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Polyalkylation of Primary Polyols by 1,4-Addition to *tert*-Butyl Acrylate and Acrylonitrile

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Abstract : The very hydrophilic primary polyols pentaerythritol (PE), 1,1,1-*tris*(hydroxymethyl)ethane and *tris*(hydroxymethyl)aminomethane (TRIS), can be polyetherified in satisfactory yield by 1,4-addition to *tert*-butyl acrylate using phase-transfer catalysis. Polycyanoethylation of these polyols can also be accomplished with acrylonitrile. Preliminary results of chelation between some polyether-acids with samarium (III) are presented.

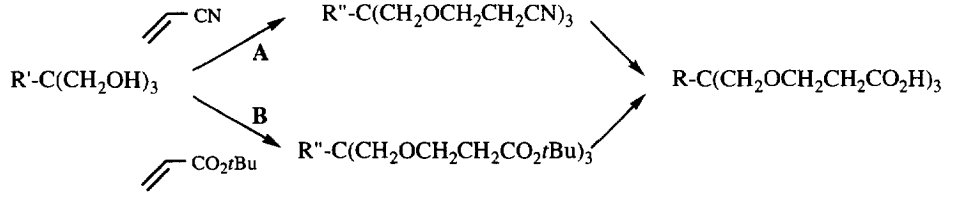
With a view toward the preparation of new complexing systems for lanthanide ions (Ln^{3+}) that could be used as biomedical labels, we undertook the synthesis of the following polyether-acids and of some derivatives for conjugation with monoclonal antibodies. These compounds are easier to prepare, *a priori*, than macrocyclic ligands bearing carboxylate groups which are well known for their complexation of lanthanides[1].

$R\text{-}C(CH_2OCH_2CH_2CO_2H)_3$

1	R= Me	**4**	R= Bn_2N
2	R= $CH_2OCH_2CH_2CO_2H$	**5**	R= CH_2OH
3	R= NH_2	**6**	R= $CH_2OCO(C_6H_4)NCS$

In this preliminary communication, we show that these compounds are easily accessible from inexpensive commercial products in two steps by 1,4-conjugate addition reactions (Scheme 1).

Scheme 1



R' = Me, CH_2OH, NH_2, Bn_2N R = Me, CH_2OH, $CH_2OCH_2CH_2CO_2H$, NH_2, Bn_2N

The first approach (**A**) is the 1,4-addition to acrylonitrile, followed by the hydrolysis of the nitrile function; the second (**B**) involves the 1,4-addition to *tert*-butyl acrylate and then hydrolysis of the ester function.

Although the 1,4-additions of carbanions (Michael addition), amines, and nucleophilic free radicals are of

current interest in organic synthesis[2], the 1,4-addition of oxygen nucleophiles is only infrequently reported[2,3] and there exist few published examples with polyols[4]. Nucleophilic substitutions are described for their polyetherification by phase-transfer catalysis[5].

The tetraalkylation of pentaerythritol (PE) had been improved by Schanzer and coll.[4a], who accomplished this reaction with acrylonitrile in the presence of a catalytic amount of sodium hydroxide (40%). We have successfully extended this 1,4-addition to some other primary polyols (method **A**). However, the experimental conditions do not give satisfactory results when acrylonitrile is replaced with *tert*-butyl acrylate. This alternative is required when procedures for the hydrolysis of the nitrile function are incompatible with functions such as an alkoxycarbonyl in the R group. In this report, we describe also a new procedure that is efficient for the polyaddition of *tert*-butyl acrylate to primary polyols[6].

In a typical experiment (method **B**), 5 mmol of PE in aqueous sodium hydroxide (4 mL, 50%) at ca. 15 °C are well stirred with *tert*-butyl acrylate (20.5 mmol) and a phase-transfer agent (1 mmol nBu$_4$N$^+$ HSO_4^- or Br^-). After 6h, the reaction mixture is diluted with cold water and extracted 3 times with ether (3x20 mL). The combined organic phases are washed with brine and dried over anhydrous sodium sulfate. The resulting tetra *tert*-butyl ester is isolated by silica gel chromatography with a hexane-ethyl acetate gradient.

The results, summarized in the Table, show that the very hydrophilic polyols give good yields of 1,4-addition products with acrylonitrile (method **A**). With *tert*-butyl acrylate, the yields are usually lower except in the case of the less hydrophilic polyol $Bn_2NC(CH_2OH)_3$[7]. Nevertheless, route **B** is interesting since the polyacids can be obtained in the next step in quantitative yield under less drastic experimental conditions.

Table: Polyalkylation of primary polyols by 1,4-addition.

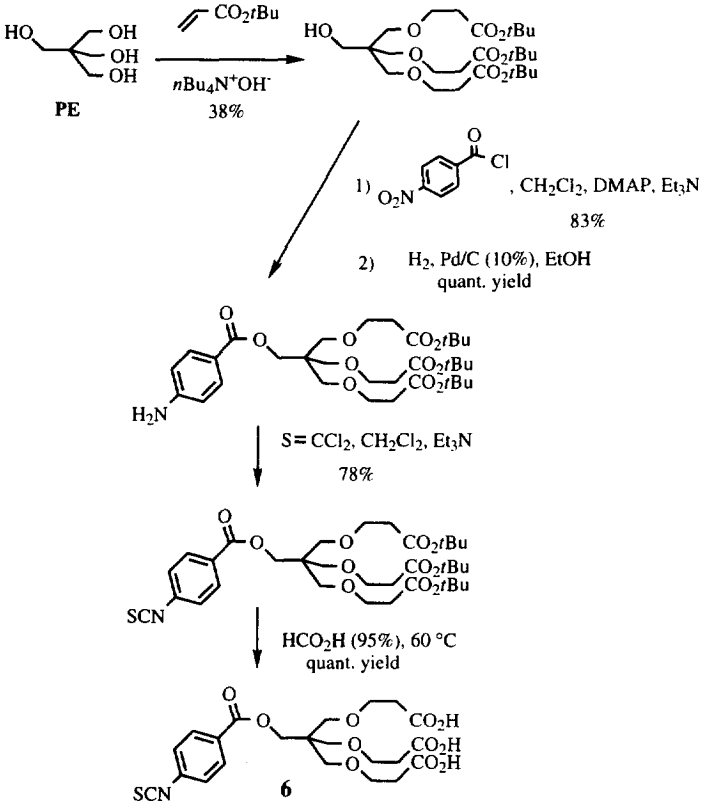
	Method	Primary polyol Polyalkylation yield[1)]			
		$MeC(CH_2OH)_3$	$C(CH_2OH)_4$	$H_2NC(CH_2OH)_3$	$Bn_2NC(CH_2OH)_3$
	**A** [2)]	99	99	71	21
	**B**	78	53[8]	38	55

1) Yields (%) for tetraalkylation of PE and trialkylation of the others. The products were isolated by column chromatography (silica gel, hexane-ethyl acetate gradient). All new compounds were fully characterized by IR, ^1H and ^{13}C NMR, MS, and elemental analysis.

2) Method **A**[4a]: cat. NaOH 40%, room temperature, overnight.

In the case of the PE polyalkylation, it is possible to obtain a mixture of tri- and tetra-addition products with less *tert*-butyl acrylate (method **B**). The triester $HOCH_2C(CH_2OCH_2CH_2CO_2tBu)_3$ can be prepared in better yield (38% isolated), however, when an aqueous solution of PE and tetrabutylammonium hydroxide (40 wt.%) is stirred at room temperature for one week with only 3 equivalents of *tert*-butyl acrylate. From this compound, polyacid **6** (Scheme 2) has been efficiently synthetized and conjugated to a monoclonal antibody via the isothiocyano group[9].

Scheme 2[10]



Samarium (III) chelates of polyethers-acids **1**,**2** and **3** were prepared in accordance with standard methods. The polyether-acid was dissolved in water (10^{-1}-10^{-3}M solution) and neutralized with sodium hydroxide. One equivalent of samarium (III) chloride in water (10^{-2}M) was added over 15 min and the pH was maintained in the range 5-7. With the compounds **1** and **2**, the samarium chelates precipitated immediately to give white powders that are insoluble in water. At this stage these precipitates were filtered off, with the exception of polyether-amino-acid **3** which remained soluble in the reaction mixture. After stirring for 2h, the pH was raised to 8.5 with 1M NaOH and the precipitate was filtered off. The aqueous solution was treated with acetone and the precipitate was filtered and washed with acetone. The yields are over 70%.

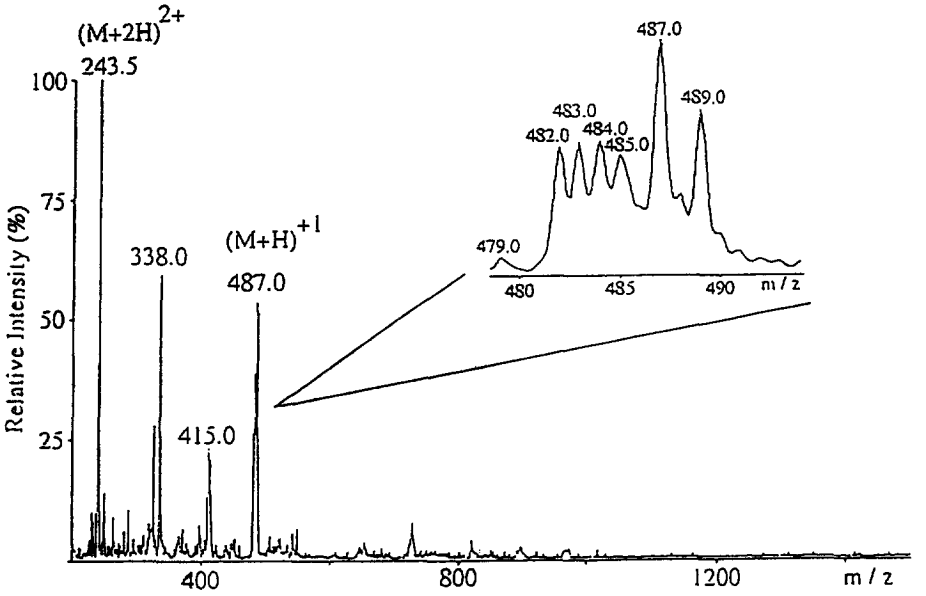
The chelation reaction was followed by Infrared spectroscopy (FT-IR) using Attenuated Total Reflectance (ATR) method. The carboxylate ions exhibited the characteristic $\nu_a(CO_2^-)$ and $\nu_s(CO_2^-)$ frequencies of unidentate complexes[11]: $RCO_2^-Na^+$: ca 1560 and 1405 cm^{-1}.

$(RCO_2^-)_3Sm^{3+}$: ca 1560 and 1450 cm^{-1}.

The reaction mixtures or chelate solutions in water were analyzed by Mass Spectroscopy using ElectroSpray technic[12] (ESI-MS). With ligands **1** and **3**, we observed the mass of the chelate formed with one ligand and one Sm^{3+} ion, with the characteristic isotopic abundance for samarium (Fig.). In the case of the ligand **2**, a fragment with one Sm^{3+}, generated from the 1:1 chelate, was detected.

The chelation of some other lanthanide ions with these polyether-acids is under investigation.

Fig. ESI-MS of the Samarium (III) chelate obtained with the polyether-amino-acid **3** (M.W.: 338).



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6. Control of the temperature (10 to 20 °C) is necessary to avoid side reactions such as 1,4-addition of hydroxide.
7. This polyol is prepared from *tris*(hydroxymethyl)aminomethane and benzyl bromide (BnBr) in H_2O with $NaHCO_3$ (68%).
8. $C(CH_2OCH_2CH_2CO_2tBu)_4$, viscous oil : Anal. Calcd for $C_{33}H_{60}O_{12}$: C, 61.08; H, 9.32. Found: C, 60.91; H, 9.02; IR (*neat*) 1736, 1485, 1457, 1375, 1264, 1159, 1119, 856 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.59 (t, 8H), 3.35 (s, 8H), 2.43 (t, 8H), 1.45 (s, 36H) ; ^{13}C NMR δ 170.9, 80.2, 69.6, 67.0, 45.2, 36.3, 28.0.
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   b) The compound **6** was coupled to a fragment of monoclonal antibody [$F(ab')_2$ anti-ACE (F_6)] by Dr. Alain Faivre-Chauvet (INSERM U.211 - University of Nantes) who is gratefully thanked.
10. Each compound (with the exception of the unstable **6**) was isolated by chromatography (SiO_2) and fully characterized by spectroscopic and analytical data.
11. Nakamoto, K. *Infrared and Raman Spectra of Inorganic and Coordination Compounds*, J. Wiley, New-York, **1978**.
12. ESI-MS was performed using a SCIEX API III+ quadrupole mass spectrometer (Perkin-Elmer Sciex Instruments, Thornhill, Canada) equiped with a nebulizer-assisted electrospray (ionspray) source. Calibration was performed using poly(propylene glycol) ions. The samples were solubilized in water then infused using a syringe pump (Harvard 22, South Natic, USA) at a flow rate of 5µl/min. The mass spectrometer was scanned from m/z = 200 to 1500 at 0.5 Da steps and 2 ms per step. Mass spectra were analyzed using a Quadra 950 data system (Apple Computer Inc., Cuppertino, USA).

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