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Synthesis of EDTA core dendrimers through a consecutive esterification-CuAAC process

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ABSTRACT

A novel class of thermostable G0 and G1-dendrimers was synthesized from the coupling of both propargyl and azido esters derived from EDTA through copper catalyzed azide-alkyne cycloaddition. The branching and size in these compounds were controlled by a simple azide-alkyne group position change in the CuAAC reaction in conjunction with the use of 1,3-diazido-propan-2-ol as a polyfunctional compound.

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dendrimer; EDTA; ester; click chemistry

1. Introduction

Dendrimers are macromolecules that have drawn attention of scientists for several years due to their properties and well-defined architectures in addition to the increasing number of applications found for these types of compounds.[1] In recent times, dendrimer chemistry has been enriched with the introduction of the click chemistry approach which has been used to prepare highly functionalized dendrimers as well as the combination of both divergent and convergent strategies for the synthesis of these products.[2]

Unlike common polymers, dendrimers present three basic architectural components: core, generations (interior of shell) and terminal functional groups (the outer shell or periphery). Hence, the dendrimer synthesis requires the construction of these components through divergent or convergent hierarchical assembly strategies.[3]

The divergent synthesis strategy initiates dendrimer growth on a molecule that will become the dendrimer core continuing outward through a sequence of coupling and activation steps, and the dendrimer branching is obtained by reaction of the core peripheral functionalities with the complementary reactive group of the monomer. In contrast, the convergent approach for dendrimer synthesis takes as departure materials molecules that will eventually become the exterior of the dendrimer progressing inward by coupling end groups to each branch of the monomer, finishing with a coupling at the focal point of the wedge-shaped dendritic fragment or dendron.[4]

On this point, CuAAC reaction and Click Chemistry concept, developed initially by the groups of Sharpless[5] and Meldal,[6] has enhanced the procedures to prepare dendrimers.[7] Since the seminal works reported by the groups of Hawker[8] and Fokin,[9] CuAAC reaction has been successfully incorporated as key reaction in the dendrimer design used in both divergent[10] or convergent[11] synthetic strategies, demonstrating that this reaction is an useful synthetic tool for the development of dendrimers.

On the other hand, a particular trend in dendrimer science is focused on the design and study of nitrogen-containing dendrimers and their use as peptidomimetics which simulate specific protein functions with promising applications in anticancer drug delivery.[12] In this regard, a potential molecule that could be used as a dendrimer core in the preparation of nitrogen-containing dendrimers is EDTA **1**. In spite of its availability, there are few reports about the utilization of EDTA as departure material in the preparation of dendrimers or analogous compounds. For example, Hirsch and coworkers described the synthesis of chiral depsipeptide dendrimers from EDTA which were complexed with diverse metals.[13]

These elements prompted us to investigate the possible synthesis of dendrimers with an EDTA nucleus based on our experience in copper-catalyzed azide-alkyne cycloaddition (CuAAC), the most important click reaction.

2. Experimental section

2.1. General Remarks

CAUTION! Although we did not have any incidents by handling, it is known that organic azides and azide rich compounds can be HIGHLY explosive. Decomposition of organic azides can be also catalyzed by certain transition metal species and by strong acids.[14]

The starting materials were purchased from Aldrich Chemical Co. and were used without further purification. 1,3-diazido-propan-2-ol[4] was prepared according to literature.[15] Solvents

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were distilled before use. Silica plates of 0.20 mm thickness were used for thin layer chromatography. Melting points were determined with a Fisher-Johns melting point apparatus and they are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance 300; the chemical shifts (δ) are given in ppm relative to TMS as internal standard (0.00). For analytical purposes the mass spectra were recorded on a Shimadzu GCMS-QP2010 Plus in the EI mode, 70 eV, 200°C via direct inlet probe. Only the molecular and parent ions (m/z) are reported. IR spectra were recorded on a Bruker Tensor 27 equipment. TGA/DSC studies were carried out in a thermal analyzer Netzsch STA 449 F3 Jupiter with a heating ramp of 10°C/min, in a nitrogen atmosphere at a flow rate of 20 mL/min. Samples were heated from room temperature to 560°C; aluminum crucibles of 5-mm diameter were used. Savitzky-Golay smoothing algorithm was employed for TGA curves.

2.2. Synthesis of EDTA esters

A solution of EDTA (1 g, 3.42 mmol) in CH_2Cl_2 (10 mL) was treated successively with the appropriate alcohol (15.41mmol), EDC (3.15 g, 15.41mmol) and 4-(dimethylamino)pyridine (2.06 g, 15.41mmol). CH_2Cl_2 (40 mL) was added dropwise and the resulting reaction mixture was stirred under a nitrogen atmosphere for 7 days at room temperature. H_2O (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (5 × 15 mL). The combined organic layers were washed with 1M HCl solution (3 × 15 mL), and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the product was used without additional purification.

2.2.1. {[2-(Bis-prop-2-ynyloxycarbonylmethyl-amino)-ethyl]-prop-2-ynyloxycarbonylmethyl-amino}-acetic acid prop-2-ynyl ester[2]

Selected spectral data. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.52 (s, 4 H), 2.97 (s, 4 H), 3.71 (s, 8 H), 4.72 (s, 8 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 51.0 (4X CH_2), 51.2 (2 X CH_2), 54.0 (4 X CH_2), 74.3 (4 X CH), 76.4 (4 X C), 169. 3 (4 X C); IR: (ATR, cm^{-1}) 2129, 1754, 1722, 758, MS [EI^+] m/z (RI%): 444 $[M]^+$.

2.2.2. ((2-Azido-1-azidomethyl-ethoxycarbonylmethyl)-{2-[bis-(2-azido-1-azidomethyl-ethoxycarbonylmethyl)-amino]-ethyl}-amino)-acetic acid 2-azido-1-azidomethyl-ethyl ester[5]

Selected spectral data. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.94 (s, 4 H), 3.38 (d, 4 H), 3.50 (d, 16 H), 3.97 (s, 4 H), 5.11 (dd, 4 H); ^{13}C NMR (CDCl3, 75 MHz) δ: 50.3 (8 X CH_2), 52.2 (2 X CH_2), 53.9 (4 X CH_2), 71.2 (4 X CH), 170. 3 (4 X C); IR: (ATR, cm^{-1}) 2095, 1739, 1624; MS [EI^+] m/z (RI%): 788 $[M]^+$.[5]

2.3. Synthesis of dendrimers derived from EDTA propargyl ester 2

A solution of EDTA propargyl ester **2** (0.444 g, 1 mmol) in CH_2Cl_2 (25 mL) was treated successively with the appropriate azide (4.2 mmol), DIPEA (0.69 mL, 0.516 g, 4.0 mmol) and CuI (0.038 g, 0.2 mmol). The resulting reaction mixture was stirred for 7 days at room temperature. MeOH (10 mL) was added and the precipitate was collected by filtration, washed successively with 0.1 M EDTA·2Na solution, H_2O and cold MeOH, and dried under vacuum to afford the corresponding dendrimer.

Compound 3a: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.74 (s, 4 H), 3.48 (s, 8 H), 4.74 (s, 8 H), 5.13 (s, 8 H), 7.22(s, 4 H), 7.23 (m, 8 H), 7.35 (m, 8 H), 7. 52 (m, 4 H), 7.62 (s, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 52.0 (2 X CH_2), 55.0 (4 X CH_2), 59.10(4 X CH2), 123.9 (4 X CH), 128.1 (8 X CH), 129.1 (8 X CH), 134.5 (4 X CH), 142.8 (4 X C), 170.9 (4 X C); IR: (ATR, cm^{-1}) 1741, 1620; HRESIMS calcd. for $[C_{50}H_{52}N_{14}O_8 + Na]^+$: 999.3990, found: 999.4079.

Compound 3b: ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.79 (s, 4 H), 3.60 (s, 12 H), 3.81 (s, 8 H), 5.19 (s, 8 H), 7.08 (d, 8 H), 7.73 (d, 8 H), 8.62 (s, 4 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 51.3 (2 X CH_2), 54.4 (4 X CH_3), 55.4 (4 X CH_2), 56.8 (4 X CH_2), 114.7 (8 X CH), 121.7 (4 X CH), 122.7 (8 X CH), 129.8 (4 X C), 142.6 (4 X C), 159.2 (4 X C), 170.56 (4 X C); IR: (ATR, cm^{-1}) 2838, 1741; HRESIMS calcd. for $[C_{50}H_{52}N_{14}O_{12} + Na]^+$: 1063.3787, found: 1063.3863.

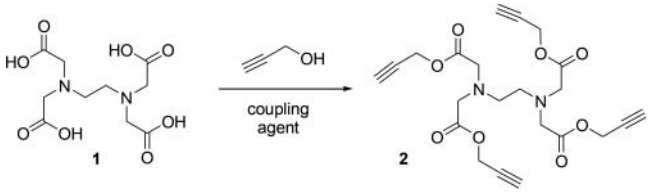
Compound 3c: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.40 (s, 12 H), 2.89 (s, 4 H), 3.62 (s, 8 H), 5.27 (s, 8 H), 7.29 (d, 8 H), 7.58 (d, 8 H), 8.05 (s, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.5 (4 X CH_3), 49.7 (2 X CH_2), 52.6 (4 X CH_2), 55.1 (4 X CH_2), 117.9 (4 X CH), 119.9 (4 X CH), 127.7 (4 X CH), 131.9 (4 X CH), 136.5 (4 X C), 140.5 (4 X C), 168.5 (4 X C); IR: (ATR, cm^{-1}) 1741, 8164; HRESIMS calcd. for $[C_{50}H_{52}N_{14}O_8 + Na]^+$: 999.3990, found: 999.3982. Compound **3d**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.86 (s, 4 H), 3.62 (s, 8 H), 5.25 (s, 8 H), 7.67 (m, 4 H), 7.80 (d, 4 H), 8.09 (d, 4 H), 8.63 (s, 4 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 51.5 (2 X CH_2), 54.6 (4 X CH_2), 56.7 (4 X CH_2), 119.2 (4 X CH), 121.5 (4 X CH), 122.3 (4 X CH), 131.1 (4 X CH), 131.7 (4 X C), 132.9 (4 x C), 135.6 (4 X C), 143.1 (4 X C), 170.3 (4 X C); IR: (ATR, cm_{-1}) 1748, 1624; HRESIMS calcd. for $[C_{46}H_{36}C_{l8}N_{14}O_8 + Na]^+$: 1192.0349, found: 1192.0386.

2.4. Synthesis of dendrimers derived from EDTA azido ester 5

A solution of EDTA azido ester **5** (0.788 g, 1 mmol) in CH_2Cl_2 (25 mL) was treated successively with the appropriate alkyne (8.4 mmol), DIPEA (1.38 mL, 1.032 g, 8.0 mmol) and CuI (0.076 g, 0.4 mmol). The resulting reaction mixture was stirred for 7 days at room temperature. MeOH (10 mL) was added and the precipitate was collected by filtration, washed successively with 0.1 M EDTA·2Na solution, H_2O and cold MeOH, and dried under vacuum to afford the corresponding dendrimer.

Compound 6a: ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.18 (s, 4 H), 3.25 (s, 8 H), 4.61 (dd, 16 H), 5.79 (dd, 4 H), 7.23–7.34 (m, 24 H), 7.43 (dd, 16 H), 8.21 (s, 8 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 49.9 (8 X CH_2), 53.1 (2 X CH_2), 55.2 (4 X CH), 68.2 (4 X CH), 122.2 (8 X CH), 125.0 (16 X CH), 127.6 (8 X CH), 128.6 (8 X C), 146.5 (8 X C), 168. 9 (4 X C); IR: (ATR, cm^{-1}) 1740, 1624; HRESIMS calcd. for $[C_{86}H_{80}N_{26}O_8 + Na]^+$: 1627.6550, found: 1628.6397.

Compound 6b: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.41 (m. 16 H), 2.83 (s, 4 H), 2.76 (t, 16 H), 2.23 (t, 16 H), 3.22 (s, 8 H), 5.63 (dd, 4 H), 4.30 (s, 4 H), 7.64 (s, 8 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 15.5 (8 X CH_2), 23.7 (8 X CH_2), 25.9 (8 X CH_2), 52.3 (4 X CH_2), 68.2 (4 X CH), 119.6 (8 X C), 122.5 (8 X CH), 146.8 (8 X C), 168. 4 (4 X C); IR: (ATR, cm^{-1}) 3303, 2243, 1740;



Scheme 1. Synthesis of EDTA propargyl ester **2**.

Table 1. Coupling agents used in esterification of EDTA **1**.

Entry	Coupling Agent	Temperature	Reaction Time (h)	% Yield
1	H_2SO_4cat.	reflux	24	30
2	H_2SO_4cat.	reflux	48	10
3	PTSA	reflux	24	15
4	PTSA	reflux	48	15
5	$SOCl_2$	0 °C-R.T.	24	25
6	$(COCl)_2$	0 °C-R.T.	24	10
7	CDI	R.T.—50 °C	48	10
8	DCC	R.T	24	15
9	DCC	R.T.	168	68
10	EDC	R.T.	24	30
11	EDC	R.T.	168	95

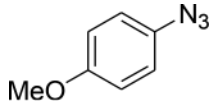
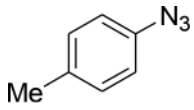
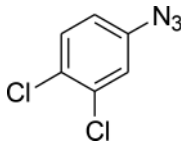
Table 2. Effect of catalyst, base, solvent and reaction time in the reaction between benzyl azide and EDTA propargyl ester **2**.

Entry	Catalyst ratio (% mol)	DIPEA ratio (mol/mol EDTA)	Solvent	Time (h)	% Yield
1	5	1	CH_2Cl_2	24	22
2	10	2	CH_2Cl_2	24	33
3	20	4	CH_2Cl_2	24	20
4	5	1	CH_2Cl_2	72	3
5	10	2	CH_2Cl_2	72	40
6	20	4	CH_2Cl_2	72	32
7	10	2	CH_2Cl_2	168	12
8	20	4	CH_3CN	168	51
9	20	4	acetone	168	51
10	20	4	MeOH	168	35
11	20	4.5	THF	168	40
12	20	4.5	CH_2Cl_2	168	55

HRESIMS calcd. for $[C_{70}H_{88}N_{34}O_8+Na]^+$: 1555.7422, found: 1555.7638.

Compound 6c: ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.56 (s, 4 H), 3.10 (s, 8 H), 4.58 (d, 16 H), 4.99 – 4.79 (dd, 4 H), 8.05 (d, 16 H), 8.24 (d, 16 H), 8.50 (s, 8 H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ: 50.1 (8 X CH_2), 53.1 (2XCH_2), 57.9 (4 X CH_2), 68.0 (4 X CH), 99.5 (8 X CH), 123.8 (16 X CH), 125.6 (16 X CH), 137.0 (8 X C), 144.3 (8 X C), 146.4 (8 X C), 170. 1 (4 X C); IR: (ATR, cm^{-1}) 1747, 1341; HRESIMS calcd. for $[C_{86}H_{72}N_{34}O_{24}+Na]^+$: 1987.5356, found: 1987.4047.

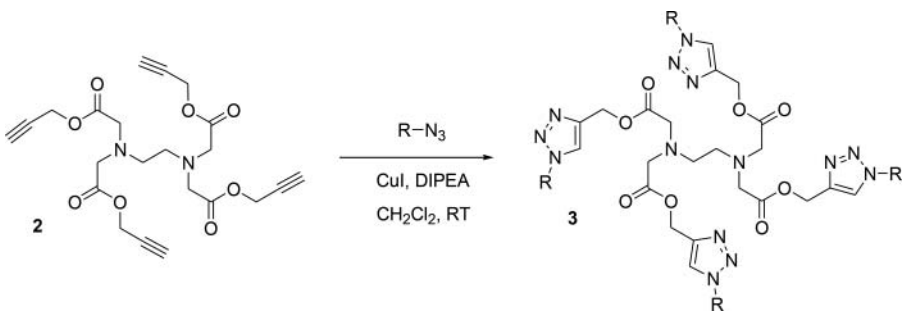
Table 3. Azides used in the synthesis of dendrimers **3**.

Compound	Azide	Time (h)	Yield (%)
3a	$Bn-N_3$	168	55
3b		120	75
3c		48	71
3d		48	20

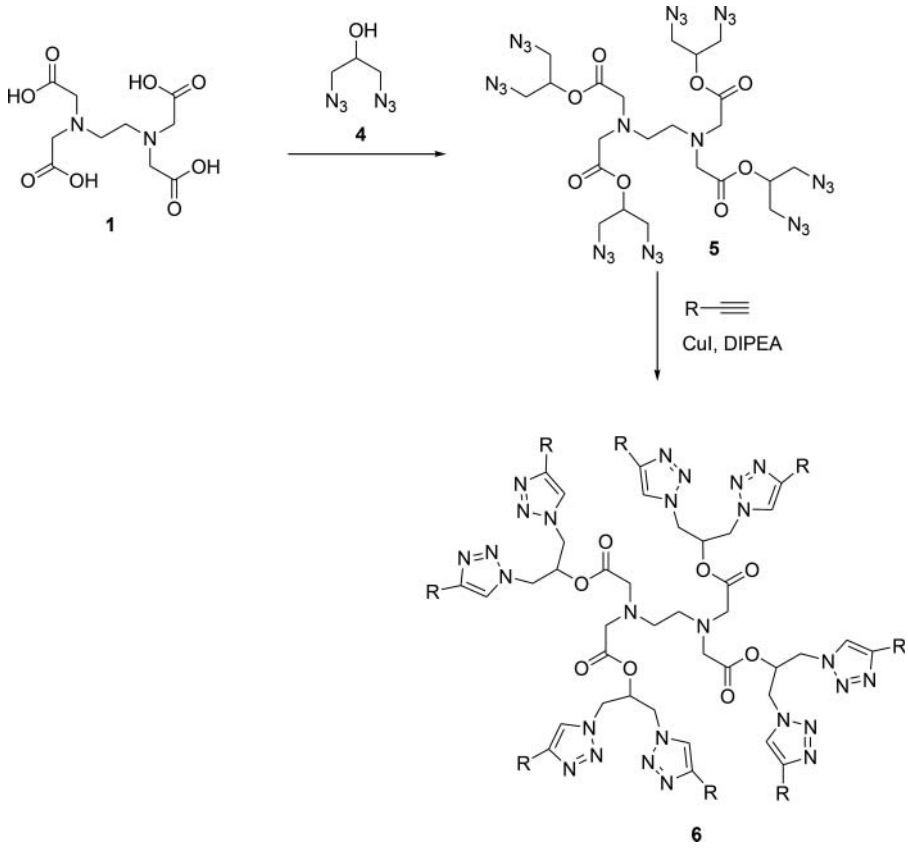
3. Results and discussion

The first studied process was the preparation of a propargyl ester derived from EDTA. For this purpose, EDTA **1** was treated with propargyl alcohol in presence of diverse coupling agents such as DCC,[13,16] CDI,[17] $SOCl_2$,[18] $(COCl)_2$,[19] EDC[13] as well as an acid catalyst[20] for yielding the ester products (scheme 1). The results summarized in table 1 show that EDC afforded the best yields (95%). As an additional advantage, the use of EDC as coupling agent did not generate by-products, and the final product was obtained in a form sufficiently pure to be used without further purification.

In a model study, EDTA propargyl ester **2** was treated with excess of benzyl azide in presence of catalytic amounts of CuI and DIPEA. In order to establish the best reaction conditions, several experiments were carried out using different concentrations of catalyst, base, solvent and reaction time (Table 2). Optimal conditions were obtained when the reaction is carried out at room temperature using 20% mol



Scheme 2. Synthesis of EDTA core dendrimer **3** from EDTA propargyl ester **2**.



Scheme 3. Synthesis of EDTA core dendrimer **6** from EDTA azido ester **5**.

catalyst and 4 molar equivalents of DIPEA during a 168 h period, being that shorter reaction times yielded only incomplete products, usually only with 2 or 3 triazole rings formed.

On the other hand, solvents evaluated for this study included acetonitrile, acetone, CH_2Cl_2, methanol and THF. From these solvents, CH_2Cl_2 was chosen because the use of this solvent combines higher efficiency with an easy side product removal and simple purification by precipitation with MeOH and subsequent washing with ether.

In addition, a series of azides was tested in the CuAAC reaction with EDTA propargyl ester **2** (scheme 2). The examples in table 3 demonstrated that dendrimer formation occurred in moderate to good yields.

In order to explore other variants, the azide-alkyne group position change in CuAAC reaction was also studied. Thus, EDTA **1** was converted to the azido ester 5 in 80% yield through the EDC mediated coupling with 1,3-diazido-propan-2-ol **4** which in turn was prepared from epichlorohydrin and sodium azide (scheme 3).[15] Diazido alcohol **4** was found to be a useful polyfunctional compound that was easily incorporated to EDTA to produce a core with a higher degree of branching.

Following a similar protocol to that described for compound **3**, EDTA azido ester **5** was reacted with phenylacetylene using CuI/DIPEA system as catalytic source, affording dendrimer **6a**. This procedure was extended to other alkynes obtaining the corresponding dendrimers presented in table 4.

The azide-alkyne group position change in CuAAC reaction has proved to be important in this synthesis owing to the fact that their use permitted an increase in the dendrimer branching, since the coupling promoted by CuAAC reaction of highly branched azido ester **5** was feasible, besides other kind of molecules such as alkynes can be used as starting materials. Accordingly, modulation of both size and branching is possible through this simple strategy.

All dendrimers were fully characterized by the conventional spectroscopic techniques which confirmed the proposed structure for these compounds. For example, the ^1H NMR spectrum for the dendrimer **3b** is presented in Figure 1 showing a characteristic triazole single sign at 8.62 ppm. The presence of triazole moiety is confirmed with the corresponding ^{13}C NMR spectrum (Figure 2)

Table 4. Alkynes used in the synthesis of dendrimers 6.

Compound	Azide	Time (h)	Yield (%)
6a	Ph—	168	98
6b	NC	120	43
6c	O_2N	48	46

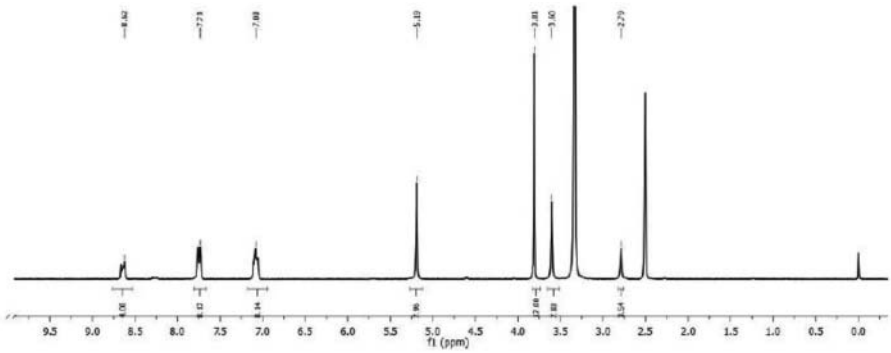


Figure 1. ^{1}H NMR spectrum of the dendrimer **3b**.

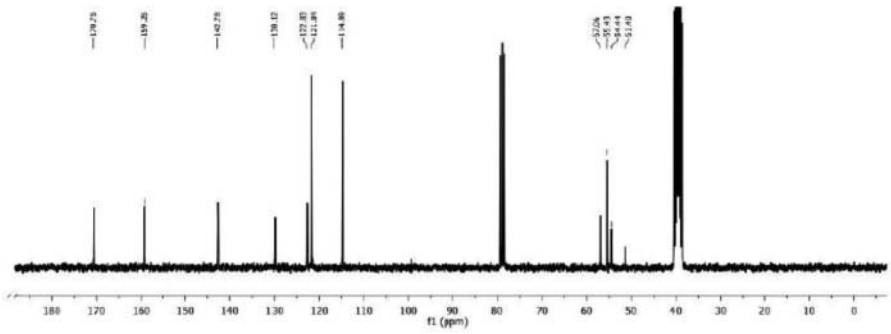


Figure 2. ^{13}C NMR spectrum of the dendrimer **3b**.

which presents signs at 142.8 and 114.9 ppm assigned to C-4 and C-5 triazole carbons respectively. Moreover, high resolution mass spectrum for compound **3b** provided a molecular weight of 1063.3863 according to the proposed structure (Figure 3).

A remarkable property observed in the synthesized dendrimers is their high thermal stability such as TGA and DSC studies performed on these compounds suggest. This behavior was determined by TG curves analysis for dendrimers **3b**, **3 c**, **6 a** and **6 c** shown in Figure 4 which display thermal stability up to 300°C. After this point, an important weight loss (about 80%) is observed for all dendrimers with a 50°C range between more stable dendrimer **3b** and less stable dendrimer **6 c** due to its continuous and immediate weight loss. The total decomposition of dendrimers occurs at 400°C.

DSC studies were determined on dendrimers **3b**, **3 c**, **6 a** and **6 c** and the corresponding DSC curves of investigated samples are plotted in Figure 5. The DSC analysis exhibits an endothermic process for dendrimer 3b at 170°C corresponding to melting point and an exothermic process at 326°C indicating decomposition thereof. Similarly, an endothermic process at 147°C corresponding to melting point and an exothermic process at 326°C owing to dendrimer decomposition are registered for compound **3 c**. In contrast, dendrimers **6 a** and **6 c** showed exothermic processes at 337 and 343°C respectively associated with degradation of both macromolecules. These results support the feature that EDTA azido ester core dendrimers present higher thermal stability as those dendrimers obtained from EDTA propargyl ester **2**.

The observed thermostability provides to EDTA core dendrimers the possibility of use of this kind of compounds in a diverse range of applications aimed to the synthesis of resistant peptoid dendrimers for biological purposes.

The experiments above described demonstrate that EDTA molecule, in conjunction with click chemistry, can be used as core and starting material for the construction of dendrimers comparable with other molecules such as cyclam,[21] tetra(ethyleneoxide),[22] PEG,[23] benzene-1,3,5-tricorboxlyic

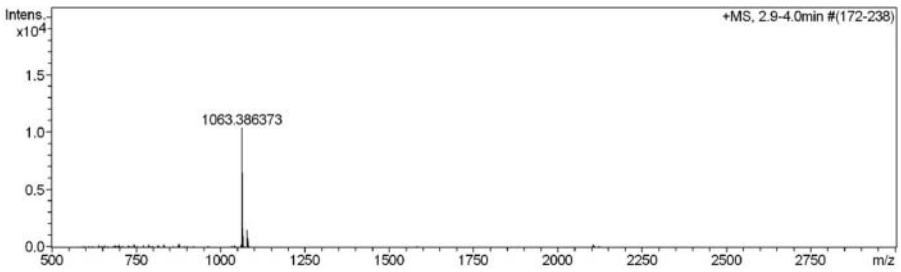


Figure 3. HRESIMS of the dendrimer **3b**.

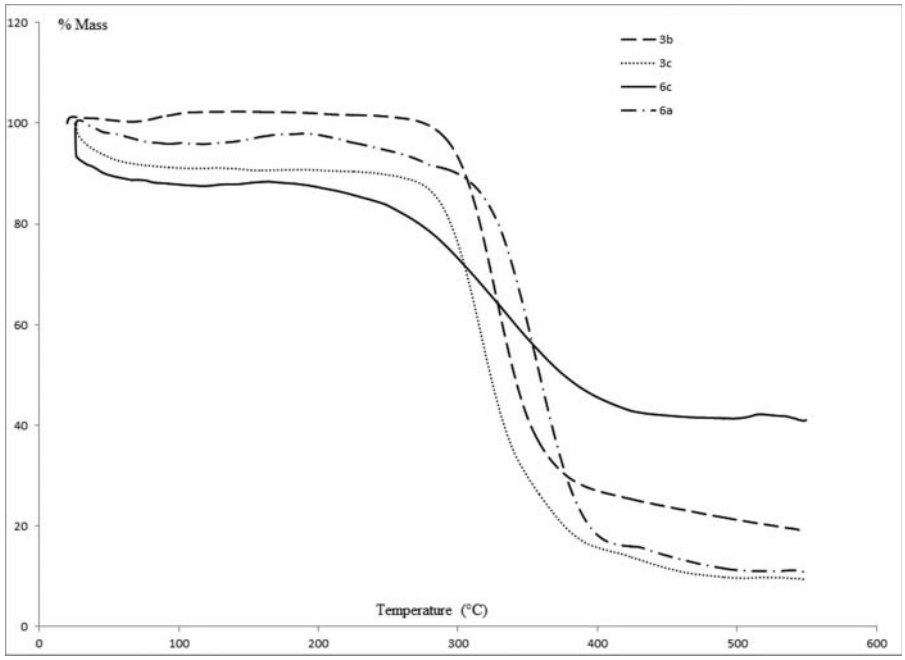


Figure 4. TG thermograms of EDTA core dendrimers **3b**, **3c**, **6a** and **6c**.

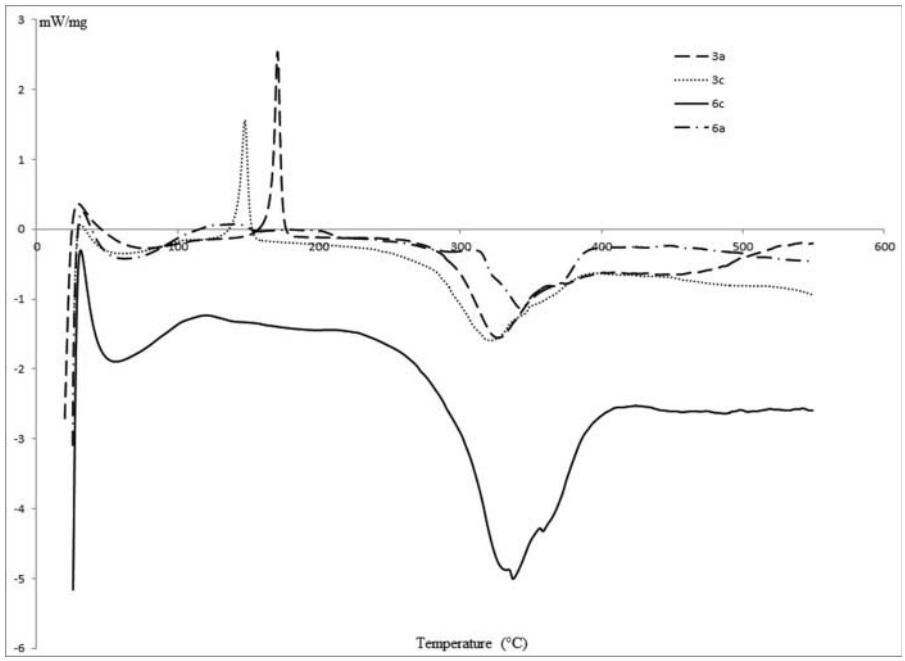


Figure 5. DSC curves for EDTA core dendrimers **3b**, **3c**, **6a** and **6d**.

amide,[24] and carbazole[25] used as cores in dendrimer synthesis.

4. Conclusions

In conclusion, the use of EDTA as nitrogen-containing core in combination with click chemistry as assembling strategy allows the divergent synthesis of new thermostable G0 and G1-dendrimers through a simple and efficient proceeding, besides a high thermal stability found in these compounds which open wide perspectives of promising applications in the future. These elements suggest a widespread application of the methodology herein described.

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