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The 4-methacrylamido-2-methyl-2-butoxy-carbonyl-function as polymerizable amino-protecting group

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SUMMARY

The synthesis of an highly acidic sensitive polymerizable amino-protecting group is described in the case of the N-protected model compound 4-methacryl-amido-2-methyl-2-butyl-N-p-chlorophenylcarbamate. The new monomer was homopolymerized and copolymerized by radical initiation. Kinetics of acidically induced p-chloroaniline cleavage from the monomer and polymers were followed by NMR spectroscopy. The influence of Calcium-ions and neighbouring group effects are discussed.

INTRODUCTION

For the solid phase synthesis of peptides introduced by Merrifield many polymeric carboxy- and amino-protecting groups with benzylic functions were developed by modifying polystyrene networks[1].
Peptide syntheses using polymerizable methacryl derivatives of the tert- butyl-oxycarbonyl (t-BOC) amino-protecting groups have not been performed, because no suitable monomers are available.
In the course of our investigations in the area of polymer chemistry with enzymes[2,3,4,5] we became interested in preparing highly sensitive polymerizable amino-protecting groups for the moderate cleavage of enzymatically modified aminoacids or peptides from the polymer side chains. In our first attempt we obtained from N-(2-hydroxy-2-methyl-propyl-)methacrylamid and isocyanates polymerizable N-protected amines which were much less reactive than the ordinary t-BOC protecting group[6]. Thus the present investigation is concerned with the synthesis and preliminary characterisation of the new 4-methacrylamido-2-methyl-2-butoxycarbonyl-function as an highly acidic sensitive polymerizable amino—protecting group.

RESULTS and DISCUSSION

The condensation of 4-amino-2-methyl-2-butanol[7] 1 with methacryloylchloride yields the new polymerizable tert-butanol derivative 4-methacrylamido-2-methyl-2-butanol 2. By addition of p-chlorophenylisocyanate to the monomer 2 the monomeric N-protected model compound 4-methacrylamido-2-methyl-2-butyl-N-p-chlorophenylcarbamate 3 is obtained.

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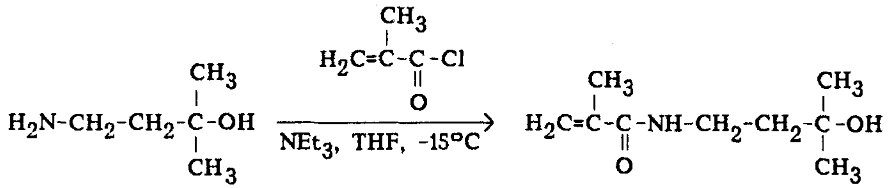

$$H_2N\text{-}CH_2\text{-}CH_2\text{-}C(CH_3)_2\text{-}OH \xrightarrow[NEt_3,\ THF,\ -15^{\circ}C]{H_2C{=}C(CH_3)\text{-}C(=O)\text{-}Cl} H_2C{=}C(CH_3)\text{-}C(=O)\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}C(CH_3)_2\text{-}OH$$

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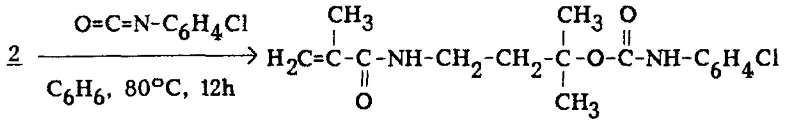
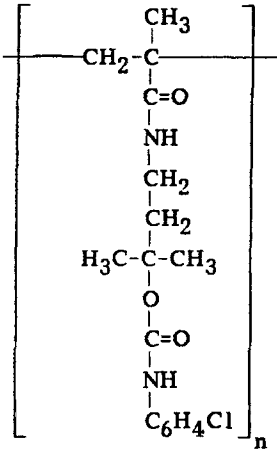


$$2 \xrightarrow[C_6H_6,\ 80^{\circ}C,\ 12h]{O{=}C{=}N\text{-}C_6H_4Cl} H_2C{=}C(CH_3)\text{-}C(=O)\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}C(CH_3)_2\text{-}O\text{-}C(=O)\text{-}NH\text{-}C_6H_4Cl$$

3

The monomer 3 was polymerized radically with azoisobutyronitrile (AIBN) as initiator to the homopolymer 4 and copolymerized with methylmethacrylate to the corresponding copolymer 5. The composition of the copolymer was analysed by ^{1}H-NMR spectroscopy and elementary analysis.



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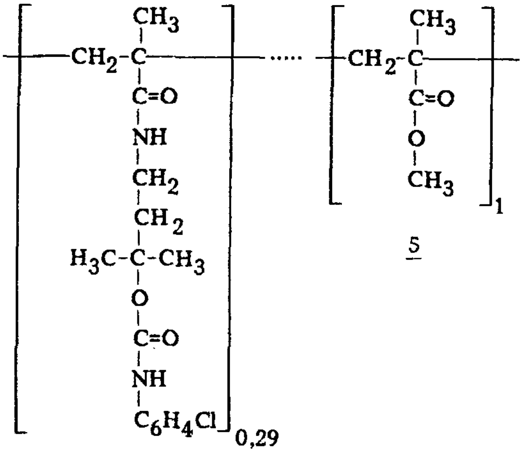

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The monomeric and polymeric urethanes 3-5 were dissolved in trifluoraceticacid (TFA) and the time-dependent release of the model-amine in this solvent was followed by NMR spectroscopy. The results of the kinetic measurements are summarized in figure 1.

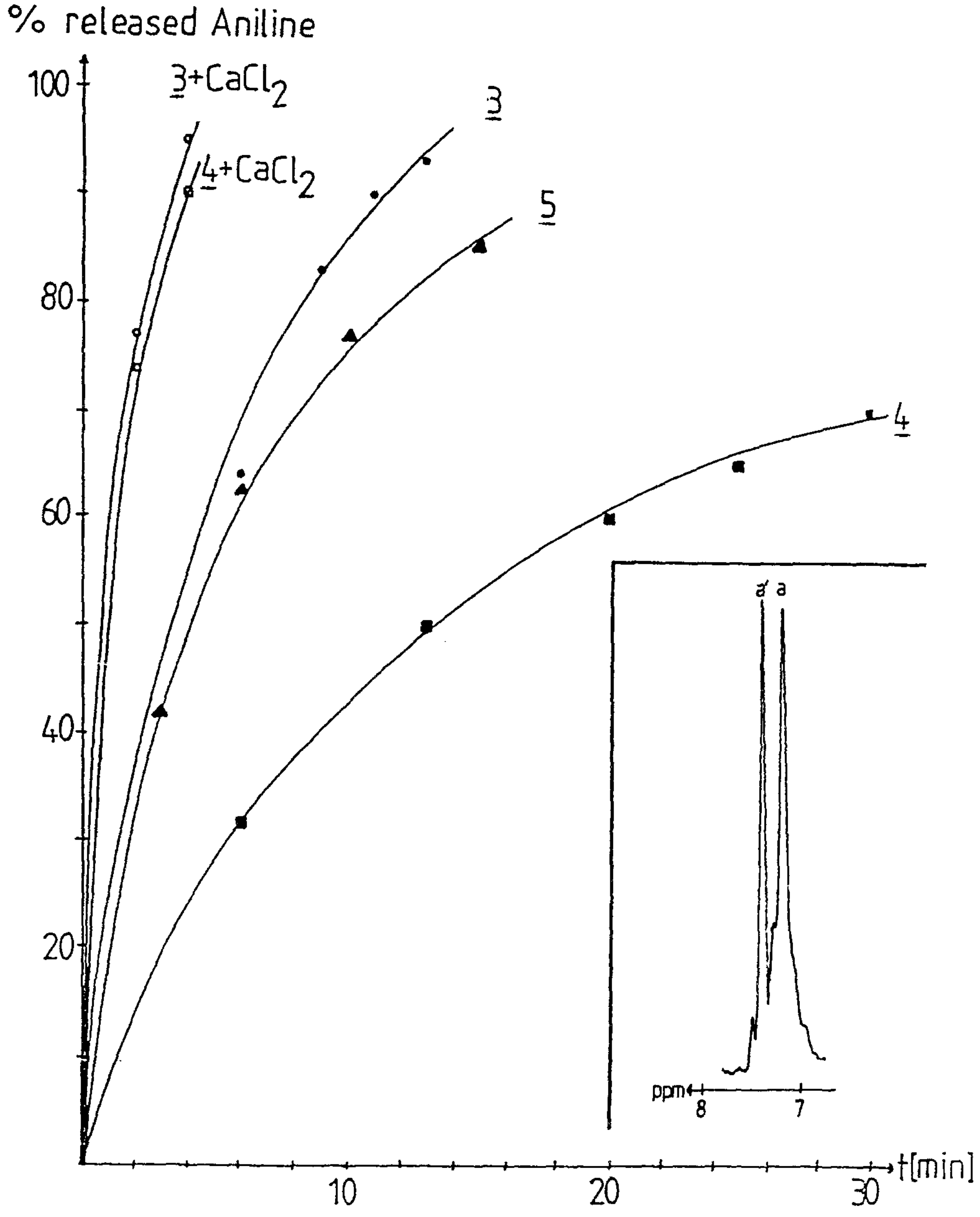
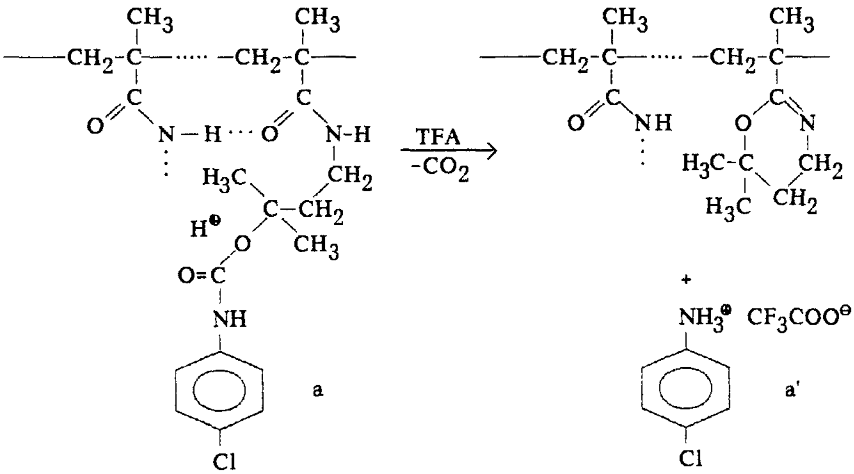


Figure 1: Typical NMR signals of polymer 4 in CF_3COOH after 15 minutes (a, a' covalently bound and released p-chloroaniline) and kinetic curves for the cleavage of p-choroaniline from substrates 3, 4, and 5 and the influence of Calcium-ions obtained by integration of the NMR signals

The significant difference in the sensitivities of the homo- and copolymer (Fig.1) can be explained by depression of the probability of hydrogen-bond-formation between neighbouring amide groups by copolymerization.



Thus, the relatively high reactivity of the monomer 3 in comparison to that of the corresponding homopolymer 4 can be connected with the lack of hydrogen bonding between neighbouring groups and the more highly nucleophilic carbonyl-oxygen of the conjugated methacrylic function. Calcium ions cause the destruction of hydrogen bonds and activate the urethane function.
From our results it can be concluded that the present polymerizable methacrylamido-2-methyl-2-butoxy-function is a potential amino-protecting group and may be used for different applications mainly in the area of peptide-chemistry.

EXPERIMENTAL

Monomers

4-N-methacryloyl-2-methyl-2-butanol (2)

To a solution of 5.15 g (0.05 mol) 4-amino-2-methyl-2-butanol and 7 ml (0.05 mol) triethylamine in 20 ml THF 5 ml (0.05 mol) methacryloylchloride are added slowly at -15°C. The suspension is stirred at 20°C for 24 h, filtered and evaporated. The resulting oil is diluted with 25 ml $CHCl_3$ and the organic phase is washed with a $NaHSO_4$ solution and water and then dried over $MgSO_4$. The solvent is evaporated and the resulting oil is covered with an ether/ petrolether phase to induce crystallisation at -10°C. Yield: 42%, m.p.: 84-85°C,

I.R. (KBr): 3310 (N-H, amid), 1655 (C=O, amid I), 1610 (C=C), 1540cm^{-1}(C=O, amid II);

M.S. m/e = 171 (M^+);

$C_9H_{17}NO_2$ (171,24)	calc.	C 63.13	H 10.01	N 8.18
	found	C 62.80	H 9.76	N 8.14

4-N-methacryloyl-2-methyl-2-butyl-N-p-chlorophenylcarbamate (3)

A solution of 1.71 g (0.01 mol) 2 ,1.54 g (0.01 mol) p-chlorophenylisocyanate and 0.002 ml dibutyltin dilaurate in 10 ml benzene is heated under reflux for 12 h. After evaporating the benzene the resulting oil is dissolved in 10 ml $CHCl_3$ and washed twice with water. The organic phase is dried over $MgSO_4$, $CHCl_3$ is evaporated and the resulting oil is covered with ether to induce crystallisation at -5°C. Yield: 67%, m.p.: 128-129°C,

I.R. (KBr): 3380 (N-H, urethane), 3260 (N-H, amid), 1690 (C=O, urethane), 1655 (C=O, amid I), 1615 (C=C), 1590 (C=C,phenyl, 1530 (C=O, amid II), 840cm^{-1} (C=C, phenyl);

M.S. m/e = 324 (M^+);

$C_{16}H_{21}N_2O_3Cl$ (324,81)	calc.	C 59.16	H 6.52	N 8.62
	found	C 58.69	H 6.46	N 8.70

Polymers

Homopolymer (4): Monomer 3, 5 mol-% AIBN as an initiator and 0.5 mol-% dodecylmercaptane are dissolved inTHF (30 weight-%). The reaction mixture is heated at 60°C for 24 h in a nitrogen atmosphere. The solution is diluted with THF and precipitated by pouring it into ether. The precipitated polymer is filtered and dried. Yield: 78%, η_{sp}/c = 6,28 ml/g (DMF, 25°C, 4 g/l)

I.R. (KBr): 3410 (N-H, urethane), 3310 (N-H, amid), 1700 (C=O, urethane), 1635 (C=O, amid I), 1590 (C=C, ring), 1530 (C=O, amid II), 825cm^{-1} (C=C, ring)

$[C_{16}H_{21}N_2O_3Cl]_n$ (324,81)	calc.	C 59.16	H 6.52	N 8.62
	found	C 58.72	H 6.59	N 8.21

Copolymer (5): 0.03 mol MMA and 0,01 mol monomer 3 were polymerized analogous the synthesis of 4 . Yield: 87%, η_{sp}/c = 7.43 ml/g (DMF, 25°C, 4 g/l)

I.R. (KBr): 1730 cm^{-1} (C=O, ester)

$[C_{16}H_{21}N_2O_3Cl]_{0,29_{a)}}[C_5H_8O_2]$ (194,31)	calc.	C 59.59	H 7.30	N 4.18
	found	C 58.73	H 7.40	N 4.43

a):in acordance with NMR spectroscopy

Cleavage of the amine:
100mg of the monomeric or polymeric urethanes are dissolved in 350 µl trifluoroacetic acid and the solutions are analysed by NMR spectroscopy (90 MHz) at 25°C. The addition of 100 mg $CaCl_2$ leads to the formation of a sediment.

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