Amphiphilic Long-chain Citric Acid Ethers

Daniel Meißner and Peter Jutzi

Department of Chemistry, University of Bielefeld, P. O. Box 100131, 33501 Bielefeld, Germany

Reprint requests to Prof. Dr. P. Jutzi. Fax: 0049-(0)521-106-6026.
E-mail: Peter.Jutzi@uni-bielefeld.de

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Dedicated to Professor Gerhard Maas on the occasion of his 60th birthday

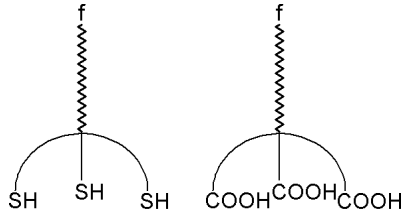
The etherification of the hydroxyl group of citric acid with saturated and unsaturated long-chain alkyl groups is described. This is a new approach to polydentate acids which may serve as ligands for metal or metal oxide nanoparticles. For this purpose we developed a synthetic route to long-chain ω-unsaturated alcohols and their triflate derivatives.

Key words: Polydentate Ligands, Alkylations, Long-chain Carboxylic Acids, Citric Acid Ethers, Nanoparticles, C-C Coupling

Introduction

In recent years much attention has been paid to the synthesis of metal and metal oxide nanoparticles with tailored size and morphology, and to appropriate functionalization in their periphery [1]. In addition to several types of polymers, long-chain organic molecules play an important role as ligands for nanoparticles to prevent their agglomeration and to provide the necessary functionalization. Long-chain organothiols are suitable ligands for "soft" [2] metal surfaces [3] and long-chain carboxylic acids for "hard" [2] metal and metal oxide surfaces [1a]. With respect to possible applications, there is further demand for sufficient surface coverage of the nanoparticles, for strong particle ligand bonding and for low ligand exchange rates. In this context, we [4] and independently the group of Lee [5] have synthesized functionalized and non-functionalized long-chain tridentate organotrithiols (type I in Fig. 1). It has been demonstrated that this type of ligands feature the smallest ratio between surface coverage and number of binding sites [4, 5b]. Furthermore, they offer excellent kinetic and thermodynamic stability of nanoparticles, which are made of "soft" metals [4]. In this paper, we present the synthesis of functionalized and non-functionalized polydentate long-chain organic acids of type II, which are promising ligands for "hard" metals and metal oxides.

Citric acid is a suitable starting material for the preparation of type-II ligands. It already contains



I II

Fig. 1. Three-legged ligands.

three carboxylic acid groups and a hydroxyl group, the latter of which has to be etherified with appropriate long-chain alkyl groups. The first etherification of trimethyl 2-hydroxypropane-1,2,3-tricarboxylate (**1**) was accomplished by Anschütz in 1903 [6]. The reaction of **1** with iodomethane and silver oxide in an autoclave for 40 h at 100 °C yielded up to 10 % of trimethyl 2-methoxypropane-1,2,3-tricarboxylate (**3a**) which was still contaminated with **1**. Acidic cleavage of the methyl ester led to 2-methoxypropane-1,2,3-tricarboxylic acid (**4a**). Since then this apparently simple reaction has hardly been studied. This may be due to the poor yields and harsh conditions of the process described in the original paper. Only recently, the synthesis of siloxy derivatives containing long-chain siloxane fragments and their application as micelle-forming materials have been described [7]. Since most reactions at the hydroxyl group are esterifications [8], there is a need for a general method to form alkyl ethers of citric acid.

Results and Discussion

The synthesis starts with trimethyl 2-hydroxypropane-1,2,3-tricarboxylate (**1**) which is prepared in good yields by standard methods from citric acid [9]. The deprotonation with sodium hydride leads to the sodium alcoholate **2**. This colorless solid is readily soluble in polar solvents like THF or diethyl ether. It turned out that **2** is a very weak nucleophile as it does not react with common alkylating agents such as alkyl halides or tosylates. This leads to the conclusion that alkylating agents with a stronger carbocationic character are necessary for the reaction with **2**. As a proof of principle, we have synthesized trimethyl 2-ethoxypropane-1,2,3-tricarboxylate (**3b**) by treatment of **2** with triethyloxonium tetrafluoroborate. Although this reaction is very slow (4 days, which shows again the strongly reduced reactivity of **2**), **3b** could be isolated in good yields. Saponification of the methyl ester leads to the 2-ethoxypropane-1,2,3-tricarboxylic acid (**4b**) (Fig. 2).

The syntheses of the title compounds require long-chain electrophiles with a strong carbocationic character. We used the alkyl triflates instead of the oxonium salts for the reaction with **2**, because some long-chain triflates are already described in the literature [10], while all known oxonium salts contain butyl groups at the most [11]. To yield the acid forms **4c** and **4d**, the methyl esters are cleaved by basic saponification (Fig. 3 and Table 1).

The alkylation proceeds within several days at r. t. with moderate yields. Compounds **3c** and **3d** can

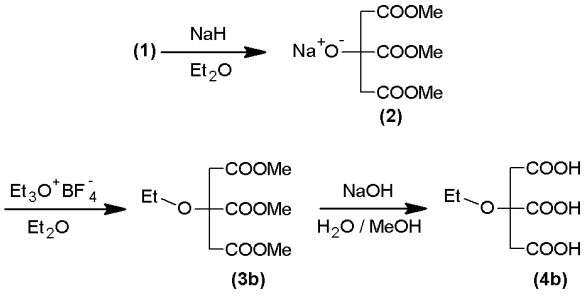


Fig. 2. Synthesis of **2**, **3b** and **4b**.

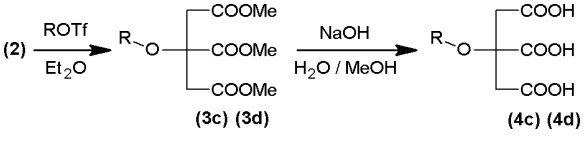


Fig. 3. Alkylation with triflates. For explanation of R see Table 1.

Table 1. Alkylating agents and resulting compounds.

ROTf	resulting methyl ester	resulting acid
$(CH_2)_{15}OSO_2CF_3$	**3c**	**4c**
$(CH_2)_{19}OSO_2CF_3$	**3d**	**4d**

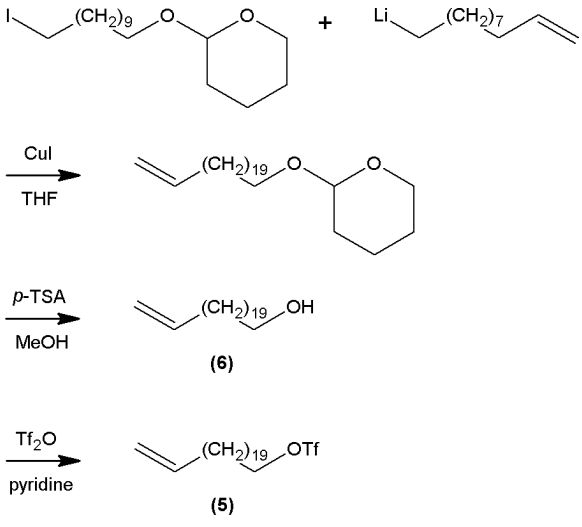


Fig. 4. Synthesis of **6** and **5**.

be purified by column chromatography. Compounds **4c** and **4d** are almost pure after the saponification. Further purification can be achieved by recrystallization.

The citric acid ethers **4c** and **4d** are colorless solids which are soluble in polar organic solvents like diethyl ether, THF or methanol. They are stable in refluxing *o*-dichlorobenzene for more than one hour, and thus they can be used employing common synthetic strategies for metallic nanoparticles [1a].

Octadecyl triflate and the novel docos-21-enyl triflate (**5**) were synthesized from the corresponding alcohols by treatment with triflic anhydride in analogy to the procedure described in literature [12]. The yields could be improved to almost 100 % by using a non-aqueous purification. While octadecanol is commercially available, we developed a multistep synthesis for docos-21-en-1-ol (**6**). The key step is the cuprate-mediated C-C coupling between undec-10-enyllithium and 2-[(11-iodoundecyl)oxy]tetrahydro-2*H*-pyran (Fig. 4). As this method is very selective and tolerates several functional groups [13], it offers a simple access to long-chain α,ω-functionalized aliphatic hydrocarbons.

Conclusion

In conclusion, citric acid could be functionalized at the hydroxyl group with an ethyl group or with two different long-chain alkyl groups. The applications of the latter two ether products as ligands for nanoparticles and of **4b** as a ligand in metal complexes are under investigation and will be published elsewhere.

Experimental Section

*Trimethyl 2-ethoxypropane-1,2,3-tricarboxylate (**3b**)*

18 g (77 mmol) of **1** was added to a suspension of 1.85 g (77 mmol) sodium hydride in 100 mL of diethyl ether. The mixture turned clear within 30 min. Afterwards, 15 g (79 mmol) of triethyloxonium tetrafluoroborate was added to the solution causing a precipitation. After 4 d at r. t. the mixture was hydrolyzed and extracted three times with diethyl ether. The combined organic fractions were dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The crude product was purified by silica column chromatography (ethyl acetate, cyclohexane 8 : 1, R_f = 0.2) to yield 15 g of **8** as a colorless liquid. Yield: 74.4 %. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (t, ^3J = 7.2 Hz, 3H, CH_3), 2.97 (d, ^2J = 15.7 Hz, 2H, CH_2COOCH$_3$), 3.14 (d, ^2J = 15.7 Hz 2H, CH_2COOCH3), 3.46 (q, ^3J = 7.2 Hz, 2H, OCH_2CH$_3$), 3.65 (s, 6H, COOCH$_3$), 3.75 (s, 3H, COOCH$_3$) ppm. – ^{13}C NMR (126 MHz, $CDCl_3$): δ = 15.3 (CH_2CH_3), 38.9 (CH_2COOCH$_3$), 51.7 (COOCH$_3$), 52.4 (COOCH$_3$), 60.1 (CH_2CH_3), 78.3 (OC(CH$_2$COOCH$_3$)$_2$(COOCH$_3$)) ppm. – MS (EI, 70 eV): *m/z* (%) = 262 (0.02) $[M]^+$, 231 (0.03) $[M-OCH_3]^+$, 203 (0.03) $[M-COOCH_3]^+$, 171 (100). – $C_{11}H_{18}O_7$ (262.3): calcd. C 50.38, H 6.92; found C 50.24, H 7.01.

*Trimethyl 2-(octadecyloxy)propane-1,2,3-tricarboxylate (**3c**)*

The procedure is similar to the synthesis of **3b**, using octadecyl triflate instead of triethyloxonium tetrafluoroborate. Purification was accomplished by silica column chromatography (ethyl acetate, cyclohexane 5 : 1, R_f = 0.7). Yield 56.5 %. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t,^3J = 6.9 Hz, 3H, CH_3), 1.23 (m, 30H,CH_2), 1.48 (q, ^3J = 6.6 Hz, 2H, CH_2CH$_2$O), 2.98 (d, ^2J = 15.7 Hz, 2H, CH_2COOCH$_3$), 3.16 (d, ^2J = 15.7 Hz, 2H, CH_2COOCH$_3$), 3.38 (t, ^3J = 6.6 Hz, 2H, OCH_2CH$_2$), 3.65 (s, 6H, COOCH$_3$), 3.75 (s, 3H, COOCH$_3$) ppm. – ^{13}C NMR (126 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7 (CH_2), 25.9 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 28.8 (CH_2), 31.9 (CH_2), 38.9 (CH_2COOCH$_3$), 51.8 (COOCH$_3$), 52.5 (COOCH$_3$), 64.7 (CH_2), 78.3 (OC(CH$_2$COOCH$_3$)$_2$(COOCH$_3$)), 170.4 (COOCH$_3$), 171.3 (COOCH$_3$). – MS (EI, 70 eV): *m/z* (%) = 486 (0.07) $[M]^+$, 427 (43) $[M-COOCH_3]^+$, 143 (100) $[M-COOCH_3-OCH_3-OC_{18}H_{37}]^+$. – $C_{27}H_{50}O_7$ (486.7): calcd. C 66.63, H 10.36; found C 66.64, H 10.41.

*Trimethyl 2-(docosa-21-enyloxy)propane-1,2,3-tricarboxylate (**3d**)*

The procedure is similar to the synthesis of **3b**, using docosa-21-enyl triflate instead of triethyloxonium tetrafluoroborate. Purification was accomplished by silica column chromatography (ethyl acetate, cyclohexane 4 : 1, R_f = 0.15). Yield: 30.4 %. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (m, 34H, CH_2), 1.48 (q, ^3J = 6.6 Hz, 2H, CH_2CH$_2$O), 2.01 (m, 2H, H$_2$C=CHCH_2), 2.99 (d, ^2J = 15.7 Hz, 2H, CH_2COOCH$_3$), 3.16 (d, ^2J = 15.7 Hz, 2H, CH_2COOCH$_3$), 3.37 (t, ^3J = 6.6 Hz, 2H, OCH_2CH$_2$), 3.66 (s, 6H, COOCH_3), 3.75 (s, 3H, COOCH_3), 4.95 (m, 2H, H_2C=CH), 5.79 (m, 1H, H$_2$C=CH) ppm. – ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.9 (CH_2), 29.0 (CH_2CH_2CH=CH$_2$), 29.2 ($CH_2CH_2CH_2$CH=CH$_2$), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.8 (CH_2), 33.8 (CH_2CH=CH$_2$), 38.9 (CH_2COOCH$_3$), 51.8 (COOCH$_3$), 52.5 (COOCH$_3$), 64.5 (CH_2O), 78.3 (OC(CH$_2$COOCH$_3$)$_2$(COOCH$_3$)), 114.1 (CH=CH_2), 139.3 (CH=CH$_2$), 170.4 (COOCH$_3$), 171.3 (COOCH$_3$) ppm. – MS (EI, 70 eV): *m/z* (%) = 540 (0.75) $[M]^+$, 143 (100) $[M-COOCH_3-OCH_3-OC_{22}H_{43}]^+$. – $C_{31}H_{56}O_7$ (540.8): calcd. C 68.85, H 6.03; found C 68.90, H 10.84.

*2-Ethoxypropane-1,2,3-tricarboxylic acid (**4b**)*

23.3 g (580 mmol) of sodium hydroxide was dissolved in a solution of 15 g (57.2 mmol) **3b** in 200 mL of methanol and 200 mL water. After the mixture was refluxed for 3 h the major fraction of methanol was evaporated under reduced pressure. The solution was slightly acidified by hydrochloric acid and extracted several times with THF. Evaporation of the solvent and recrystallization from *o*-dichlorobenzene / THF yielded 9.8 g of **3** as a colorless solid. Yield: 77.8 %. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.05 (t, ^3J = 6.9 Hz, 3H, CH_3), 2.80 (d, ^2J = 15.7 Hz, 2H, CH_2COOH), 2.96 (d, ^2J = 15.7 Hz, 2H, CH_2COOH), 3.43 (q, ^3J = 6.9 Hz, 2H, OCH_2CH$_3$), 12.66 (s, 3H, COOH) ppm. – ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 15.8 (CH_2CH_3), 39.1 (CH_2COOH), 59.4 (CH_2CH_3), 78.2 (OC(CH$_2$COOH)$_2$(COOH)), 171.7 (COOH), 172.3 (COOH) ppm. – MS ((–)-ESI): *m/z* (%) = 219 (100) $[M-H]^-$. – HRMS ((–)-ESI): *m/z* = 219.0510 (calcd. 219.0510 for $C_8H_{11}O_7$, $[M-H]^-$).

*2-(Octadecyloxy)propane-1,2,3-tricarboxylic acid (**4c**)*

3 g (75.0 mmol) of sodium hydroxide was dissolved in a suspension of 2.2 g (4.5 mmol) **3c** in 30 mL of methanol and 40 mL of water. After the reaction mixture was refluxed

for 20 h the main fraction of methanol was evaporated under reduced pressure. The resulting suspension was slightly acidified by hydrochloric acid and extracted several times with diethyl ether. Evaporation of the solvent yielded a white solid, which could be recrystallized from chloroform / diethyl ether (1.6 g). Yield: 79.9 %. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 0.85 (t, ^3J = 6.6 Hz, 3H, CH_3), 1.23 (m, 30H, CH_2), 1.40 (q, ^3J = 5.7 Hz, 2H, CH_2CH$_2$O), 2.80 (d, ^2J = 15.7 Hz, 2H, CH_2COOH), 2.97 (d, ^2J = 15.7 Hz, 2H, CH_2COOH), 3.36 (q, ^3J = 5.7 Hz, 2H, CH_2O), 12.48 (s, 3H, COOH) ppm. – ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 14.4 (CH_3), 22.6 (CH_2), 25.9 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.8 (CH_2), 31.8 (CH_2), 38.8 (*C*H$_2$ COOCH$_3$), 63.7 (CH_2), 78.0 (O*C*(CH$_2$COOH)$_2$(COOH)), 171.7 (*C*OOH), 172.2 (*C*OOH) ppm. – MS ((–)-ESI): *m/z* (%) = 443 (100) [M–H]$^-$. – HRMS ((–)-ESI): *m/z* = 443.3000 (calcd. 443.3014 for $C_{44}H_{43}O_7$ [M–H]$^-$).

*2-(Docos-21-enyloxy)propane-1,2,3-tricarboxylic acid (**4d**)*

The procedure is similar to the synthesis of **4c**. Yield: 71.2 %. – ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 1.23 (m, 30H, CH_2), 1.40 (q, ^3J = 5.7 Hz, 2H, CH_2CH$_2$O), 2.00 (m, 2H, H$_2$C=CHCH_2), 2.80 (d, ^2J = 15.7 Hz, 2H, CH_2COOH), 2.97 (d, ^2J = 15.7 Hz, 2H, CH_2COOH), 3.38 (q, ^3J = 5.7 Hz, 2H, CH$_2$CH_2O), 4.96 (m, 2H, H_2C=CH), 5.78 (m, 1H, H$_2$ C=C*H*), 12.52 (s, 3H, COOH) ppm. – ^{13}C NMR (126 MHz, THF/C$_6$D$_6$): δ = 26.0 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.9 (CH_2), 33.8 (*C*H$_2$CH=CH$_2$), 37.8 (*C* H$_2$COOCH$_3$), 63.7 (*C*H$_2$), 78.0 (O(CH$_2$COOH)$_2$(COOH)), 113.7 (CH=*C*H$_2$), 138.8 (*C*H=CH$_2$), 171.1 (COOH), 171.2 (COOH) ppm. – MS ((–)-ESI): *m/z* (%) = 497 (100) [M–H]$^-$. – HRMS ((–)-ESI): *m/z* = 497.3467 (calcd. 497.3484 for $C_{28}H_{49}O_7$ [M–H]$^-$).

*Docos-21-en-1-ol (**6**)*

1.3 g of lithium metal was stirred for 16 at r. t. in a solution of 13 g 1-bromo-undec-10-ene (56 mmol) in 200 mL of diethyl ether. After filtration the solution was cooled to −40 °C and treated with 5.34 g CuI (28 mmol). 6.6 g 2-[(11-iodoundecyl)oxy]tetrahydro-2*H*-pyran (28.7 mmol) in 20 mL of diethyl ether was added to the resulting black solution. The mixture was stirred for 2 h at −40 °C and subsequently hydrolyzed with 100 mL of water. The aqueous phase was extracted with diethyl ether. The combined organic fractions were extracted with brine and dried over Na_2SO_4 before the solvent was removed under reduced pressure. The crude product was purified by column chromatography over neutral aluminium oxide (eluent: cyclohexane). Acid cleavage of the THP group led to docos-21-en-1-ol. Yield: 21.4 %. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (m, 32H, CH_2), 1.34 (q, ^3J = 6.9 Hz, 2H, CH_2CH$_2$CH$_2$OH), 1.54 (q, ^3J = 6.9 Hz, 2H, CH_2CH$_2$OH), 2.01 (m, 2H, CH_2CH=CH$_2$), 3.62 (t, ^3J = 6.9 Hz, 2H, CH_2OH), 4.93 (m, 2H, CH=CH_2), 5.79 (m, 1H, CH=CH$_2$) ppm. – ^{13}C NMR (126 MHz, $CDCl_3$): δ = 25.7 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 32.8 (CH_2), 33.8 (CH_2), 63.1 (CH_2), 114.1 (CH=*C*H$_2$), 139.3 (*C*H=CH$_2$) ppm. – MS (EI, 70 eV): *m/z* (%) = 324 (0.5) [M]$^+$, 307 (6.2) [M – OH]$^+$. – $C_{22}H_{44}O$ (324.6): calcd. C 81.22, H 13.74; found C 81.41, H 13.66.

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