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 (\( k = 0.67 \cdot 10^{-5} \text{ s}^{-1} \)). The values range from \( 0.66 \cdot 10^{-5} \text{ s}^{-1} \) to \( 9.3 \cdot 10^{-5} \text{ s}^{-1} \). 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 \( C^* \) 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 syneriplanar 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 \( 7.5 \cdot 10^{-5} \text{ s}^{-1} \) (uncatalyzed) to \( 14.8 \cdot 10^{-5} \text{ s}^{-1} \) (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 (\( A_{Ac2} \) 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.

Results

Kinetic studies

The alcohol 2a (or 1-hexanol) (\( c = 0.125 \text{ M} \)) was converted into the corresponding ester 3a (or 4) under...
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 Na₂SO₄ 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 \( k_{3a} = 7.5 \cdot 10^{-5} \) s⁻¹ and \( k_{4} = 0.67 \cdot 10^{-5} \) 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 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 monoeponential 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-toluensulfonic acid (p-TsOH) the pseudo-first order rate constant increased from \( k_4 = 0.67 \cdot 10^{-5} \) s⁻¹ (uncatalyzed) to \( k_4 = 4.5 \cdot 10^{-5} \) s⁻¹. With 2.5 mol-% of p-TsOH the value \( k_4 \) 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 \( k_{3a} \) 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 $k_{3a}$ barely exceeding the value for the uncatalyzed reaction ($k_{3a} = 7.5 \cdot 10^{-5}$ 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 scyello-diastereoisomer 6 was determined as 2.2·$10^{-5}$ s$^{-1}$. The myo-diastereoisomer 7 was hydrolyzed more slowly with a rate constant of 1.0·$10^{-5}$ 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 $A^\#$ with either a water molecule (as in $A^\#$) or a hydroxide ion as the nucleophile (Fig. 4). For the given example in Fig. 3 the scyello-diastereoisomer 6 can adopt 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 $C^\#$ 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-dialkylaminoethanol [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 tran-

![Fig. 3. Structure of the aminocyclitols 6 and 7, the hydrolyses of which was studied by Holland et al. [7a].](image1)

![Fig. 4. Structure of the two transition states $A^\#$ (ester hydrolysis) and $C^\#$ (esterification) leading to the presumed tetrahedral intermediate B.](image2)
the imidazole (5, entry 9) disappointingly failed. We therefore conclude that an efficient catalyst for the esterification of $N,N$-dialkylaminol alcohol 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-alkoxyalkyl esters, is responsible for a rate increase in the esterification of 2-$N,N$-dialkylaminol alcohol. It was shown by variation of the amino alcohol that the esterification rate constant is high for substrates which favor an intermolecular hydrogen bonding. Contrary to this, 2-$N,N$-dialkylaminol 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 normal 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 (6.3 ml, 5.81 g, 50.0 mmol) and Na$_2$SO$_4$ (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$_2$CO$_3$ (3 × 50 ml), brine (50 ml) and was dried with Na$_2$SO$_4$. 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, 3 $^J$ = 6.9 Hz, 3 H, CH$_3$CH$_2$), 1.18 – 1.32 (m, 4 H, CH$_3CH$CH$_2$), 1.56 (virt. qu, 3 $^J$ = 7.5 Hz, 2 H, CH$_2$CH$_2$CO), 2.23 (s, 6 H, N(CH$_3$)$_2$), 2.27 (t, 3 $^J$ = 7.5 Hz, 2 H, CH$_2$CO), 2.50 (t, 3 $^J$ = 5.7 Hz, 2 H, CH$_2$O), 4.11 (t, 3 $^J$ = 5.7 Hz, 2 H, CH$_2$N) ppm. – $^{13}$C NMR (90.6 MHz, CDCl$_3$): $\delta = 14.0$ (q, CH$_3$CH$_2$), 22.4 (t, CH$_2$CH$_2$), 24.6 (t, CH$_2$CH$_2$CO), 31.3 (t, CH$_3$CH$_2$CH$_2$), 34.2 (t, CH$_2$CO), 45.8 (s, N(CH$_3$)$_2$), 57.9 (t, CH$_2$N), 62.0 (t, CH$_2$CO), 174.0 (s, CO) ppm. – IR (NaCl): $\nu =$ 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), 1042 (s), 968 (m), 850 (m), 782 (m), 734 (m). – GC-MS (EI, 70 eV, $r_t = 10.5$ min): $m/z$ (%) = 99 (1) [C$_6$H$_11NO$_3$]+, 76 (2) [C$_6$H$_11NO$_3$]+, 58 (100) [C$_7$H$_13$N]+. – C$_{10}$H$_{15}$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, 3 $^J$ = 6.3 Hz, 3 H, CH$_3$CH$_2$), 1.26 – 1.32 (m, 4 H, CH$_3$CH$_2$CH$_2$), 1.40 – 1.47 (m, 1 H, CH/CH/HN), 1.55 – 1.64 (m, 3 H, CH$_2$CH$_2$CO / CH$_2$/CH/HN), 1.73 – 1.79 (m, 2 H, CH$_2$/CH/CH/HN), 2.24 – 2.33 (m, 7 H, CH$_2$CO / CH/CH/CH/CH/HN / NCH$_2$), 2.38 – 2.43 (m, 1 H, CH/CH/CH/HN), 2.67 – 2.65 (m, 1 H, CH/CH/CH/HN), 4.85 – 4.90 (m, 1 H, CH/O) ppm. – $^{13}$C NMR (90.6 MHz, CDCl$_3$): $\delta = 14.0$ (q, CH$_3$CH$_2$), 22.4 (t, CH$_3$CH$_2$), 22.6 (t, CH$_2$CO), 24.8 (t, CH$_2$CO), 28.9 (t, CH$_2$/CH/N), 31.4 (t, CH$_3$CH$_2$CH$_2$), 34.6 (t, CH$_2$CO), 46.5 (q, NCH$_3$), 55.5 (t, CH$_2$/CH/CH$_2$/N), 59.3 (t, CH$_2$/CH/CH$_2$/CO), 69.2 (q, CH/CH/CH/CO), 173.5 (s, CO) ppm. – IR (NaCl): $\nu =$ 2951 cm$^{-1}$ (vs, C-H), 2860 (s, C-H), 2813 (s, C-H), 1732 (s, 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, $r_t = 13.2$ min): $m/z$ (%) = 114 (1) [C$_7$H$_{12}$NO$_2$]+, 95 (5) [C$_8$H$_{11}$O$_3$]+, 97 (100) [C$_8$H$_{11}$N$_2$]+. – C$_{12}$H$_{15}$NO$_2$ (213.22): 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-propanyl hexanoate (3c)

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

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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). – 1H NMR (360 MHz, CDCl3): δ = 0.87 (t, 3J = 7.0 Hz, 3 H, CH3(CH2)2), 1.05 (s, 6 H, (CH3)2CH), 1.24 – 1.33 (m, 4 H, CH3CH2CH2), 1.61 (vitr. qu, 3J = 7.5 Hz, 2 H, CH2CH2CH2), 2.28 (s, 6 H, (CH3)2N), 2.32 (t, 3J = 7.5 Hz, 2 H, CH2N), 3.97 (s, 2 H, CH2O) ppm. – 13C NMR (90.6 MHz, CDCl3): δ = 14.0 (q, CH3CH2), 22.4 (t, CH3CH2), 24.8 (t, CH2CH2CO), 27.1 (t, CH2CH2N), 31.4 (t, CH2CH2CH2), 34.4 (t, CH2CO), 45.5 (s, (CH3)2N), 56.4 (t, CH2N), 62.7 (t, CH2O), 174.0 (s, CO) ppm. – IR (NaCl): υ = 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, tR = 12.0 min): m/z (%) = 201 (1) [C6H11O+], 84 (3) [C6H9O2]+, 58 (100) [C5H8N]+, –C11H23NO2 (201.31): calcd. C 65.63, H 11.52, N 11.2%, found C 65.63, H 11.48, N 11.0%.

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, 5.0 mmol). – 1H NMR (360 MHz, CDCl3): δ = 0.87 (t, 3J = 6.9 Hz, 3 H, CH2CH2), 1.16 – 1.36 (m, 8 H, CH3CH2CH2 / CHHCHHCHHCHHCH), 1.61 (vitr. qu, 3J = 7.4 Hz, 2 H, CH2CH2CO), 1.66 – 1.74 (m, 2 H, CHCHHCHHCH2CH2), 1.80 – 1.83 (m, 1 H, CHHHCN), 1.96 – 2.00 (m, 1 H, CHHCHO), 2.27 – 2.31 (m, 2 H, CH2CO), 2.28 (s, 6 H, N(CH2)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, CO) ppm. – 13C NMR (90.6 MHz, CDCl3): δ = 14.1 (q, CH3CH2), 22.5 (t, CH2CH2), 24.3 (t, CH2CH2CHO), 24.8 (t, CH2CH2N+), 24.8 (t, CH2CH2CO+), 24.9 (t, CH2CH2CH2N+), 31.4 (t, CH2CH2CH2), 31.8 (t, CH2CHO), 35.0 (t, CH2CO), 41.2 (q, CH2)2N), 66.0 (d, CHN), 72.5 (d, CHO), 173.5 (s, CO) ppm. – IR (NaCl): υ = 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, tR = 14.8 min): m/z (%) = 241 (6) [M]+, 142 (22) [(M – C6H11O)+], 125 (35) [C6H11N]+, 99 (11) [C6H11O]+, 84 (100) [C6H9O2]+. – C14H27NO2 (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 (0.5 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/mg ethyl acetate (r² = 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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