Supporting Information

Synthesis and Biological Evaluation of New Bisphosphonate-Dextran Conjugates Targeting Breast Primary Tumor

Evelyne Migianu-Griffoni,*,† Imène Chebbi,† Souad Kachbi,† Maelle Monteil,† Odile Sainte-Catherine,† Frédéric Chaubet,‡ Olivier Oudar,‡ and Marc Lecouvey*,†

† Université Paris 13, Sorbonne Paris Cité, Laboratoire de Chimie, Structure, Propriétés de Biomatériaux et d'Agents Thérapeutiques (CSPBAT), CNRS UMR 7244, 74, Rue Marcel Cachin F-93017 Bobigny, France

‡ Université Paris 13, Sorbonne Paris Cité, Laboratoire BPC, INSERM U 698, 99, Avenue Jean-Baptiste Clément F-93430 Villetaneuse, France

** To whom correspondence should be addressed*

Determination of the degree of substitution (D.S.) in CarboxyMethyl (CM) groups of CMD 1

The CM content was determined on dried aliquots of dextran derivatives (25-45 mg) by acidimetric titration with NaOH solution in water/acetone mixture (1/1-v/v) acidified with 2N HNO_3. Two equivalence volumes were distinguished : the first one V_{eq1} corresponding to the equivalence of the excess of strong acid HNO_3; and the second one assigned to the equivalence of the weak carboxylic acid groups of CMD **1**. Thus, the amount of CM functions per gram of polymer n_{CM} could be calculated by the relation (1) and was about 3.87±0.04 mmol.g^{-1}.

$$n_{CM} = (V_{eq2}-V_{eq1}) \text{ x } C_{NaOH}/m_{CMD} \qquad (1)$$

The amount of remaining free hydroxyl groups $n_{R\text{-}O\text{-}H}$ per gram of polymer must be determined by the equation (2).

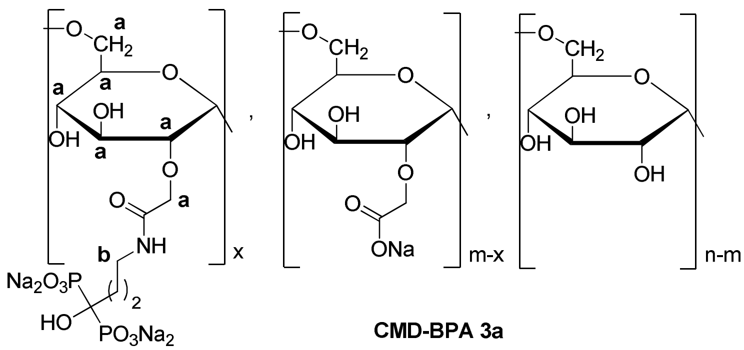
$$(n_{R\text{-}O\text{-}H} \text{ x } M_{R\text{-}O\text{-}H}) + (n_{CM} \text{ x } M_{R\text{-}O\text{-}CM}) = 1 \qquad (2)$$

Besides, each glucosidic unit of the dextran macromolecule has a molecular weight of 162.16 Da. Each unit bears three hydroxyl groups on carbon atoms 2, 3 and 4 which could be replaced by a CM group. So, the average molecular weight of one glucosidic unit can be assimilated to three R-O-H subunits with $M_{R\text{-}O\text{-}H}$ = 54.05 Da. When the hydrogen atom is replaced by a CM group, the molecular weight $M_{R\text{-}O\text{-}CM}$ of the subunit is equal to 134.07 Da (CM = CH_2-COONa). Thus, equation (2) gave $n_{R\text{-}O\text{-}H}$ = 8.90±0.09 mmol.g^{-1}. Finally, the D.S. of CMD **1** (0.91) could be determined by the equation (3).

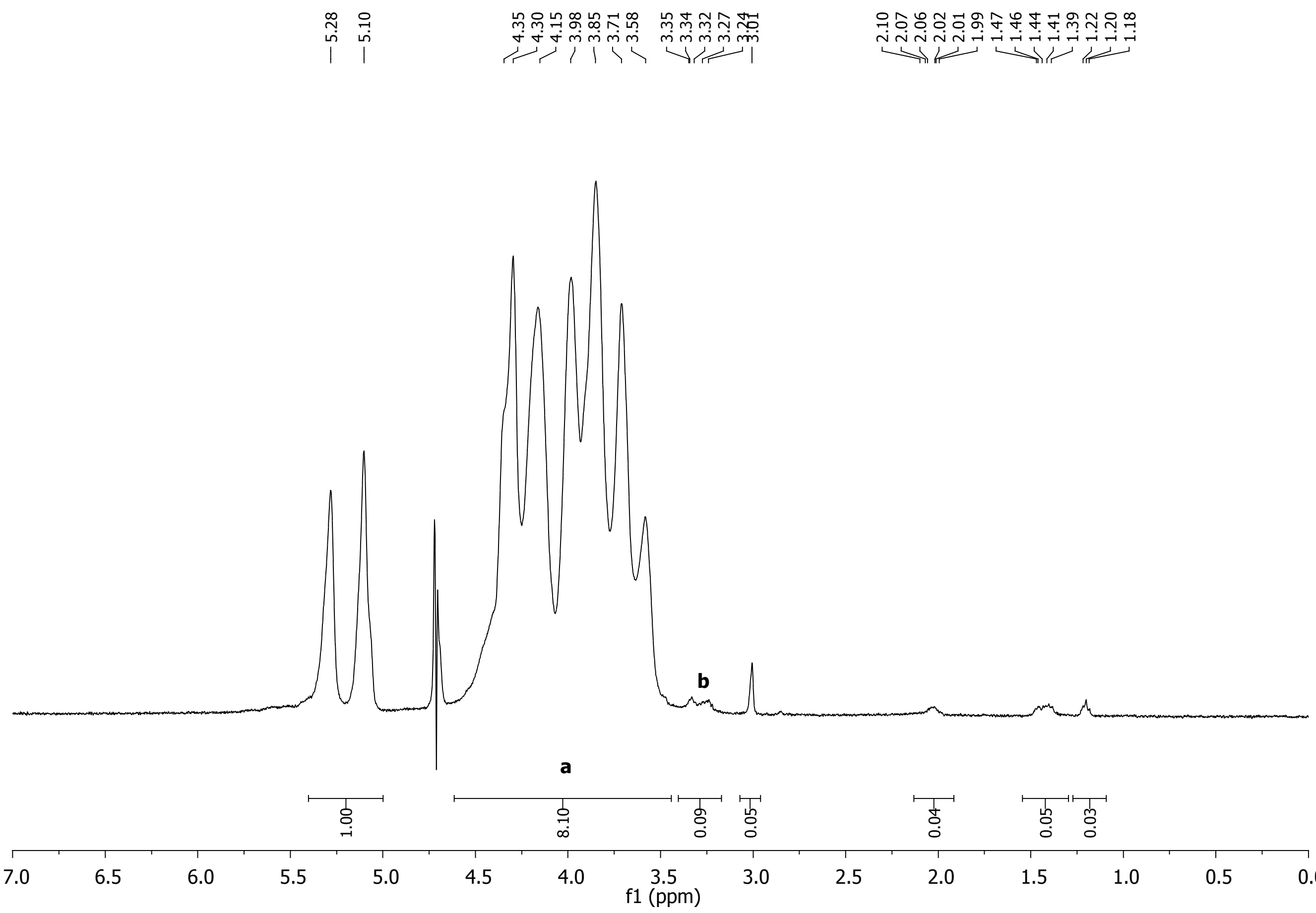
$$\text{D.S.} = (3 \text{ x } n_{CM}) / (n_{CM} + n_{R\text{-}O\text{-}H}) \qquad (3)$$

NMR spectra :

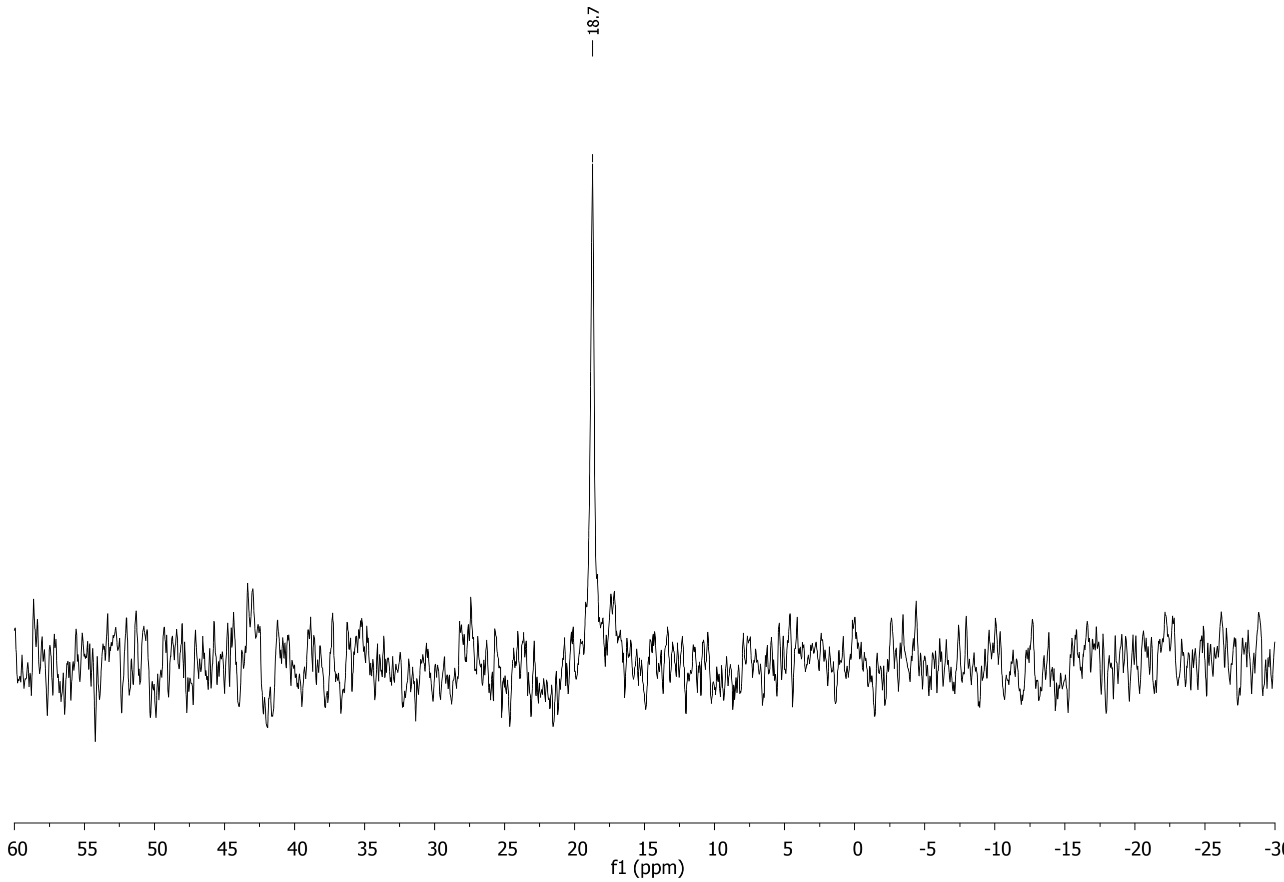
CMD-BPA2 3a – ^{1}H NMR



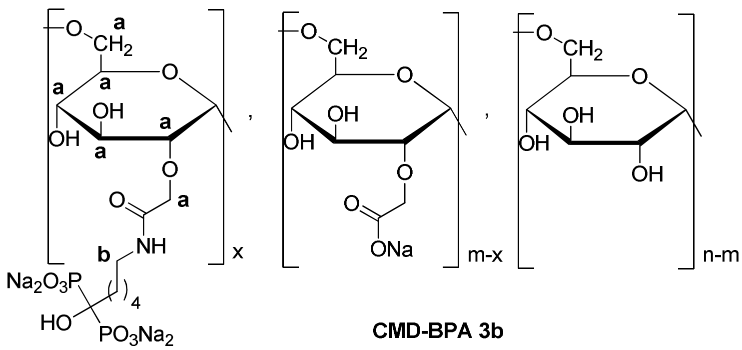
CMD-BPA 3a



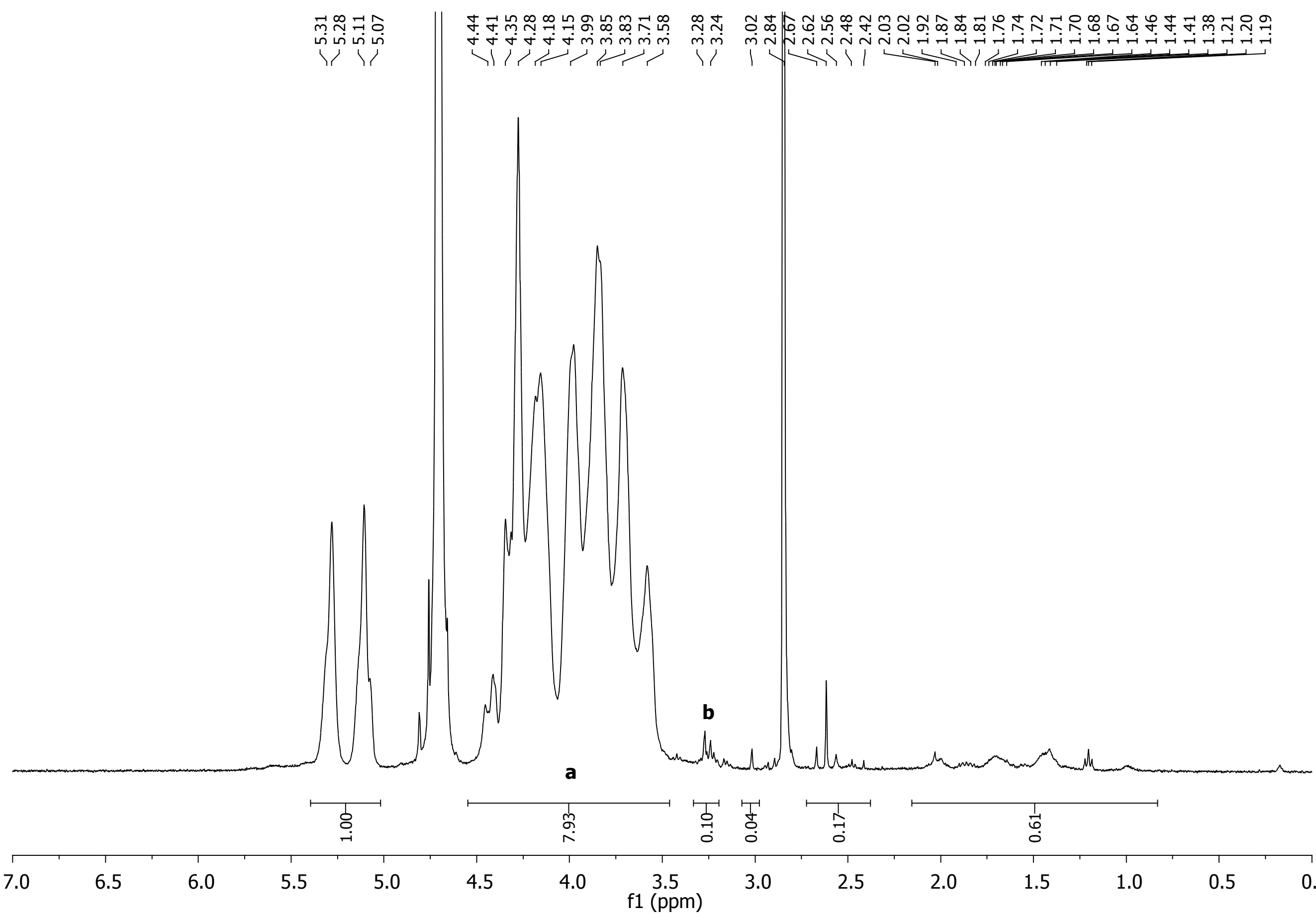
CMD-BPA2 3a – ^{31}P NMR



CMD-BPA3 3b – ^{1}H NMR



CMD-BPA 3b



CMD-BPA3 3b – ^{31}P NMR