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Modified tert-Butoxycarbonyl(*m* -BOC) Derivatives as Monomeric and Polymeric Aminoprotecting Groups - VII.

Marcus Gormanns, Helmut Ritter *

Bergische Universität Wuppertal, Fb 9 Organische Chemie
Gausstr. 20, D-42097 Wuppertal, Germany

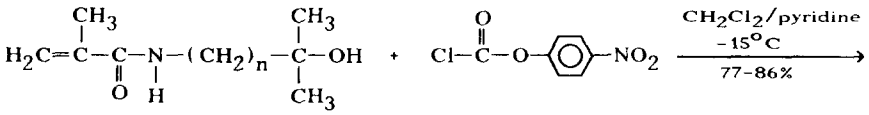
Abstract: Polymerizable N-methacrylamino *m*-BOC-type 1,1-dimethyl-2-methacrylmethanamido-ethoxy-carbonyl- and 1,1-dimethyl-3-methacrylmethanamido-butoxy-carbonyl group, derived from the corresponding *t*-alkohols have been developed as acid labile aminoprotecting groups. The synthesis of monomeric and polymeric N-methacrylamino *m*-BOC amino acids and amino acid methyl esters and their application for peptide synthesis following the (N→C)-assembly method are described. The rapid, acid induced cleavage of the protecting group leads to the formation of oxazole resp. oxazine derivatives.

To continue our investigations on low molecular weight and polymerizable N-acylamino modified (*m*-BOC) protecting groups,[1-5] here we present an application of two polymerizable *m*-BOC protecting groups based on a N-methacrylamino modification.

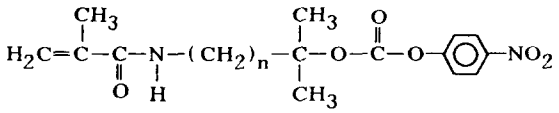
The novel *m*-BOC protecting groups, in general, are rapidly cleaved under strong acidic conditions (e.g. HBr/HOAc) without formation of a *t*-butyl cation or isobutene that are typical for the classical BOC protecting group.[6-9] It is known that these reactive species undergo typical side reactions.[10] This is not expected in the case of the *m*-BOC groups because of the formation of relatively stable oxazole and oxazine derivatives. A further advantage of the *m*-BOC group is a controlled solubility by variation of the N-acyl residue that can be done and adjust e.g. by copolymerization.

To evaluate the use of the polymerizable N-methacylamino *m*-BOC group in peptide chemistry, some derivatives of amino acids and amino acid methyl esters and, in addition, dipeptides were prepared.

First of all, activated carbonates **1b** and **2b** were synthesized starting from N-(2-hydroxy-2-methyl-propyl)-methacrylamide **1a** and N-(3-hydroxy-3-methyl-butyl)-methacrylamide **2a** (scheme 1):



n = 1: **1a**, n = 2: **2a**

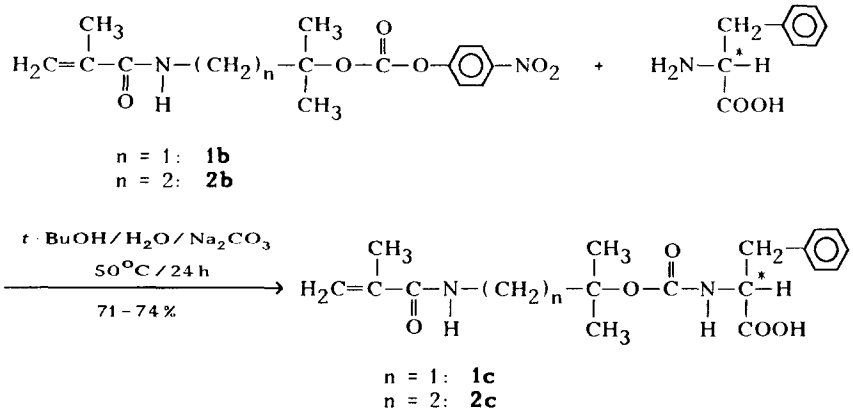


n = 1: **1b**, n = 2: **2b**

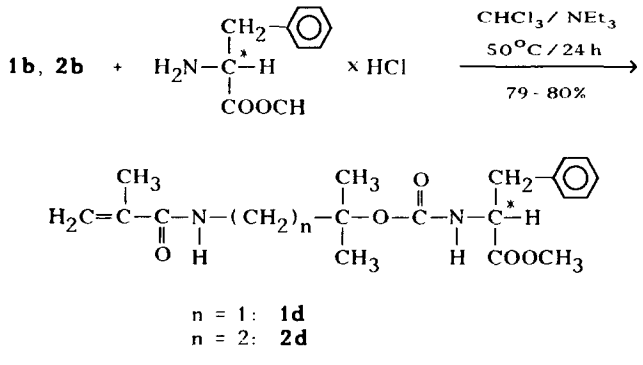
Scheme 1

Furthermore, the monomers **1b** and **2b** were copolymerized with methyl methacrylate in the presence of 2,2'-azoisobutyronitrile (AIBN) as radical initiator yielding the polymeric activated carbonates **3b** and **4b**. The composition of the copolymers were determinated by means of the ^1H NMR spectroscopy and elemental analysis.

The preparation of the N-methacrylamino *m*-BOC derivatives was accomplished by treating L-phenylalanine or L-phenylalanine methyl ester with the activated carbonates **1b**, **2b** under mild conditions (scheme 2 and 3).

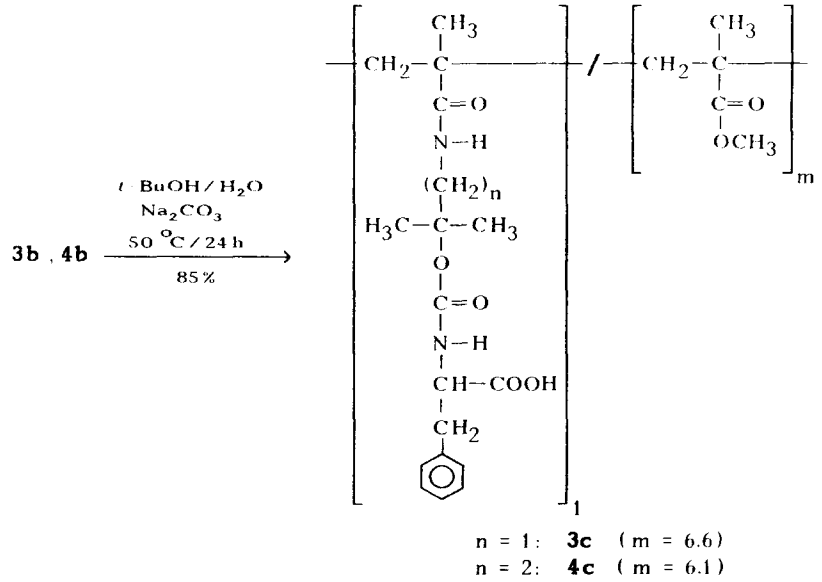


Scheme 2



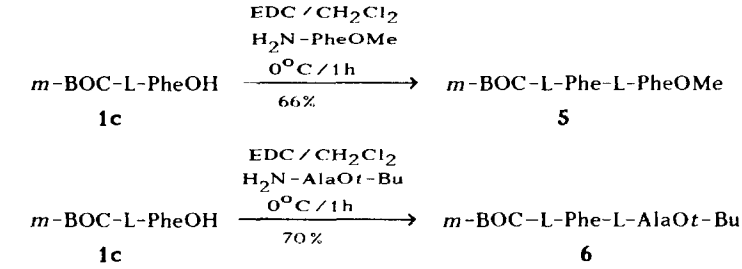
Scheme 3

Analogously, the polymeric activated carbonates **3b** and **4b** were treated with phenylalanine to obtain the polymeric N-protected amino acid derivatives **3c** and **4c** (scheme 4). These compounds are soluble in many organic solvents as benzene, chloroform, THF or DMF. In principle, it is possible to adjust any desired solubility by variation of the comonomer in the polymeric activated carbonates.



Scheme 4

Two dipeptide derivatives, N-(1,1-dimethyl-2-methacrylmethanamido-ethoxy-carbonyl)-L-phenylalanyl-L-phenylalanine methyl ester **5** and the analogous N-protected L-phenylalanyl-L-alanine *t*-butyl ester **6** were prepared by a carbodiimide-coupling procedure, using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) (scheme 5):



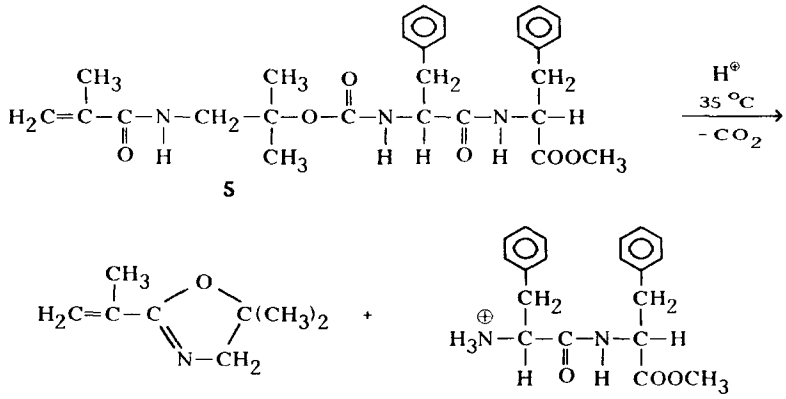
Scheme 5

These methods represent an approach to the stepwise peptide synthesis starting from the N-terminal residue (N→C-strategy), that was originally developed by Letsinger.[11] In contrast, the (C→N)-assembly method was established by Merrifield.[12]

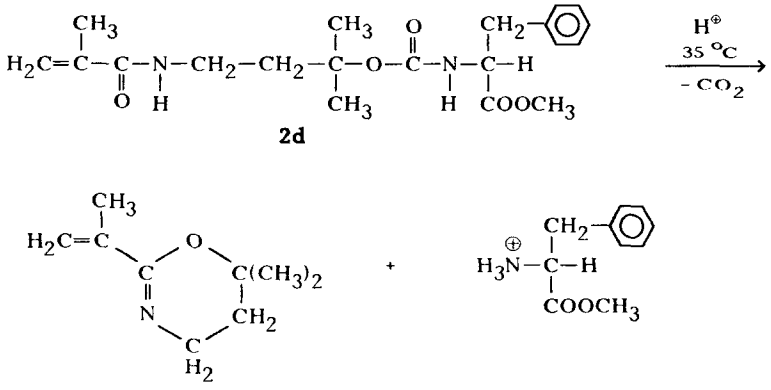
As expected, the N-methacrylamino *m*-BOC group was found to be very sensitive towards the common deprotecting reagents for the classical BOC group, like TFA or HBr/HOAc. The cleavage of the *m*-BOC group in HBr/HOAc occurs within 5 minutes. That is much more faster than in TFA because of the higher acidity.[13] The half time value of deprotection of *m*-BOC in TFA is in the region of 15 to 60 minutes, depending on the structure of the acyl residue. For example, derivatives

protected with the 1,1-dimethyl-2-methacrylmethanamido-ethoxy-carbonyl group, e.g. **1c** and **1d**, show a lower reactivity (half time value about 60 minutes) than the corresponding derivatives with the 1,1-dimethyl-3-methacrylmethanamido-butoxy-carbonyl group, e.g. **2c** and **2d** (half time value about 15 minutes). The structure of the amine or amino acid component does not influence the reactivity significantly.[3]

As mentioned above, under acidic conditions the 1,1-dimethyl-2-methacrylmethanamido-ethoxy-carbonyl protecting group leads to 5,5-dimethyl-2-methacryl-4,5-dihydro-oxazole (scheme 6) whereas the 1,1-dimethyl-3-methacrylmethanamido-butoxy-carbonyl group leads to 6,6-dimethyl-2-methacryl-5,6-dihydro-4*H*-oxazine as shown in scheme 7:



Scheme 6



Scheme 7

In each case, the resulting compounds were characterized by FAB measurements.

The results suggest that numerous polymeric *m*-BOC functions could be useful as acid labile protecting groups especially in peptide chemistry according to the (N→C)-strategy.

EXPERIMENTAL

The synthesis of **N-(2-hydroxy-2-methyl-propyl)-methacrylamide (1a)** and **N-(3-hydroxy-3-methyl-butyl)-methacrylamide (2a)** are published elsewhere.[1,2] The applied reagents are commercially available (Fluka Chemie AG, Buchs) if not noted otherwise. All solvents were purified by standard methods and dried if necessary. Melting points were determined on a Büchi Melting Point Determinator 510 and are not corrected. The NMR spectra were recorded on Bruker AC 250 (^{1}H: 250.13 MHz; ^{13}C: 62.98 MHz) with TMS as external standard. The ^{13}C NMR spectra were measured proton-decoupled. IR spectra were obtained using Perkin-Elmer spectrometer 397 and 1420. The FAB-MS were measured on Finnegan MAT 90. The elemental analyses were carried out with a Perkin-Elmer Elementar Analyser 204 B, the polarimetric measurements with a Perkin-Elmer 241 and the viscosity with an Ostwald viscosimeter coupled with a water bath Haake W 13 and a thermostat Haake D 8. The flash column chromatography was performed by using silica gel 60 (0.040-0.063 mm; Fa. Merck).

1,1-Dimethyl-2-methacrylmethanamido-ethyl-(4-nitrophenyl)-carbonate (1b)

To a stirred solution of N-(2-hydroxy-2-methyl-propyl)-methacrylamide (**1a**) (1.57g, 10 mmol) and pyridine (0.79 g, 10 mmol) in dichloromethane (30 ml) p-nitrophenyl chloroformate (2.01 g, 10mmol) were added slowly at -15 °C. The reaction mixture was stirred at room temperature for 3 h while an initial precipitate dissolved. The solution was washed with portions of *N* hydrochloric acid (5 mL) until the organic layer turned colourless. The solution was washed with saturated sodium carbonate solution and water, finally dried over magnesium sulfate and evaporated nearly to dryness. The precipitation of colourless crystals was induced by covering ether/petrolether (20 mL, 2:1 v/v) and completed at -10 °C. Yield: 2.40g (77%); mp 87-88 °C (dec.); Analysis calcd. for $C_{15}H_{18}N_2O_6$ (322.3) C, 55.90; H, 5.59; N, 8.69. Found: C, 55.71; H, 5.45; N, 8.64; IR(KBr) 3400 (N-H), 1760 (C=O, carbonate), 1660 (amide I), 1620 (C=C, olefin.), 1595/1510 (C=C, aromat.), 1530 (amide II) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 6H, $C(C\underline{H}_3)_2$), 1.97 (s, 3H, $=C-C\underline{H}_3$), 3.67 (d, ^{3}J = 6.2 Hz, 2H, $NH-C\underline{H}_2-$), 5.36, 5.72 (AB, 2H, $C=C\underline{H}_2$), 6.41 (b, 1H, NH), 7.35-8.27 (AA'XX', 4H, $C_6\underline{H}_4-$); ^{13}C NMR ($CDCl_3$) δ 18.51 (1C, $=C-\underline{C}H_3$), 23.23 (2C, $C(\underline{C}H_3)_2$), 47.40 (1C, $NH-\underline{C}H_2$), 86.13 (1C, $\underline{C}(CH_3)_2$), 119.60 (1C, $H_2\underline{C}=$), 121.74 (2C, C-2), 125.06 (2C, C-3), 139.71 (1C, $=\underline{C}-CH_3$), 145.10 (1C, C-4($\underline{C}-NO_2$)), 150.56 (1C, $\underline{C}=O$, carbonate), 155.24 (1C, C-1($\underline{C}-O-$)), 168.47 (1C, $\underline{C}=O$, amide); MS (FAB) 323 ($M^{+}+1$).

1,1-Dimethyl-3-methacrylmethanamido-propyl-(4-nitrophenyl)-carbonate (2b)

In alteration of the synthesis of 1a, N-(3-hydroxy-3-methyl-butyl)-methacrylamide (**2a**) (1.71 g, 10 mmol) was used and colourless crystals were obtained. Yield: 2.89g (86%); mp 103-104 °C (dec.); Analysis calcd. for $C_{16}H_{20}N_2O_6$ (336.3) C, 57.14; H, 5.99; N, 8.33. Found: C, 57.00; H, 5.84; N, 8.50; IR(KBr) 1760 (C=O, carbonate), 1655 (amide I), 1615 (C=C, olefin.), 1595/1495 (C=C, aromat.), 1525 (amide II) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.61 (s, 6H, $C(C\underline{H}_3)_2$), 1.95 (s, 3H, $=C-C\underline{H}_3$), 2.08 (t, ^{3}J = 7.7 Hz, $NH-CH_2-C\underline{H}_2-$), 3.50 (q, ^{3}J = 7.5 Hz, 2H, $NH-C\underline{H}_2-$), 5.32, 5.70 (AB, 2H, $C=C\underline{H}_2$), 6.06 (b,

1H, NH), 7.33-8.27 (AA'XX', 1H, $C_6\underline{H}_4$-); ^{13}C NMR ($CDCl_3$) δ 18.45 (1C, =C-$\underline{C}H_3$), 25.37 (2C, $C(\underline{C}H_3)_2$), 35.12 (1C, NH-CH_2-$\underline{C}H_2$), 39.86 (1C, NH-$\underline{C}H_2$), 85.88 (1C, $\underline{C}(CH_3)_2$), 119.55 (1C, $H_2\underline{C}$=), 121.73 (2C, C-2), 125.12 (2C, C-3), 139.64 (1C, =$\underline{C}$-CH_3), 145.21 (1C, C-4($\underline{C}$-NO_2)), 150.22 (1C, $\underline{C}$=O, carbonate), 155.35 (1C, C-1($\underline{C}$-O-)), 168.11 (1C, $\underline{C}$=O, amide); MS (FAB) 337 (M^++1).

Poly-[1,1-dimethyl-2-methacrylmethanamido-ethyl-(4-nitrophenyl)-carbonate-co-methyl-methacrylate] (3b)

A mixture of **1b** (322 mg, 1 mmol), methyl methacrylate (500 mg, 5 mmol), 2,2'-azoisobutyronitrile (AIBN) (40 mg, 0.30 mmol=5 mol%) and THF (2 mL) was stirred for 24 h at 60 °C under nitrogen. The solution was poured into ether (100 mL). The polymer obtained is colourless. Yield: 756 mg (92%); Analysis calcd. for $[C_{15}H_{18}N_2O_6]_1[C_5H_8O_2]_{6.6}$ $(982.3)_n$ C, 58.65; H, 7.21; N, 2.85. Found: C, 58.34; H, 7.42; N, 3.24; IR(KBr) 1760 (C=O, carbonate), 1720 (C=O, ester), 1650 (amide I), 1600/1500 (C=C, aromat.), 1525 (amide II) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.60-2.00 (C-$C\underline{H}_2$-, $C(C\underline{H}_3)_2$), C-$C\underline{H}_3$), 3.40-3.70 ($OC\underline{H}_3$, NH-$C\underline{H}_2$), 6.30 (N$\underline{H}$-), 7.30-7.50 and 8.20-8.35 ($C_6\underline{H}_4$-); η_{spez}/c = 14.3 [10^{-3} L/g] with c = 4.0 g/L (DMF, 25 °C).

Poly-[1,1-dimethyl-3-methacrylmethanamido-propyl-(4-nitrophenyl)-carbonate-co-methyl-methacrylate] (4b)

Analogeously, **2b** (336 mg, 1 mmol) was copolymerized to produce a colourless copolymeric activated carbonate. Yield: 752 mg (90%); Analysis calcd. for $[C_{16}H_{20}N_2O_6]_1[C_5H_8O_2]_{6.1}$ $(946)_n$ C, 58.98; H, 7.27; N, 2.96. Found: C, 58.18; H, 7.07; N, 3.09; IR(KBr) 1760 (C=O, carbonate), 1720 (C=O, ester), 1650 (amide I), 1600/1500 (C=C, aromat.), 1525 (amide II) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.60-2.20 (C-$C\underline{H}_2$-, $C(C\underline{H}_3)_2$), C-$C\underline{H}_3$, NH-CH_2-$C\underline{H}_2$-), 3.40-3.70 ($OC\underline{H}_3$, NH-$C\underline{H}_2$), 6.40 (N$\underline{H}$-), 7.30-7.50 and 8.15-8.30 ($C_6\underline{H}_4$-); η_{spez}/c = 13.2 [10^{-3} L/g] with c = 4.0 g/L (DMF, 25 °C).

The syntheses of N-protected phenylalanine derivatives **1c**, **2c**, **4c** and **5c** took place analogeously. Based on ref.[7] as an example, the synthesis of **1c** is described.

A mixture of L-phenylalanine (825 mg, 5mmol), 7 mmol of the activated carbonate (**1b**, **2b**, **4b** or **5b**), sodium carbonate (2.10g, 20mmol), *t*-butyl alcohol (10 mL) and water (7 mL) was heated at 50 °C for 24 h. All solids dissolved during this period and gave a deep yellow solution. The mixture was then concentrated in vacuo to remove *t*-BuOH. Crystallized sodium p-nitrophenolate dihydrate was filtered off, and the filtrate was diluted with water (10 mL). The solution was adjusted to pH 3 to 4 with citric acid and extracted with 5 mL portions of EtOAc until the organic layer turned to colourless. For further purification, the combined organic layer was concentrated and submitted to a flash column chromatography. After separation and removal of the remaining p-nitrophenol with EtOAc/toluene (v/v=1:5) the product was extracted with methanol/ethanol (v/v=1:1). Evaporation of the solvent led to a solid residue. In the case of the polymeric derivatives **4c** and **5c** the flash column chromatography was omitted. The combined organic layer was concentrated (5 mL) and dropped into ether (200 mL) to precipitate the copolymer.

N-(1,1-Dimethyl-2-methacrylmethanamido-ethoxy-carbonyl)-L-phenylalanine (1c)

Yield: 1.28g (74%); mp 65-67°C (dec.); Analysis calcd. for $C_{15}H_{24}N_2O_5$ (348.2) C, 62.07; H, 6.89; N, 8.05. Found: C, 61.45; H, 6.57; N, 7.99; IR(KBr) 1720 (amide I, urethane), 1700 (C=O, acid), 1650 (amide I, amide), 1610 (C=C, olefin.), 1600/1500 (C=C, aromat.), 1530 (amide II) cm^{-1}; ^1H NMR (CD_3OD) δ 1.45 (d, J = 9.0 Hz, 6H, $C(C\underline{H}_3)_2$), 1.93 (s, 3H, =C-$C\underline{H}_3$), 2.85-3.25 (AM of AMX, 2H, ν_A = 2.90, ν_M = 3.20, J_{AM} = 13.7 Hz, J_{AX} = 4.7 Hz, J_{MX} = 8.9 Hz, -CH-$C\underline{H}_2$-), 3.47 (d, ^3J = 5.9 Hz, 2H, NH-$C\underline{H}_2$-), 4.29-4.35 (X of AMX, 1H, ν_X = 4.32, -$C\underline{H}$-CH_2-), 5.38, 5.69 (AB, 2H, C=$C\underline{H}_2$), 6.54 (1H, NH), 7.20-7.32 (AA'MM'X, 5H, $C_6\underline{H}_5$-); ^{13}C NMR (CD_3OD) δ 18.86 (1C, =C-CH_3), 24.59, 27.01 (2C, $C(\underline{C}H_3)_2$), 38.90 (1C, CH-$\underline{C}H_2$-), 47.98 (1C, NH-$\underline{C}H_2$-), 57.02 (1C, $\underline{C}$H-CH_2-), 82.01 (1C, $\underline{C}(CH_3)_2$), 120.57 (1C, $H_2\underline{C}$=), 127.56 (1C, C-4), 129.13 (2C, C-2), 130.38 (2C, C-3), 138.94 (1C, C-1 ($\underline{C}$-CH_2-)), 141.29 (1C, =$\underline{C}$-CH_3), 157.55 (1C, $\underline{C}$=O, urethane), 169.30 (1C, $\underline{C}$=O, amide), 178.30 (1C, $\underline{C}$=O, acid); MS (FAB) 349 (M^++1); $[\alpha]_D^{20}$ = +14.3 (c = 1.005, methanol).

N-(1,1-Dimethyl-3-methacrylmethanamido-propoxy-carbonyl)-L-phenylalanine (2c)

Yield: 1.28 g (71%); mp 85-87°C; Analysis calcd. for $C_{19}H_{26}N_2O_5$ (362.3) C, 63.34; H, 7.22; N, 7.77. Found: C, 63.00; H, 7.01; N, 7.59; IR(KBr) 1720 (amide I, urethane), 1700 (C=O, acid), 1650 (amide I, amide), 1610 (C=C, olefin.), 1600/1500 (C=C, aromat.), 1530 (amide II) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (d, J = 5.6 Hz, 6H, $C(C\underline{H}_3)_2$), 1.87 (5H, =C-$C\underline{H}_3$, NH-CH_2-$C\underline{H}_2$-), 2.90-3.35 (AM of AMX, 2H, ν_A = 2.93, ν_M = 3.29, J_{AM} = 13.7 Hz, J_{AX} = 4.6 Hz, J_{MX} = 8.8 Hz, -CH-$C\underline{H}_2$-), 3.63 (q, ^3J = 6.9 Hz, 2H, NH-$C\underline{H}_2$-), 4.35-4.45 (X of AMX, 1H, ν_X = 4.40, -$C\underline{H}$-CH_2-), 5.25, 5.68 (AB, 2H, C=$C\underline{H}_2$), 7.10-7.20 (AA'MM'X, 5H, $C_6\underline{H}_5$- und 1H, N$\underline{H}$-); ^{13}C NMR ($CDCl_3$) δ 18.26 (1C, =C-$\underline{C}H_3$), 24.31, 26.82 (2C, $C(\underline{C}H_3)_2$), 34.77 (1C, NH-CH_2-$\underline{C}H_2$-), 38.50 (1C, CH-$\underline{C}H_2$-), 47.78 (1C, NH-$\underline{C}H_2$-CH_2-), 57.75 (1C, $\underline{C}$H-CH_2-), 81.20 (1C, $\underline{C}(CH_3)_2$), 120.18 (1C, $H_2\underline{C}$=), 126.43 (1C, C-4), 128.04 (2C, C-2), 129.13 (2C, C-3), 136.59 (1C, C-1 ($\underline{C}$-CH_2-)), 139.08 (1C, =$\underline{C}$-CH_3), 155.53 (1C, $\underline{C}$=O, urethane), 168.68 (1C, $\underline{C}$=O, amide), 178.68 (1C, $\underline{C}$=O, acid); MS (FAB) 363 (M^++1); $[\alpha]_D^{20}$ = +12.2 (c = 1.100, methanol).

Poly-[N-(1,1-dimethyl-2-methacrylmethanamido-ethoxy-carbonyl)-L-phenylalanine-co-methyl-methacrylate] (4c)

Yield: 85%; Analysis calcd. for $[C_{18}H_{24}N_2O_5]_1$ $[C_5H_8O_2]_{6.6}$ $(1008.3)_n$ C, 60.71; H, 7.62; N, 2.78. Found: C, 59.99; H, 7.54; N, 2.64; IR(KBr) 1710-1730 (C=O, ester and amide I, urethane), 1655 (amide I, amide), 1600/1500 (C=C, aromat.), 1520-1545 (amide II) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70-2.10 (C-$C\underline{H}_2$-, $C(C\underline{H}_3)_2$, C-$C\underline{H}_3$), 3.40-3.80 ($OC\underline{H}_3$, NH-$C\underline{H}_2$-, $C\underline{H}$-CH_2-, CH-$C\underline{H}_2$-), 7.25-7.30 ($C_6\underline{H}_5$-). $[\alpha]_D^{20}$ = +14.5 (c = 0.960, methanol); η_{spez}/c = 18.4 [10^{-3} L/g] c = 4.0 g/L (DMF, 25 °C).

Poly-[N-(1,1-dimethyl-3-methacrylmethanamido-propoxy-carbonyl)-L-phenylalanine-co-methyl-methacrylate] (5c)

Yield: 85%; Analysis calcd. for $[C_{19}H_{26}N_2O_5]_1$ $[C_5H_8O_2]_{6.1}$ $(972.2)_n$ C, 61.11; H, 7.69; N 2.88. Found: C, 60.78; H, 7.53; N, 2.70; IR(KBr) 1710-1730 (C=O, ester and amide I, urethane), 1655 (amide I, amide), 1600/1500 (C=C, aromat.), 1520-1545 (amide II) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70-2.20 (C-$C\underline{H}_2$-,

$C(C\underline{H}_3)_2$), $C-C\underline{H}_3$, $NH-CH_2-C\underline{H}_2-$), 3.35 - 3.85 ($OC\underline{H}_3$, $NH-C\underline{H}_2-$, $C\underline{H}-CH_2-$, $CH-C\underline{H}_2-$), 7.25-7.30 ($C_6\underline{H}_5-$); $[\alpha]_D^{20} = +13.9$ (c = 0.930, methanol); $\eta_{spez}/c = 18.4$ [10^{-3} L/g], c = 4.0 g/L (DMF, 25 °C).

N-(1,1-Dimethyl-2-methacrylmethanamido-ethoxycarbonyl)-L-phenylalanine methyl ester (1d)

1,1-Dimethyl-2-methacrylmethanamido-ethyl-(4-nitrophenyl)-carbonate (**1b**) (1.28g, 4mmol) was added to a stirred solution of L-phenylalanine methyl ester hydrochloride (840mg, 4mmol) and triethylamine (0.56mL, 4mmol) in absol. chloroform (10mL). The mixture was heated for 24h at 50°C. The yellow solution was washed with 1mL portions of cold N NaOH until the organic layer was nearly colourless. Then the organic layer was treated with N HCl and water (1mL portions (0-5 °C) respectively) and dried over magnesium sulfate. The solvent was evaporated. The residue was dissolved in a small amount of acetoacetic acid ethyl ester, covered with ether (10mL) and cooled at -20°C to induce light yellow crystals. The product is a waxy oil at room temperature. Yield: 1.15g (80%); Analysis calcd. for $C_{19}H_{26}N_2O_5$ (362.4) C, 62.90; H, 7.17; N, 7.72. Found: C, 62.46; H, 7.00; N, 7.61; IR(neat) 1740 (C=O, ester), 1710 (amide I, urethane), 1660 (amide I, amide), 1620 (C=C, olefin.), 1600/1500 (C=C, aromat.), 1520-1530 (amide II) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (d, J = 9.0 Hz, 6H, $C(C\underline{H}_3)_2$), 1.94 (s, 3H, $=C-C\underline{H}_3$), 2.90-3.10 (AM of AMX, 2H, $\nu_A = 2.95$, $\nu_M = 3.05$, $J_{AM} = 13.6$ Hz, $J_{AX} = 4.7$ Hz, $J_{MX} = 9.1$ Hz, $-CH-C\underline{H}_2-$), 3.52 (d, $^3J = 5.9$ Hz, 2H, $NH-C\underline{H}_2-$), 3.70 (s, $-OC\underline{H}_3$), 4.50-4.60 (X of AMX, 1H, $\nu_X = 4.55$, $-C\underline{H}-CH_2-$), 5.30, 5.71 (AB, 2H, $C=C\underline{H}_2$), 7.00-7.40 (7H, $C_6\underline{H}_5-$ and 2 N-H); ^{13}C NMR ($CDCl_3$) δ 18.48 (1C, $=C-\underline{C}H_3$), 23.34, 24.52 (2C, $C(\underline{C}H_3)_2$), 38.01 (1C, $CH-\underline{C}H_2-$), 47.83 (1C, $NH-\underline{C}H_2-$), 52.22 (1C, $-O\underline{C}H_3$), 54.50 (1C, $\underline{C}H-CH_2-$), 81.80 (1C, $\underline{C}(CH_3)_2$), 119.50 (1C, $H_2\underline{C}=$), 125.11 (1C, C-4), 128.45 (2C, C-2), 129.08 (2C, C-3), 135.71 (1C, C-1($\underline{C}-CH_2-$)), 139.81 (1C, $=\underline{C}-CH_3$), 155.27 (1C, $\underline{C}=O$, urethane), 168.31 (1C, $\underline{C}=O$, amide), 172.06 (1C, $\underline{C}=O$, ester); MS (DCI) 363 ($M^+ + 1$); $[\alpha]_D^{20} = -6.2$ (c = 1.010, methanol).

N-(1,1-Dimethyl-3-methacrylmethanamido-propoxycarbonyl)-L-phenylalanine methyl ester (2d)

The synthesis of **2d** was performed similar to **1d** using 1,1-dimethyl-3-methacrylmethanamido-propyl-(4-nitrophenyl)- carbonate (**2b**) (1.34g, 4mmol). A bright yellow, waxy product was obtained. Yield: 1.15g (79%); Analysis calcd. for $C_{20}H_{28}N_2O_5$ (376.4) C, 63.75; H, 7.44; N, 7.44. Found: C, 63.45; H, 7.20; N, 7.29; IR(neat) 1740 (C=O, ester), 1710 (amide I, urethane). 1660 (amide I, amide), 1620 (C=C, olefin.), 1600/1500 (C=C, aromat.), 1520-1530 (amide II) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 6H, $C(C\underline{H}_3)_2$), 1.93 (s, 3H, $=C-C\underline{H}_3$), 2.00 (t, $NH-CH_2-C\underline{H}_2-$), 2.95-3.30 (AM of AMX, 2H, $\nu_A = 3.00$, $\nu_M = 3.25$, $J_{AM} = 13.6$ Hz, $J_{AX} = 4.7$ Hz, $J_{MX} = 9.1$ Hz, $-CH-C\underline{H}_2-$), 3.50 (q, $^3J = 6.9$ Hz, 2H, $NH-C\underline{H}_2-$), 3.70 (s, $-OC\underline{H}_3$), 4.50-4.55 (X of AMX, 1H, $\nu_X = 4.52$, $-C\underline{H}-CH_2-$), 5.30, 5.71 (AB, 2H, $C=C\underline{H}_2$), 7.10-7.50 (7H, $C_6\underline{H}_5-$ und 2 N-H); ^{13}C NMR ($CDCl_3$) δ 18.49 (1C, $=C-\underline{C}H_3$), 24.20, 26.64 (2C, $C(\underline{C}H_3)_2$), 34.62 (1C, $NH-CH_2-\underline{C}H_2-$), 39.66 (1C, $CH-\underline{C}H_2-$), 51.80 (1C, $NH-\underline{C}H_2-$), 52.02 (1C, $-O\underline{C}H_3$), 54.28 (1C, $\underline{C}H-CH_2-$), 80.86 (1C, $\underline{C}(CH_3)_2$), 121.62 (1C, $H_2\underline{C}=$), 124.90 (1C, C-4), 128.97 (2C, C-2), 129.07 (2C, C-3), 135.66 (1C, C-1($\underline{C}-CH_2-$)), 139.57 (1C, $=\underline{C}-CH_3$), 155.28 (1C, $\underline{C}=O$, urethane), 168.07 (1C, $\underline{C}=O$, amide), 171.97 (1C, $\underline{C}=O$, ester); MS (FAB) 377 ($M^+ + 1$); $[\alpha]_D^{20} = -4.5$ (c = 1.020, methanol).

N-(1,1-Dimethyl-2-methacrylmethanamido-ethoxy-carbonyl)-L-phenylalanyl-L-phenylalanine methyl ester (5)

The dipeptide **5** was synthesized by the EDC-procedure.[14] A mixture of N-(1,1-dimethyl-2-methacrylmethanamido-ethoxy-carbonyl)-L-phenylalanine (**1d**) (200mg, 0.57 mmol), L-phenylalanine methyl ester hydrochloride (130mg, 0.57mmol) and triethylamine (0.08mL, 0.57mmol) in methylene chloride (10mL) was cooled and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) 109mg, 0.60mmol) was added at 0°C. The reaction mixture was stirred and kept for 30 min at 0°C and additional 30 min at room temperature. The precipitated triethylamine hydrochloride was filtered off and the solution washed successively with portions (2mL) of water, cold hydrogen chloride, sat. sodium carbonate and water. The solution was dried and the solvent evaporated. A pure waxy product was obtained. Yield: 205mg (66%); Analysis calcd. for $C_{28}H_{35}N_3O_6$ (509.3) C, 66.00; H, 6.88; N, 8.25. Found: C, 65.61; H, 6.60; N, 7.98; IR(neat) 1740-1710 (C=O, ester; amide I, urethane), 1660 (amide I, amide), 1620 (C=C, olefin.), 1600/1500 (C=C, aromat.), 1520-1530 (amide II) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (d, J = 9.0 Hz, 6H, $C(C\underline{H}_3)_2$), 1.95 (s, 3H, $=C-C\underline{H}_3$), 2.94-3.13 (two AM of AMX, 4H, $-CH-C\underline{H}_2-$), 3.52 (d, 2H, $NH-C\underline{H}_2-$), 3.67 (s, 3H, $-OC\underline{H}_3$), 4.35 and 4.80 (two X of AMX, 2H, $2*-C\underline{H}-CH_2-$), 5.24 (d, 1H, $N\underline{H}-CH-$), 5.33, 5.71 (AB, 2H, $C=C\underline{H}_2$), 6.99-7.30 (11H, $2*C_6\underline{H}_5-$ und $N-\underline{H}$); ^{13}C NMR ($CDCl_3$) δ 18.79 (1C, $=C-\underline{C}H_3$), 23.34, 24.55 (2C, $C(\underline{C}H_3)_2$), 38.20 (1C, $CH-\underline{C}H_2-$), 39.09 (1C, $CH-\underline{C}H_2-$), 47.91 (1C, $NH-\underline{C}H_2-$), 52.00 (1C, $-O\underline{C}H_3$), 52.88 (1C, $\underline{C}H-CH_2-$), 59.82 (1C, $\underline{C}H-CH_2-$), 82.00 (1C, $\underline{C}(CH_3)_2$), 120.75 (1C, $H_2\underline{C}=$), 126.98, 127.55, 127.60, 128.44, 129.12, 130.20, 130.31, (C-1,2, 3, 1', 2', 3'), 135.41, 138.80 (C-4, 4'), 140.72 (1C, $=\underline{C}-CH_3$), 156.20 (1C, $\underline{C}=O$, urethane), 171.20 (1C, $\underline{C}=O$, amide), 172.59 (1C, $\underline{C}=O$, amide), 172.08 (1C, $\underline{C}=O$, ester); MS (FAB) 510 (M^++1); $[\alpha]_D^{20}$ = + 8.9 (c = 1.001, methanol).

N-(1,1-Dimethyl-2-methacrylmethanamido-ethoxycarbonyl)-L-phenylalanyl-L-alanine *t*-butyl ester (6)

The dipeptide **6** was synthesized by the same way as **5** with L-alanine *t*-butyl ester hydrochloride (103mg, 0.57 mmol) as second component yielding a waxy product. Yield: 190mg (70%); Analysis calcd. for $C_{25}H_{37}N_3O_6$ (475.3) C, 63.16; H, 7.79; N, 8.84. Found: C, 62.70; H, 7.61; N, 8.59; IR(neat) 1740-1710 (C=O, ester; amide I, urethane), 1660 (amide I, amide), 1620 (C=C, olefin.), 1600/1500 (C=C, aromat.), 1520-1530 (amide II) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (d, J = 9.8 Hz, 3H, $CH-C\underline{H}_3$), 1.40 (d, J = 9.0 Hz, 6H, $C(C\underline{H}_3)_2$), 1.53 (s, 9H, $C(C\underline{H}_3)_3$), 1.90 (s, 3H, $=C-C\underline{H}_3$), 2.90-3.10 (AM of AMX, 2H, $-CH-C\underline{H}_2-$), 3.48 (d, ^3J = 5.9 Hz, 2H, $NH-C\underline{H}_2-$), 4.10-4.40 (2H, $-C\underline{H}-CH_2-$, $-C\underline{H}-CH_3$), 5.43, 5.78 (AB, 2H, $C=C\underline{H}_2$), 7.10-7.40 (7H, $C_6\underline{H}_5-$ and 2 $N-\underline{H}$); ^{13}C NMR ($CDCl_3$) δ 18.06 (1C, $CH-\underline{C}H_3$), 18.75 (1C, $=C-\underline{C}H_3$), 19.03 (3C, $C(\underline{C}H_3)_3$, 23.34, 24.52 (2C, $C(\underline{C}H_3)_2$), 38.20 (1C, $CH-\underline{C}H_2-$), 47.90 (1C, $NH-\underline{C}H_2-$), 54.50 (1C, $\underline{C}H-CH_2-$), 79.30 (1C, $\underline{C}(CH_3)_3$), 82.30 (1C, $\underline{C}(CH_3)_2$), 119.90 (1C, $H_2\underline{C}=$), 125.11 (1C, C-4), 128.59 (2C, C-2), 129.13 (2C, C-3), 135.63 (1C, C-1($\underline{C}-CH_2-$)), 139.81 (1C, $=\underline{C}-CH_3$), 156.27 (1C, $\underline{C}=O$, urethane), 169.31 (1C, $\underline{C}=O$, amide), 171.01 (1C, $\underline{C}=O$, amide), 173.06 (1C, C=O, ester); MS (FAB) 476 (M^++1); $[\alpha]_D^{20}$ = + 4.3 (c = 1.001, methanol);

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