conditions. A tenfold excess of the carboxylic acid was used and the kinetics were studied by GLC analysis using an internal standard (see Experimental Section). The water was removed to guarantee an irreversible reaction. In preliminary experiments it was shown that Na_2SO_4 is best suited for this purpose while the water removal by 4 Å molecular sieves or by a Dean-Stark trap was incomplete. Fig. 1 depicts the product development (conversion) for compounds **3a** and **4** with respect to time in an uncatalyzed esterification. The conversion was recorded upon addition of the amino alcohol to the acid in refluxing toluene (111 °C). From these data the pseudo-first order rate constants were calculated as $k_{\mathbf{3a}} = 7.5 \cdot 10^{-5}$ s^{-1} and $k_{\mathbf{4}} = 0.67 \cdot 10^{-5}$ s^{-1}. In other words, the reaction of amino alcohol **2a** occurs ten times faster than the reaction of an aliphatic primary alcohol such as 1-hexanol.

For comparison other amino alcohols **2** were studied. While amino alcohols **2b** – **2d** are commercially available, *trans*-2-(*N*,*N*-dimethylamino)cyclohexanol (**2e**) was prepared from *trans*-2-aminocyclohexanol by reductive amination [4]. The compounds are listed in Fig. 2 and the rate constants for the formation

Table 1. The effect of potentially active catalytic additives in the reaction **2a** → **3a**.

Entry	Catalyst[a]	Amount [mol-%]	r^{2}[b]	$k_{\mathbf{3a}}$[a] [s^{-1}]
1	NaH_2PO_2	2.5	0.983	$7.3 \cdot 10^{-5}$
2	H_3PO_2	2.5	0.999	$8.7 \cdot 10^{-5}$
3	$Yb(OTf)_3$	2.5	0.995	$6.8 \cdot 10^{-5}$
4	$Cu(OTf)_2$	2.5	0.992	$14.8 \cdot 10^{-5}$
5	$Fe_2(SO_4)_3$[c]	1.0	0.991	$9.5 \cdot 10^{-5}$
6	$P(C_6F_5)_3$	2.5	0.995	$10.5 \cdot 10^{-5}$
7	PPh_3	2.5	0.990	$9.3 \cdot 10^{-5}$
8	imidazole	5.0	0.994	$10.0 \cdot 10^{-5}$
9	 **5**	2.5	0.986	$8.0 \cdot 10^{-5}$

[a] For experimental details, see the Experimental Section; [b] the coefficient of determination is provided as square of Pearson's correlation coefficient *r*; [c] the experiment was carried out in a Dean-Stark trap apparatus without the addition of Na_2SO_4.

of the corresponding hexanoates are given. The rate constants vary by a factor of 15. The fastest reaction was observed with the conformationally restricted *trans*-amino alcohol **2e**. A small induction period (up to 10 min) was noticed in almost all esterification reactions of the amino alcohols. This period was subtracted from the elapsed time and it was not taken into account when fitting the curve to the monoexponential regression. In general, 10 – 12 data points were obtained (see Fig. 1) and the coefficient of determination r^2 varied in all measurements between 0.991 and 0.997. Several of the measurements were repeated for accuracy. The variation of the data was within the experimental error ($\Delta k = \pm 5\%$). It was shown that the reaction **2a** → **3a** proceeded to full conversion.

Catalysis experiments were carried out under the conditions specified above. The well established acid catalysis was nicely corroborated by the esterification of 1-hexanol. Upon addition of 1 mol-% of *para*-toluenesulfonic acid (*p*-TsOH) the pseudo-first order rate constant increased from $k_{\mathbf{4}} = 0.67 \cdot 10^{-5}$ s^{-1} (uncatalyzed) to $k_{\mathbf{4}} = 4.5 \cdot 10^{-5}$ s^{-1}. With 2.5 mol-% of *p*-TsOH the value $k_{\mathbf{4}}$ increased further to $13.8 \cdot 10^{-5}$ s^{-1}. Contrary to these results, *p*-TsOH did not influence the rate of the esterification with amino alcohol **2a**. The rate constant $k_{\mathbf{3a}}$ remained unchanged within the range of error. Other catalysts were screened. Support for the claimed catalytic effect of phosphinic acid [5] was not obtained (entries 1, 2). Among the Lewis acids screened, most of them had no or only a small effect. As examples the data for ytterbium trifluoromethanesulfonate ($Yb(OTf)_3$, entry 3), iron(III) sulfate (entry 5), and tris(pentafluorophenyl)phosphane (entry 6)

are provided in Table 1. Only the twofold rate increase observed with $Cu(OTf)_2$ was significant. Other nucleophilic catalysts (entries 7–9) had a limited influence, the rate constant $k_{\mathbf{3a}}$ barely exceeding the value for the uncatalyzed reaction ($k_{\mathbf{3a}} = 7.5 \cdot 10^{-5}$ s^{-1}).

Discussion

Kinetic data for the esterification of carboxylic acids with 2-amino alcohols are rare [6]. The reverse reaction, however, *i.e.* the saponification and hydrolysis of 2-aminoalkyl esters, has been intensively studied [7]. An example for an early kinetic study concerns the aminocyclitol derivatives depicted in Fig. 3. Hydrolyses of these compounds were carried out at 25 °C in a supporting aqueous medium containing 0.088 M NaCl as electrolyte and 12.5% *v*/*v* methanol at pH = 7.7. The first-order rate constant for the hydrolysis of the *scyllo*-diastereoisomer **6** was determined as $2.2 \cdot 10^{-5}$ s^{-1}. The *myo*-diastereoisomer **7** was hydrolyzed more slowly with a rate constant of $1.0 \cdot 10^{-5}$ s^{-1} [7a].

Hansen summarized previous work in the field [7b] and concluded that "the mechanism of the hydrolysis of tertiary aminoalkyl esters in alkaline solution is better explained in terms of an intramolecular hydrogen bonding than by any other mechanism." The suggested transition state leading to the tetrahedral intermediate **B** can be written as $\mathbf{A}^{\neq}$ with either a water molecule (as in $\mathbf{A}^{\neq}$) or a hydroxide ion as the nucleophile (Fig. 4). For the given example in Fig. 3 the *scyllo*-diastereoisomer **6** can adopt such a transition state more readily than the *myo*-diastereoisomer **7**. In **6** the all-equatorial arrangement of the substituents facilitates the approach of the oxygen nucleophile. Hansen ended his account with the words "In order to confirm this result it would be interesting to study some compounds in which the hydrogen bond for steric reasons is very unlikely".

The results we collected in the esterification of hexanoic acid with amino alcohols **2** lend support to a related transition state $\mathbf{C}^{\neq}$ in the rate-determining step of this transformation. The intermediate **B** is formed by attack of the amino alcohol at the carboxyl group, which is in turn activated by hydrogen bonding to the protonated amino group of **2**. Based on the pK_a values tabulated for hexanoic acid ($pK_a = 4.89$) [8] and *N*,*N*-dialkylamino alcohols [*e.g.* 2-(*N*,*N*-dimethylamino)ethanol: $pK_a = 9.42$] [9] the amino alcohols are almost quantitatively protonated under the reaction conditions. The activation *via* a seven-membered transition state nicely explains the rate difference observed for 1-hexanol and compound **2a**. If the formation of a cyclic transition state is restricted or even impossible the rate constants for the esterification decrease. Amino alcohol **2b** served as a model for a conformationally locked 2-(*N*,*N*-dialkylamino)ethanol with the hydroxyl group and the amino group in an antiperiplanar arrangement, which cannot react *via* transition state $\mathbf{C}^{\neq}$. The rate of the esterification is consequently as low ($k_{\mathbf{3b}} = 0.60 \cdot 10^{-5}$ s^{-1}) as for 1-hexanol ($k_{\mathbf{4}} = 0.67 \cdot 10^{-5}$ s^{-1}). For 3-(*N*,*N*-dimethylamino)propanol (**2c**) a cyclic transition state is feasible but the eight-membered ring transition state is disfavoured ($k_{\mathbf{3c}} = 2.7 \cdot 10^{-5}$ s^{-1}) compared to the transition state of its nor-analogue **2a** ($k_{\mathbf{3a}} = 7.5 \cdot 10^{-5}$ s^{-1}). Similar arguments hold for the formation of esters **3d** and **3e**. The slightly lower rate constant for **2d** ($k_{\mathbf{3d}} = 6.3 \cdot 10^{-5}$ s^{-1}) suggests that the *gem*-dimethyl substitution and the increased steric strain induced by the additional methyl groups cancel out each other while amino alcohol **2e** as a model for a conformationally locked synperiplanar 2-(*N*,*N*-dialkylamino)ethanol reacted fastest ($k_{\mathbf{3e}} = 9.3 \cdot 10^{-5}$ s^{-1}).

The results obtained with the various additives (Table 1) are subtle and more difficult to explain. Their influence was apparently not very pronounced, only $Cu(OTf)_2$ leading to a significant rate increase (entry 4). In this instance, the Lewis acidic copper cation presumably coordinates to the oxygen of the carboxyl group and further enhances its electrophilicity. Nucleophilic catalysis was suspected to be responsible for the rate increase observed with imidazole (Table 1, entry 8). However, an attempt to further increase the reaction rate by introducing an amino methyl group into

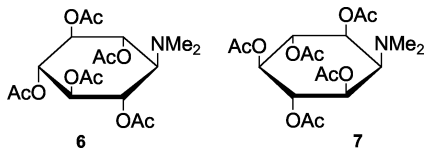


Fig. 3. Structure of the aminocyclitols **6** and **7**, the hydrolyses of which was studied by Holland *et al.* [7a].

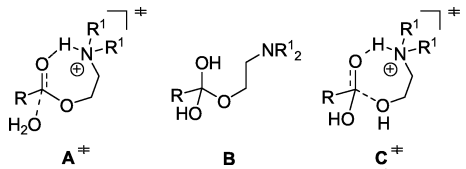


Fig. 4. Structure of the two transition states $\mathbf{A}^{\neq}$ (ester hydrolysis) and $\mathbf{C}^{\neq}$ (esterification) leading to the presumed tetrahedral intermediate **B**.

the imidazole (**5**, entry 9) disappointingly failed. We therefore conclude that an efficient catalyst for the esterification of *N*,*N*-dialkylamino alcohols has not been found.

In summary, our study has proven that the activation of carboxylic acid derivatives by hydrogen bonding, which has been earlier postulated for the saponification of 2-aminoalkyl esters, is responsible for a rate increase in the esterification of 2-(*N*,*N*-dialkylamino) alcohols. It was shown by variation of the amino alcohols that the esterification rate constant is high for substrates which favor an intermolecular hydrogen bonding. Contrary to this, 2-(*N*,*N*-dialkylamino) alcohols which for steric reasons cannot form an intermolecular hydrogen bond (*e. g.* substrate **2b**) react with the same rate constant as normal aliphatic alcohols such as 1-hexanol.

Experimental Section

General remarks

2-(*N*,*N*-Dimethylamino)-2-methyl-1-propanol and common solvents [ethyl acetate, toluene, methanol (MeOH) and dichloromethane (DCM)], were distilled prior to use. All other amino alcohols, 1-hexanol, hexanoic acid and all other reagents were used as received. IR: Perkin Elmer 241 FT-IR. GC-MS: Agilent 6890 (GC system, flow: 1.3 ml/min, column: HP 5MS (30 m), temperature: 50 → 250 °C at 10 °C/min, 10 min at 250 °C), Agilent 5973 (Mass selective detector). ^{1}H and ^{13}C NMR: Bruker AV-360 and AV-500. Chemical shifts are reported relative to tetramethylsilane as internal reference. Apparent multiplets that occur as a result of accidental equality of coupling constants to magnetically non-equivalent protons are marked as virtual (virt.). The multiplicities of the ^{13}C NMR signals were determined by DEPT experiments. TLC: Merck glass sheets 0.25 mm silica gel 60-F_{254}. Detection by coloration with Bromocresol Green. Flash chromatography: Merck silica gel 60 (230 – 400 mesh) (*ca.* 50 g for 1 g of material to be separated), eluent given in brackets.

General procedure for preparation of esters **3**

Amino alcohol **2** (5.0 mmol) was added to a refluxing solution of hexanoic acid (6.31 ml, 5.81 g, 50.0 mmol), dodecane (100 μl, 75.3 mg, 442 μmol) and Na_2SO_4 (6.0 g) in toluene (40 ml). The corresponding ester **3** was obtained from the reaction mixture of the kinetic experiment after complete data collection (5 h). At ambient temperature the reaction mixture was washed with saturated Na_2CO_3 (3 × 50 ml), brine (50 ml) and was dried with Na_2SO_4. After filtration, the solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica, DCM/MeOH = 15 : 1). Average yields were around 70 – 75% after chromatography.

2-(N,N-Dimethylamino)ethyl hexanoate (**3a**)

The reaction was carried out according to the general procedure with 2-(*N*,*N*-dimethylamino)ethanol (**2a**) (502 μl, 496 mg, 5.00 mmol). – $R_f = 0.34$ (DCM/MeOH, 12 : 1). – ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 0.83$ (t, $^3J = 6.9$ Hz, 3 H, C*H*$_3$CH$_2$), 1.18 – 1.32 (m, 4 H, CH$_3$C*H*$_2$C*H*$_2$), 1.56 (virt. qu, $^3J \cong 7.5$ Hz, 2 H, C*H*$_2$CH$_2$CO), 2.23 (s, 6 H, N(CH$_3$)$_2$), 2.27 (t, $^3J = 7.5$ Hz, 2 H, CH$_2$CO), 2.50 (t, $^3J = 5.7$ Hz, 2 H, CH$_2$O), 4.11 (t, $^3J = 5.7$ Hz, 2 H, CH$_2$N) ppm. – ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 14.0$ (q, *C*H$_3$CH$_2$), 22.4 (t, CH$_3$*C*H$_2$), 24.6 (t, *C*H$_2$CH$_2$CO), 31.3 (t, CH$_3$CH$_2$*C*H$_2$), 34.2 (t, *C*H$_2$CO), 45.8 (s, N(CH$_3$)$_2$), 57.9 (t, CH$_2$N), 62.0 (t, *C*H$_2$CO), 174.0 (s, CO) ppm. – IR (NaCl): $\tilde{\nu} = 2957$ cm^{-1} (vs, C-H), 2861 (s, C-H), 2821 (s, C-H), 2770 (s, C-H), 1737 (vs, C=O), 1456 (s), 1377 (m), 1244 (s), 1171 (vs, C-O), 1100 (s), 1042 (s), 968 (m), 850 (m), 782 (m), 734 (m). – GC-MS (EI, 70 eV, $t_R = 10.5$ min): m/z(%) = 99 (1) [$C_6H_{11}O^+$], 72 (6) [$C_4H_{10}N^+$], 58 (100) [$C_3H_8N^+$]. – $C_{10}H_{21}NO_2$ (187.28): calcd. C 64.13, H 11.30, N 7.48; found C 64.00, H 11.42, N 7.43.

1-Methyl-3-piperidyl hexanoate (**3b**)

The reaction was carried out according to the general procedure with 3-hydroxy-1-methylpiperidine (**2b**) (576 μl, 576 mg, 5.00 mmol). – $R_f = 0.48$ (DCM/MeOH, 12 : 1). – ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 0.87$ (t, $^3J = 6.3$ Hz, 3 H, C*H*$_3$CH$_2$), 1.26 – 1.32 (m, 4 H, CH$_3$C*H*$_2$C*H*$_2$), 1.40 – 1.47 (m, 1 H, CHC*H*HN), 1.55 – 1.64 (m, 3 H, C*H*$_2$CH$_2$CO / CH$_2$C*H*HN), 1.73 – 1.79 (m, 2 H, CH*H*NCH*H*), 2.24 – 2.33 (m, 7 H, CH$_2$CO / C*H*HCH*H*N / NCH$_3$), 2.38 – 2.43 (m, 1 H, CH*H*CHHN), 2.60 – 2.65 (m, 1 H, CH$_2$CH*H*CHO), 4.85 – 4.90 (m, 1 H, CHO) ppm. – ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 14.0$ (q, *C*H$_3$CH$_2$), 22.4 (t, CH$_3$*C*H$_2$), 22.6 (t, CH$_2$*C*H$_2$N), 24.8 (t, *C*H$_2$CH$_2$CO), 28.9 (t, CH*C*H$_2$N), 31.4 (t, CH$_3$CH$_2$*C*H$_2$), 34.6 (t, *C*H$_2$CO), 46.5 (q, NCH$_3$), 55.5 (t, *C*H$_2$CH$_2$N), 59.3 (t, CH$_2$*C*H$_2$CHO), 69.2 (d, CHO), 173.5 (s, CO) ppm. – IR (NaCl): $\tilde{\nu} = 2941$ cm^{-1} (vs, C-H), 2860 (s, C-H), 2783 (s, C-H), 1732 (vs, C=O), 1467 (s), 1245 (s), 1172 (vs, C-O), 1013 (s), 978 (m), 914 (w), 872, (m), 787 (w), 734 (w). – GC-MS (EI, 70 eV, $t_R = 13.2$ min): m/z(%) = 114 (1) [$C_6H_{12}NO^+$], 99 (5) [$C_6H_{11}O^+$], 97 (100) [$C_6H_{11}N^+$]. – $C_{12}H_{23}NO_2$ (213.32): calcd. C 67.57, H 10.87, N 6.57; found C 67.21, H 11.03, N 6.57.

3-(N,N-Dimethylamino)-1-propyl hexanoate (**3c**)

The reaction was carried out according to the general procedure with 3-(*N*,*N*-dimethylamino)propanol (**2c**) (592 μl, 516 mg, 5.00 mmol). – $R_f = 0.15$ (DCM/MeOH, 12 : 1). –

^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 0.87$ (t, $^3J = 6.9$ Hz, 3 H, C*H*$_3$CH$_2$), 1.23 – 1.36 (m, 4 H, CH$_3$C*H*$_2$C*H*$_2$), 1.60 (virt. qu, $^3J \cong 7.5$ Hz, 2 H, C*H*$_2$CH$_2$CO), 1.78 (virt. qu, $^3J \cong 6.7$ Hz, 2 H, C*H*$_2$CH$_2$N), 2.21 (s, 6 H, (CH$_3$)$_2$N), 2.27 (t, $^3J = 7.5$ Hz, 2 H, CH$_2$CO), 2.32 (t, $^3J = 7.5$ Hz, 2 H, CH$_2$N), 4.09 (t, $^3J = 6.5$ Hz, 2 H, CH$_2$O) ppm. – ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 14.0$ (q, *C*H$_3$CH$_2$), 22.4 (t, CH$_3$*C*H$_2$), 24.8 (t, *C*H$_2$CH$_2$CO), 27.1 (t, *C*H$_2$CH$_2$N), 31.4 (t, CH$_3$CH$_2$*C*H$_2$), 34.4 (t, *C*H$_2$CO), 45.5 (s, (CH$_3$)$_2$N), 56.4 (t, CH$_2$N), 62.7 (t, CH$_2$O), 174.0 (s, CO) ppm. – IR (NaCl): $\tilde{\nu} = 2957$ cm^{-1} (vs, C-H), 2860 (s, C-H), 2816 (s, C-H), 2765 (s, C-H), 1737 (vs, C=O), 1462 (s), 1387 (m), 1246 (s), 1173 (vs, C-O), 1099 (s), 1042 (s), 902 (w), 839 (w), 734 (w). – GC-MS (EI, 70 eV, $t_R = 12.0$ min): m/z (%) = 201 (1) [M$^+$], 99 (1) [C$_6$H$_{11}$O$^+$], 84 (3) [C$_5$H$_{10}$N$^+$], 58 (100) [C$_3$H$_8$N$^+$]. – C$_{11}$H$_{23}$NO$_2$ (201.31): calcd. C 65.63, H 11.52, N 6.96; found C 65.53, H 11.68, N 7.01.

2-(N,N-Dimethylamino)-2-methylpropyl hexanoate (**3d**)

The reaction was carried out according to the general procedure with 2-(*N*,*N*-dimethylamino)-2-methyl-1-propanol (**2d**) (586 mg, 5.0 mmol). – $R_f = 0.23$ (DCM/MeOH, 12 : 1). – ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 0.87$ (t, $^3J = 7.0$ Hz, 3 H, C*H*$_3$CH$_2$), 1.05 (s, 6 H, (CH$_3$)$_2$C), 1.24 – 1.33 (m, 4 H, CH$_3$C*H*$_2$C*H*$_2$), 1.61 (virt. qu, $^3J \cong 7.5$ Hz , 2 H, C*H*$_2$CH$_2$CO), 2.28 (s, 6 H, (CH$_3$)$_2$N), 2.32 (t, $^3J = 7.5$ Hz, 2 H, CH$_2$CO), 3.97 (s, 2 H, CH$_2$O) ppm. – ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 14.0$ (q, *C*H$_3$CH$_2$), 20.8 (q, (*C*H$_3$)$_2$C), 22.4 (t, CH$_3$*C*H$_2$), 24.8 (t, *C*H$_2$CH$_2$CO), 31.4 (t, CH$_3$CH$_2$*C*H$_2$), 34.5 (t, *C*H$_2$CO), 39.0 (q, (CH$_3$)$_2$N), 56.1 (s, (CH$_3$)$_2$*C*), 69.0 (t, CH$_2$O), 174.0 (s, CO) ppm. – IR (NaCl): $\tilde{\nu} = 2957$ cm^{-1} (vs, C-H), 2872 (s, C-H), 2825 (s, C-H), 2783 (s, C-H), 1740 (vs, C=O), 1465 (m), 1462 (m), 1244 (m), 1170 (vs, C-O), 1097 (m), 1017 (m). – GC-MS (EI, 70 eV, $t_R = 12.4$ min): m/z (%) = 100 (8) [C$_6$H$_{14}$N$^+$], 99 (3) [C$_6$H$_{11}$O$^+$], 86 (100) [C$_5$H$_{12}$N$^+$]. – C$_{12}$H$_{25}$NO$_2$ (215.33): calcd. C 66.93, H 11.70, N 6.50; found C 66.60, H 11.92, N 6.43.

trans-2-(N,N-Dimethylamino)cyclohexyl hexanoate (**3e**)

The reaction was carried out according to the general procedure with *trans*-2-(*N*,*N*-dimethylamino)cyclohexanol (**2e**) (716 mg, 5.00 mmol). – $R_f = 0.35$ (DCM/MeOH, 12 : 1). – ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 0.88$ (t, 3 H, $^3J = 6.9$ Hz, C*H*$_3$CH$_2$), 1.16 – 1.36 (m, 8 H, CH$_3$C*H*$_2$C*H*$_2$ / C*H*HC*H*HC*H*HC*H*HCH), 1.61 (virt. qu, $^3J \cong 7.4$ Hz, 2 H, C*H*$_2$CH$_2$CO), 1.66 – 1.74 (m, 2 H, CH*H*CH*H*CH$_2$CHN), 1.80 – 1.83 (m, 1 H, CH*H*CHN), 1.96 – 2.00 (m, 1 H, CH*H*CHO), 2.27 – 2.31 (m, 2 H, CH$_2$CO), 2.28 (s, 6 H, N(CH$_3$)$_2$), 2.45 (dt, $^3J = 3.6$ Hz , $^3J = 10.1$ Hz , 1 H, CHN), 4.83 (dt, $^3J = 4.5$ Hz, $^3J = 10.1$ Hz, 1 H, CHO) ppm. – ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 14.1$ (q, *C*H$_3$CH$_2$), 22.5 (t, CH$_3$*C*H$_2$), 24.3 (t, *C*H$_2$CH$_2$CHO), 24.8 (t, *C*H$_2$CHN*), 24.8 (t, *C*H$_2$CH$_2$CO*), 24.9 (t, *C*H$_2$CH$_2$CHN*), 31.4 (t, CH$_3$CH$_2$*C*H$_2$), 31.8 (t, *C*H$_2$CHO), 35.0 (t, *C*H$_2$CO), 41.2 (q, (CH$_3$)$_2$N), 66.0 (d, CHN), 72.5 (d, CHO), 173.5 (s, CO) ppm. – IR (NaCl): $\tilde{\nu} = 2932$ cm^{-1} (vs, C-H), 2860 (s, C-H), 2827 (m, C-H), 2780 (m, C-H), 1732 (vs, C=O), 1452 (m), 1378 (m), 1245 (m), 1176 (s, C-O), 1048 (m), 953 (m), 871 (m). – GC-MS (EI, 70 eV, $t_R = 14.8$ min): m/z (%) = 241 (6) [M$^+$], 142 (22) [(M – C$_6$H$_{11}$O)$^+$], 125 (35) [C$_8$H$_{15}$N$^+$], 99 (11) [C$_6$H$_{11}$O$^+$], 84 (100) [C$_5$H$_{10}$N$^+$]. – C$_{14}$H$_{27}$NO$_2$ (241.37): calcd. C 69.66, H 11.27, N 5.80; found C 69.33, H 11.34, N 5.95.

Kinetic studies

All reactions were carried out according to the general procedure and data collection started with the addition of the alcohol ($t = 0$ min). A sample (0.3 ml) was taken every ten minutes in the first hour of the esterification and subsequently every 30 min. The data collection was stopped after four hours. The samples were filtered over basic alumina with ethyl acetate as eluent and analyzed by gas chromatography. Dodecane was used as the internal standard. Calibration curves for dodecane and the esters were constructed with concentrations injected into the GLC ranging from 0.1 to 3.0 μl/ml ethyl acetate ($r^2 = 0.995 – 0.999$ in all cases). Dodecane and the esters were calibrated to correlate area percentage and concentration of each compound. With the knowledge of the theoretical concentration of dodecane in the reaction mixture and its measured concentration after filtration, a dilution factor can be calculated which allows to work back to the concentration of the ester in the reaction mixture from the measured concentration of the ester after filtration.

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