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Effect of the Molecular Structure on the Reactivity in a Family of Tetra-Amine Compounds Derived from Jeffamines

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Abstract: The effect of the molecular structure on the reactivity of four first-generation linear-dendritic block copolymers derived from Jeffamines and bearing amine end groups is presented and discussed. Different parameters were investigated *via* chemical modifications and nuclear magnetic resonance analysis, showing that chain length, hydrophilic/hydrophobic character, and flexibility of the central oligoether block did not produce any change in the amine moiety reactivity. In contrast, the type of branches and the nature of the amine end groups strongly affected the reactivity in an unusual manner. In fact, the copolymer bearing aromatic amine end groups showed better reactivity than those based on aliphatic counterparts.

Keywords: block copolymers, dendritic jeffamines, amines, hydrogen bonds, aggregation, reactivity.

Introduction

In linear-dendritic copolymers both moieties produce strong effects on the characteristics and the behavior of these kind of macromolecules and give rise to the formation of a macromolecule with modified and promising properties.[1,2] Thus, it has been reported that while the presence of the dendritic portion in a copolymer decreases its viscosity, the presence of the linear polyether increases its flexibility.[3] Jeffamines for instance, *i.e*. linear oligo(ethylene oxide) or poly(propylene oxide) molecules bearing amine end-groups, have been extensively used as building blocks in the preparation of different materials, since they can be easily modified in order to improve their properties, such as hydrophilic/hydrophobic balance[4] and biocompatibility.[5] Branched jeffamines have also been found to contribute in improving the final properties of different materials, such as conductivity.[6] They also offer the possibility to handle the glass transition temperature (T_g) values for a system with similar crosslink density.[7] Moreover, in comparison with linear-linear block copolymers, linear-dendritic block copolymers have shown a distinct self-assembly behavior because of the higher asymmetry between the dendritic moieties and the linear segment.[8-11]

The synthesis of dendritic first- and second-generation jeffamines (G1 and G2, respectively) bearing aliphatic amine end-groups has been reported and showed that the ensuing macromolecules displayed a lack of reactivity.[12] In fact, long reaction times and high temperatures were necessary to synthesize the dendritic products. In addition, the dendritic G2 jeffamine showed lower reactivity than their G1 homologues. The reactivity of the latter was even lower than that of the unmodified jeffamines. Similar features were observed for other products, where -NH_2 groups are located in dendrimers or dendritic moieties.[13-15] However, the synthesis of a different linear-dendritic copolymer bearing aromatic amine groups in the dendritic fragments was also reported and showed to be more reactive than the aliphatic counterparts,[16] which is unusual for such functional groups. It has been suggested that this unusual reactivity could be because these amines are implied in the formation of intra- and/or inter molecular hydrogen bonds of different nature and extends.[16]

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Based on these reports, the present work investigates the effect of the molecular structure on those intra- and/or inter molecular hydrogen bonds and how they could affect the reactivity of the first generation tetra-amine dendritic jeffamines. Thus, four different linear-dendritic copolymers containing combinations of diverse cores and dendritic fragments were synthesized and studied through a combination of chemical methodologies (chemical derivatization and crosslinking polymerization) and characterized spectroscopically (^{1}H NMR, one and two dimensional nuclear overhauser effect spectroscopy (NOESY) and rotating-frame overhauser effect spectroscopy (ROESY) experiments). Specifically, on the one hand, the structure of the central segment was varied keeping the type of branches and the end functional groups (same dendritic growth) constant in order to study the effect of the length and the nature (hydrophobic versus hydrophilic) of the linear oligoether central block, and, on the other hand, while the linear block (jeffamine) remained unchanged, the branches and the nature of the terminal groups were modified (different dendritic growth) to evaluate how the nature of the amine groups (aliphatic *versus* aromatic) affects the behavior of the macromolecules.

Experimental

Synthesis of the Copolymers and Di-2,5-furylene Vinylene (DFV). All dendritic jeffamines used in the present study were synthesized following reported procedures. Thus, compounds **1**, **2**, and **3** were synthesized as previously described,[12] whereas compound **4** and di-2,5-furylene vinylene (DFV) were obtained according to a published procedure.[17]

Formation of Networks Through Crosslinking Polymerization. The preparation of polyureas was carried out as follow: the chosen tetra-amine core (1.0 mmol) was dissolved in dimethyl sulfoxide (DMSO) (10 mL) in a flask equipped with a magnetic stirrer and a nitrogen inlet. The solution was stirred at room temperature for 1 h before adding dropwise a solution of methyl phenyl diisocyanate oligomer (MDI) with 2.7 eq./mol (1 mmol in 2.5 mL of DMSO). The reaction mixture was stirred for 24 h, then an excess of methanol (MeOH) was added to the reaction medium in order to neutralize the excess of isocyanates, thus forming soluble urethane molecules. Finally, the reaction medium was submitted to Soxhlet extractions with MeOH to purify and quantify the gel fraction. It is worth mentioning that the quantity of the methanol-MDI-adducts (di- and tri-urethanes) was calculated from the reaction stoichiometry, in order to determine the gel fraction of each polyurethane network prepared.

^{1}H NMR, 1D and 2D NOESY and ROESY Studies. NMR spectra were recorded on a Brüker Avance II (400.16 MHz, 5 mm BBI 1H/D-BB Z- grad Z8202/0349 probe) spectrometer. One and two-dimensional NOESY and ROESY experiments were performed on a 25 mM copolymer solution at 298 K using pulsed field gradient sequences for signal selection. The solvents used were water-d_2, methanol-d_4, or DMSO-d_6 (Aldrich).

The following acquisition parameters were used: i) 2D-ROESY: with *cw* spinlock for mixing, phase sensitive, water suppression, using a 3-9-19 pulse sequence with gradients p15=250 ms, p1=7.9 μs and a relaxation delay of 2 s; ii) 2D-NOESY: 2D homonuclear correlation *via* dipolar coupling (it may be due to NOE or chemical exchange), phase sensitive, with gradient pulses in mixing time, with several mixing times ranging from 200 to 900 ms and a relaxation delay of 3 s; iii) 1D selective ROESY: with cw spinlock for mixing, using selective refocusing with a shaped pulse of p15= 250 ms, d1=1s; iv) 1D selective NOESY: using selective refocusing with a shaped pulse (dipolar coupling may be due to NOE or chemical exchange) d1 of 1s.

The spectra were processed using standard Bruker programs. The following processing parameters were applied: i) 2D-ROESY: SI=2K and 1K (in F2 and F1, respectively), WDW=QSINE function in both domains, LB=0.0 and 0.3 Hz; ii) 2D-NOESY: SI=2K and 1K (F2/F1), WDW=QSINE function in both domains, LB=2.0 and 0.3 Hz; iii) 1D selective ROESY: SI=32K, WDW=EM function, LB=1.0; iv) 1D selective NOESY: SI=32K, WDW=EM function and LB=1.0.

Results and Discussion

Figure 1 shows the four synthesized first generation linear-dendritic block copolymers containing three different

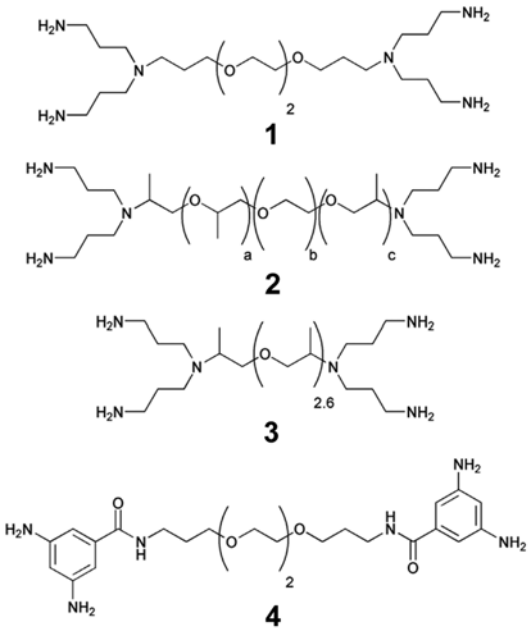

Figure 1. Family of tetra-amines prepared from different jeffamines. In compound **2**, b ~ 9.0 and a + c ~ 3.6.

jeffamines as central segments and two different dendritic growths, namely:

i) 4,7,10-trioxa-1,13-tridecanediamine, a poly(ethylene oxide) backbone with a molecular weight of 220, is a flexible and hydrophilic short segment which was used to synthesize compound **1**;

ii) *O*,*O*'-bis(2-aminopropyl) poly(ethylene glycol), jeffamine ED600 with a molecular weight of ~600, was used in the synthesis of **2** in order to maintain the hydrophilic character and the flexibility of the central block, while increasing its length. This longer linear segment would offer the system the possibility to hold the two dendritic moieties far enough to avoid their direct intra-molecular interaction;

iii) *O*,*O*'-bis(2-aminopropyl) poly(propylene glycol), jeffamine D230 with a molecular weight close to 230, has approximately the same length as that of the first one, but with much lower hydrophilicity and flexibility than those associated with previous structures. This molecule was employed in the synthesis of **3**;

iv) 4,7,10-trioxa-1,13-tridecanediamine was also used to obtain compound **4**. This allowed to keep the length, the flexibility and the hydrophilic character of the central block (compared with compound **1**), while the type of ramification and the nature of the end functional groups were modified, introducing stiff dendritic moieties and aromatic amines.

All tetra-functional jeffamines prepared in this work presented a similar solubility in most common solvents, *viz*. good solubility in water, DMSO and MeOH, very poor solubility in DMF (even non-soluble aggregates appear after some hours at room temperature), and insolubility in THF and all tested chlorinated solvents. As expected, the solubility of these extremely hygroscopic copolymers was higher in polar solvents.

Study of the Reaction Between the Synthesized Tetra-Amine Jeffamines and the Aldehyde-Containing Chromophore DFV. A comparative reactivity investigation was carried out through Schiff's base formation between the different tetra-functional jeffamines and the aldehyde-containing chromophore DFV. Several reaction conditions were assayed to prepare the products, *viz*. solvent-free, different solvents, stoichiometry, temperatures and reaction times. Table I summarizes the conditions tested for the reaction between compound **1** and DFV. The same reaction conditions were studied for all the other tetra-functional jeffam-

Table I. Reaction Conditions for the Reaction Between Tetra-Amine Jeffamine 1 and DFV

	1/DFV[a] (eq./eq.)	Solvent (mL)	Et_3N (mL)	Medium	*T* (°C)	*t* (h)	Yield (%)
1	1/1	EtOH (2)	---	---	reflux	24	0
2	1/1	EtOH (5)	---	---	reflux	24	0
3	1/1	EtOH (10)	---	---	reflux	24	0
4	1/1	EtOH (10)	---	HCOOH; Molec. sieves	reflux	24	0
5	1/3	EtOH (2)	---	HCOOH; Molec. sieves	reflux	24	0
6	1/1	MeOH (3)	---	---	reflux	48	0
7	1/1	MeOH (5)	---	---	reflux	48	0
8	1/1	MeOH (5)	---	HCOOH; Molec. sieves	reflux	48	0
9	1/1	MeOH (8)	---	---	reflux	48	0
10	1/1	MeOH (8)	---	HCOOH; Molec. sieves	reflux	48	0
11	1/1	MeOH (8)	1	---	reflux	48	0
12	1/1	MeOH (8)	1	Molec. sieves	reflux	24	0
13	1/1	MeOH (8)	1	TEOF[b]	reflux	24	0
14	1/3	MeOH (3)	0,5	---	reflux	48	0
15	1/3	MeOH (8)	0,5	---	reflux	72	0
16	1/3	MeOH (8)	0,5	TEOF	reflux	72	0
17	1/3	DMSO (3)	---	---	reflux	24	0
18	1/3	DMSO (3)	---	TEOF	reflux	24	0
19	1/3	DMSO (3)	---	HCOOH	reflux	24	0
20	1/1	-----	---	vacuum	90	24	0
21	1/3	-----	---	vacuum	90	24	0

[a]DFV refers to di-2,5-furylene vinylene. [b]TEOF refers to triethyl orthoformate.

ines (not shown).

None of aliphatic tetra-amine reacted under any condition. However, compound **4** reacted with DFV in the absence of solvent and under vacuum, yielding the corresponding Schiff's tetra-base. The degree of conversion of compound **4** reached 90%, as calculated from the ^{1}H NMR spectrum, and the yield of this reaction was 85% what is consistent with previously reported data.[17]

Study of the Reaction Between the Synthesized Jeffamine Tetra-Amines and the Isocyanate-Containing Derivative (MDI). Qualitative and comparative studies were conducted to evaluate the reactivity of the jeffamine tetra-amines with an isocyanate-containing derivative. Usually, isocyanates display a much higher reactivity than aldehydes toward amines.[18] The experiments consisted in the chemical reaction between each jeffamine and a polyisocyanate. For this purpose, a commercial methylene diphenyl diisocyanate oligomer (MDI) with a functionality of 2.7 was used to produce polymeric networks. The reaction between each copolymer and MDI was carried out following the same experimental procedures, described above.

The reactions between MDI and **1**, **2**, and **3**, respectively, did not yield any gel fraction, whereas with **4** formed a cross-linked product with a gel fraction of 100%, as determined by the mass balance after extraction with MeOH or DMSO.

From these results, compound **4**, which bears aromatic amines was found to be more reactive than the corresponing aliphatic tetra-amines.

^{1}H NMR Studies. Figure 2 shows the ^{1}H NMR spectrum of the tetra-amine derivative **1**, using water-d_2 as solvent and focusing on the region between 1.8 and 3.8 ppm. This spectrum can be divided in three regions:

i) the signals in the region between 1.8 and 2.2 ppm, assigned to the protons belonging to methylene groups located between two methylene groups, *i.e.*, -$CH_2CH_2CH_2$- specifically: protons **d** and **g** in Figure 2;

ii) the signals between 2.9 and approximately 3.5 ppm, attributed to the protons belonging to methylene groups placed between another methylene group and an amine (primary or tertiary), *i.e.*, H_2N-$CH_2CH_2CH_2N$=(protons **h**) and H_2N-$CH_2CH_2CH_2N$=(protons **e** and **f** in Figure 2);

iii) finally, the signals between 3.5 and 3.7 ppm, attributed to the protons belonging to methylene groups incorporated between another methylene group and an oxygen atom from the oligoether linear segment, *i.e.*, -O-CH_2CH_2- (protons **a**, **b** and **c** in Figure 2).

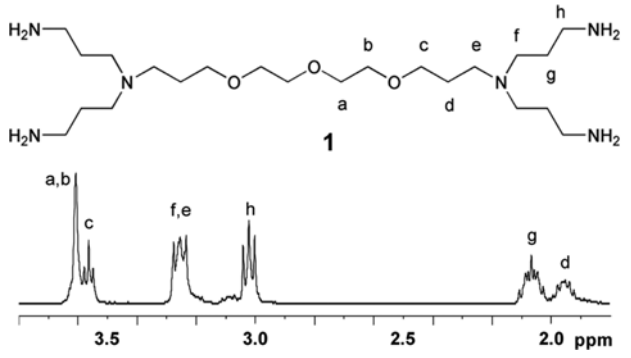

Figure 2. ^{1}H NMR spectrum of compound **1** in water-d_2 in the region between 1.8 and 3.8 ppm.

Figure 2 shows that in the spectrum of **1** there are signals with different resolution belonging to the same molecule. To evaluate the influence of the concentration of compound **1** on the quality of the spectrum, a new ^{1}H NMR spectrum of **1** was recorded using a sample that was diluted tenfold. The resulting spectrum (not shown) was identical to that shown in Figure 2, indicating that the concentration of the sample did not affect the spectral resolution.

In addition, ^{1}H NMR spectra of **1** were recorded in deuterated MeOH and DMSO. Methanol is a good donor and a good acceptor for hydrogen bonding, while DMSO is only a good acceptor. The spectra of compound **1** using methanol-d_4 as solvent showed a similar broadness in all signals (Figure 5(b-i)), whereas the spectra recorded using DMSO-d_6 showed once again different resolution for different protons (Figure 9(b-i)).

A different degree of solvation of the copolymer blocks directly affects their mobility, causing differences in the peak resolutions within the ^{1}H NMR spectrum. Thus, it has been reported that the mobility of protons located in the interior of aggregates (*i.e.* in the core of micelles) is hindered to such an extent that the width of the corresponding NMR signal undergoes broadening of the order of hundreds of Hz.[19,20]

It is important to emphasize that even using water-d_2 as solvent (which is a good solvent for compound **1**) and diluting progressively the sample, different signals from the same copolymer presented different resolutions in the ensuing spectra. Thus, while the signals belonging to protons **a**, **b**, and **c** were sharp and well resolved, signals from protons **d**, **e**, **f**, **g**, and **h** were broad (Figure 2). This shows that the oligoether segment is well solvated, while the terminal arms are less so. A lower solvation induces reduced mobility, which in the case of jeffamines and in accordance with Dušek,[21] is due to the formation of aggregates through strong hydrogen bond interactions involving the -NH_2 end-groups. These intra- and inter-molecular associations induce a high sterical hindrance on the terminal functional groups, thus rendering jeffamines less reactive.[21]

Similar results were obtained for compound **2** and **3**, as seen in Figure 3(a) and (b). Additionally, the spectrum of compound **3** showed that all the signals had broadened, since the central segment is less hydrophilic, despite the fact that **3** was still soluble in water-d_2.

Figure 4 shows the ^{1}H NMR spectrum of compound **4** in water-d_2, where all the signals were now sharp and well resolved, which suggests that the entire molecule was well

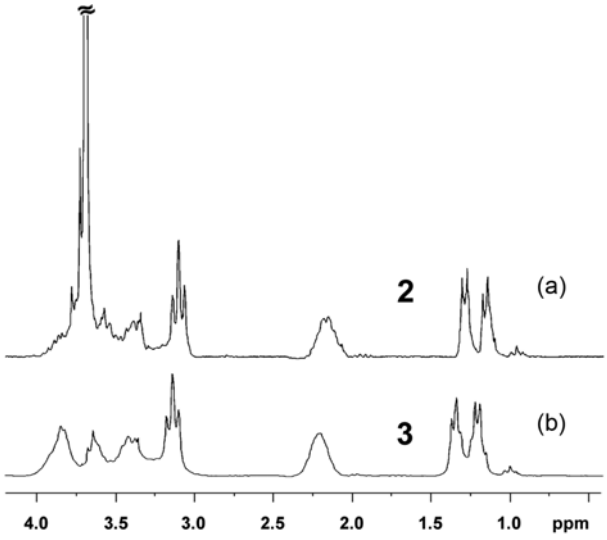

Figure 3. ^{1}H NMR spectra of compounds **2** (a) and **3** (b) in water-d_2 in the region between 0.45 and 4.2 ppm.

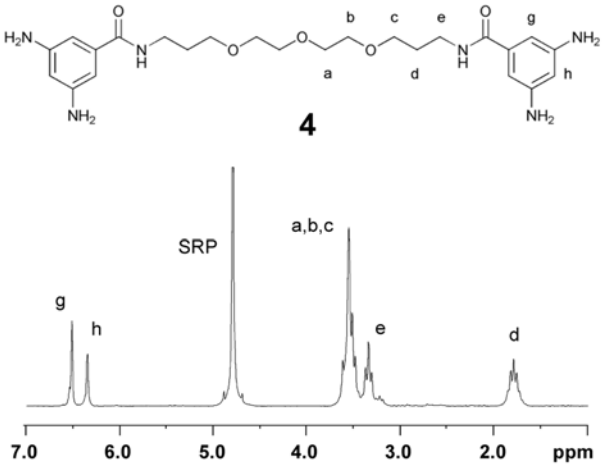

Figure 4. ^{1}H NMR spectrum of compound **4** in water-d_2. SRP refers to the solvent residual peak.

solvated, including the terminal functional groups (-NH_2). Therefore, it can be expected that in this case, the amine end-groups should be accessible for further chemical reaction.

1D and 2D NOESY and ROESY Studies. Homonuclear two-dimensional NOE spectroscopy (2D NOESY), and its selective 1D analogue employing pulsed field gradients for signal selection, are used as powerful tools in 3D structural elucidation. With improved instrument sensibility and stability, the 2D NOESY experiment finds extensive applications in routine small-molecule (M_w <1,000 daltons) studies. Moreover, gradient-selected 1D transient NOE experiments have made a significant impact on small-molecule studies, in particular because of their high quality resolution. This experiment efficiently removes those signals not arising from the NOE.[22]

Alternatively, the rotating-frame overhauser effect spectroscopy (ROESY) is a useful analogue of the NOE difference experiment. ROESY experiments also correlate protons that are close to each other in space.[23] 2D ROESY and 1D selective experiments are also used.

An additional feature of 2D NOESY and ROESY spectra is that they can conveniently be represented as 1D spectra by extracting the selected rows from the original spectra, thus making possible a direct and straightforward comparison between the normal ^{1}H NMR spectra and the respective 1D NOESY and ROESY counterparts, as well as with the 1D selective NOESY and ROESY experiments.

Based on the previous results, where all differences were found to be exclusively between the aliphatic and the aromatic tetra-functional jeffamine derivatives, we focused these studies exclusively on compound **1**, since compound **4** did not show lack of reactivity or aggregation through hydrogen bonding. A series of 2D and 1D selective NOESY as well as ROESY experiments was thus carried out to gain a deeper insight about aggregates (three-dimensional structures) that compound **1** and/or **4** may form in solution. To this end, three different solvents were used, namely: methanol-d_4, water-d_2, and DMSO-d_6. Only these three solvents were used given that they were the only ones dissolving the compounds. The use of these solvents was also based on the properties aforementioned, water and methanol are good donors and acceptors for hydrogen bonding, while DMSO is only a good acceptor; as well as MeOH and DMSO have organic groups whereas water do not.

Methanol-d_4 as Solvent: Figure 5(a) shows the ^{1}H-^{1}H 2D NOESY spectrum of **1** with a mixing time of 800 ms, while Figure 5(b) shows a comparison between the ^{1}H NMR spectrum of **1** (i) and the 1D representation of the extracted rows (ii to vi) from the ^{1}H-^{1}H 2D NOESY spectrum. In Figure 5(b-ii), the multiplet at 3.67 ppm belonging to protons **a**, **b**, and **c** is arbitrarily presented in a positive phase, thus showing the correlated signals in a negative phase. It can be seen in this case, that protons **d**, **e**, **f**, **g**, and **h** are correlated to protons **a**, **b**, and **c**.

It was assumed that the relative intensity for a selected signal and its correlated one gives information about how strong or weak this correlation is. The higher the intensity of the correlated signals, the closer to a selected signal these protons are. For example, protons **a**, **b**, and **c** showed a stronger correlation with signals **d**, **e**, and **f** than with protons **g** and **h**, suggesting that protons **a**, **b**, and **c** were spatially closer to protons **d**, **e**, and **f** than to those labeled **g** and **h**. Although the simple experiments carried out in this work are not sufficiently powerful to provide a precise estimate of the distances between the correlated protons, it is possible to affirm that these are not longer than 4-5 Å.[23-25]

Figure 5(b-iii) shows that protons **f** and **e** (signal at 3.35 ppm, arbitrarily in a positive phase) are weakly correlated with protons **d**, **g**, and **h**. Next, it can be seen in Figure 5(iv)

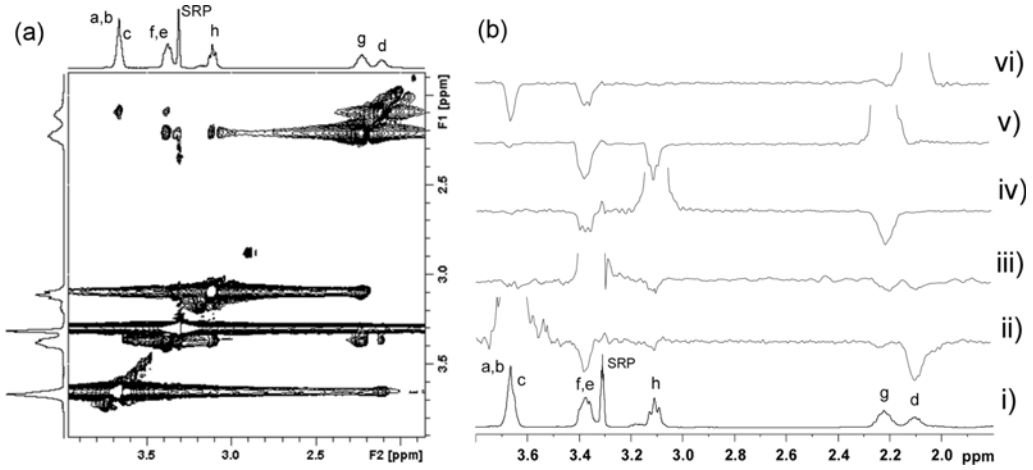

Figure 5. ^{1}H-^{1}H 2D NOESY spectra of compound **1** in methanol-d_4 with a mixing time of 800 ms. (a) 2D NOESY spectra. (b) Comparison between the assigned ^{1}H NMR spectrum of **1** (i) and the rows extracted from the 2D NOESY spectrum (ii to vi). Solvent residual peak (S.R.P.) refers to the solvent residual peak.

that protons **h** (at 3.1 ppm and arbitrarily in a positive phase) are strongly correlated with protons **e**, **f**, and **g**. Protons **g** (2.22 ppm, arbitrarily in a positive phase) are strongly correlated with protons **e**, **f**, and **h**, as shown in Figure 5(b-v). Finally, Figure 5(vi) shows that protons **d** (at 2.1 ppm and arbitrarily in a positive phase) are strongly correlated with protons **a**, **b**, **c**, **e**, and **f**.

NOESY correlations are frequently observed between protons separated by only a few chemical bonds due to their proximity in space. For instance, in compound **1**, it is not surprising to find that protons **d** showed through-space correlation with protons **c** and **e**, as well as protons **g** with **f** and **h**. However, it is important to point out that in methanol, protons **h** (located at the very end of the dendritic arms) were correlated with protons **a**, **b**, and **c** (at the central part of the central block) and with **e** (at the end of the central block), as previously mentioned and shown in Figure 5(b).

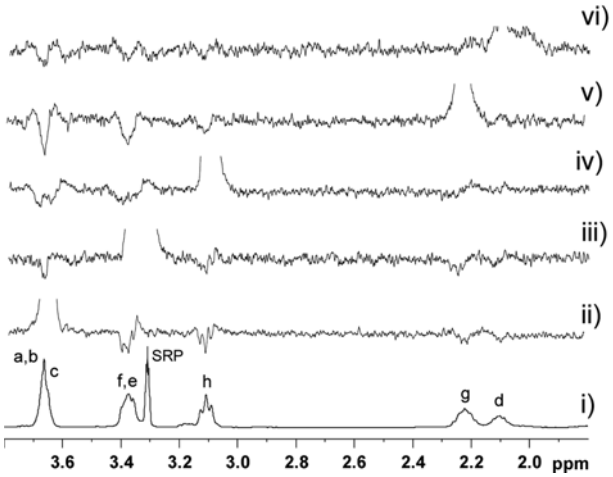

Figure 6. Comparison between the assigned ^{1}H NMR spectrum of **1** in CD_3OD (i) and the corresponding 1D selective NOESY spectra (ii to vi). S.R.P. means the solvent residual peak.

This result suggests that protons **h** are close through-space to protons located in the linear central-block. A reason for this vicinity is the hydrogen bonds that terminal -NH_2 groups may form with the oxygen atoms from the ether central block, as well as with the tertiary amine nitrogen atoms. These bonds could be intra- and/or inter-molecular, but in any case, they would always involve the terminal -NH_2 groups into hindered aggregates, thus reducing or limiting their reactivity.

To corroborate the previous results, we also performed 1D selective NOESY studies. Figure 6 shows the comparison between the ^{1}H NMR spectrum of **1** in methanol-d_4 (i) and 1D selective NOESY spectra (ii to vi). The most important information was obtained from: a) spectrum ii, where protons **a**, **b**, and **c** (from the central block) were correlated with **f**, **g**, and **h** (from the dendritic arms); b) spectrum iv where protons **h** were correlated with **a**, **b**, and **c**; and c) spectrum v where protons **g** were correlated with protons **a**, **b**, and **c**. All these results are in agreement with the idea of aggregation through hydrogen bond formation.

Another ^{1}H-^{1}H 2D NOESY spectrum of **1** with a mixing time of 250 ms was recorded to obtain additional information about the system. The results were in agreement with the above evidence, although no further information was obtained.

Complementary studies were also carried out by 2D ROESY and 1D selective ROESY experiments (Figures S1 and S2 in the Supporting Information). Once again, they showed to be in agreement with all the previous results.

Water-d_2 as Solvent: It has already been shown that compound **1** presented a reduced reactivity in water.[12,16] Although water was not used as solvent in any of the reaction condition investigated in the present work, it was interesting to

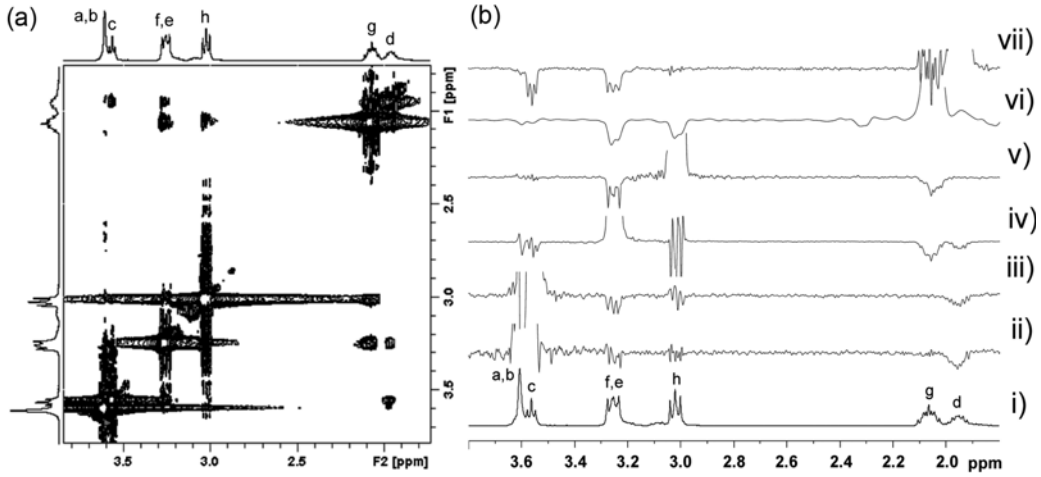

Figure 7. (a) ^{1}H-^{1}H 2D NOESY spectra of compound **1** in water-d_2 with a mixing time of 900 ms. (a) 2D NOESY spectra. (b) Comparison between the assigned ^{1}H NMR spectrum of **1** (i) and the rows extracted from the 2D NOESY spectrum (ii to vi).

study the behavior of this compound in water, since it could provide additional information about hydrogen bonding formation even in water, which is an excellent donor and acceptor for such interactions.

A ^{1}H-^{1}H 2D NOESY spectrum of compound **1** was recorded using water-d_2 as solvent with a mixing times of 800 ms, as shown in Figure 7, which also presents the corresponding 1D extracted rows compared with the ^{1}H NMR spectrum.

Figure 7(b) shows the comparison between the assigned ^{1}H NMR spectrum of **1** in water-d_2 and the 1D extracted rows from the ^{1}H-^{1}H 2D NOESY spectrum with a mixing time of 800 ms, shown in Figure 7(a). The most important information concerning aggregation *via* hydrogen bonds was obtained from: (a) spectra ii and iii, where it can be detected that protons **a**, **b**, and **c** (from the central part of the linear central-block) were weakly correlated through-space with protons **d**, **e**, **f**, and **h** (**d** and **e** are at the end of the linear block, while **f** and **h** are part of the dendritic arms); and (b) spectrum vi, where protons **g** from the dendritic arms were weakly correlated with **a**, **b**, and **c** from the central part of the lineal central-block.

The corresponding ^{1}H-^{1}H 2D NOESY experiment with a mixing time of 200 ms was in agreement with the previous results (Figure S3 in the Supporting Information). 1D selective NOESY experiments fully agreed with the previous results, as it can be seen in Figure S4 in the Supporting Information. 1D selective ROESY experiments, however, were not only in agreement with NOESY experiments, but also gave complementary information. Figure 8 shows a comparison between the assigned ^{1}H NMR (i) and 1D selective ROESY (ii) spectra of compound **1** belonging to protons **d**. In spectrum ii the signal corresponding to proton **d** is arbitrary presented in a positive phase, thus showing that protons **d** were weakly through-space correlated with protons **h**, which is once again suggesting the existence of aggregates *via* hydrogen bonds involving the terminal -NH_2 groups and the oxygen atoms from the linear oligoether and/or the tertiary amines.

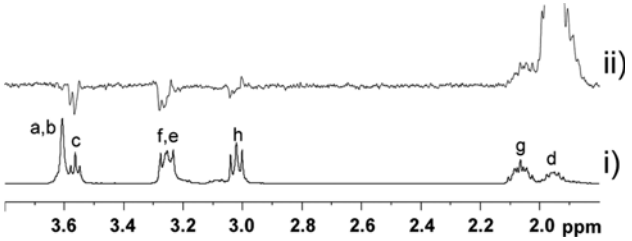

Figure 8. Comparison between the assigned ^{1}H NMR spectrum of **1** in water-d_2 (i) and the corresponding 1D selective NOESY spectra (ii) belonging to protons **d**.

DMSO-d_6 as Solvent: As previously pointed out (entries 17 to 19 in Table I), **1** did not react under any condition involving DMSO as the solvent. Therefore, we decided to explore the behavior of copolymer **1** in this solvent, hoping to gain further information on aggregates or hydrogen bond formation, but also about the through-space correlations involving the hydrogen atoms belonging to amine end-groups and other protons in the rest of the structure.

Figure 9 shows the ^{1}H-^{1}H 2D NOESY spectra of compound **1** in DMSO-d_6 using a mixing time of 200 ms, where (a) corresponds to the 2D NOESY spectra and (b) shows the assigned ^{1}H NMR spectrum compared to the rows extracted from the 2D NOESY spectra. In both cases, the most important regions are shown, namely from 1.8 to 4.0 ppm and from 7.5 to 9 ppm.

This study corroborated the previous results. However, the most relevant new information is presented in Figure 9(b), which shows the protons spatially correlated to hydrogen atoms from the amine end-groups (**NH**). It can be seen

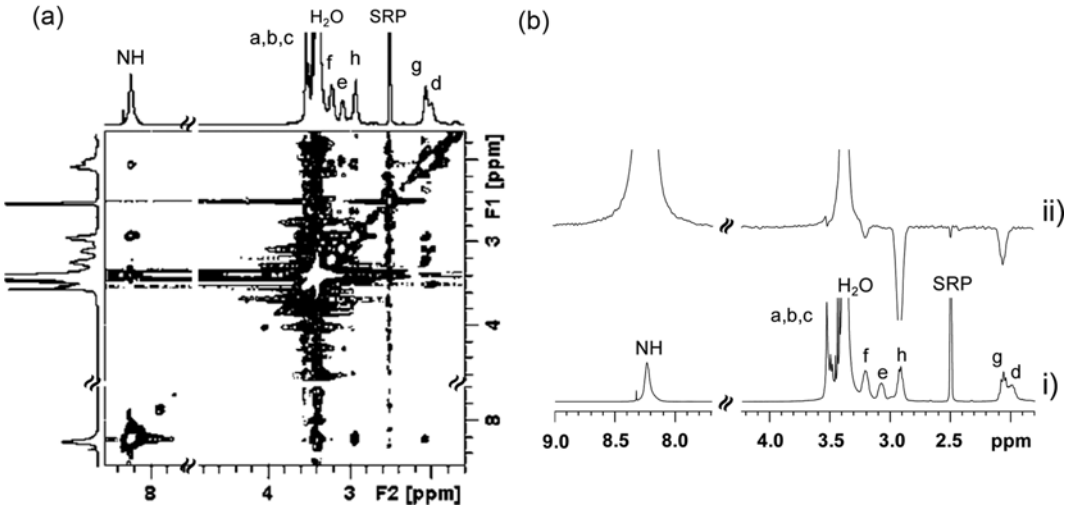

Figure 9. (a) ^{1}H-^{1}H 2D NOESY spectra of compound **1** in DMSO-d_6 with a mixing time of 200 ms. (a) 2D NOESY spectra. (b) Comparison between the assigned ^{1}H NMR spectrum of **1** (i) and the rows extracted from the 2D NOESY spectrum (ii) belonging to **NH** protons. S.R.P. means solvent residual peak.

that protons in **NH** (arbitrary presented in a positive phase) were strongly correlated to those labeled **h** and **g** (located at the end and center, respectively, of the dendritic arms, but before the amine end-group) and weakly through-space correlated with protons **f** (located at the very beginning of the dendritic arms). This evidence also confirmed the occurrence of aggregation through hydrogen bond formation.

In addition, other complementary studies were carried out, such as ^{1}H-^{1}H 2D NOESY spectra with a mixing time of 800 ms and 2D ROESY experiments (Figures S5 and S6 in the Supporting Information). They completely agreed with the conclusions reached from the previous results.

In a previous study,[16] we reported the synthesis and the non-linear polymerization of a photo-cross-linkable tetra-functional jeffamine. This monomer was obtained through Schiff's base formation from the respective tetra-amine modified jeffamine and a photo-active chromophore bearing an aldehyde group. It was established then that the Schiff's tetra-base could only be synthesized with aromatic-bearing amine end-groups.

The present work investigated the effect of the molecular structure on the reactivity of first-generation tetra-amine dendritic jeffamines. Thus, three factors were studied to evaluate the reactivity of the synthesized tetra-amine jeffamines, namely:

i) the hydrophilic/hydrophobic balance of the oligoether,

ii) the length of the central block, and

iii) the nature of the moiety directly linked to the amine end-group (aliphatic or aromatic).

Both chemical studies carried out by reacting each jeffamine with DFV and MDI, respectively, showed that only compound **4** reacted. Compound **4** bears aromatic amine end-groups attached to a stiff moiety (aromatic ring), while compounds **1**, **2**, and **3** display aliphatic amines at the end of flexible arms, which grew from 4,7,10-trioxa-1,13-tridecanediamine for compound **1**, *O*,*O'*-bis(2-aminopropyl) poly (ethylene glycol) for compound **2**, and *O*,*O'*-bis(2-aminopropyl) poly(propylene glycol) for compound **3**. Whereas compound **1** and **2** differ by the length of their central blocks, compound **1** and **3** do so by the hydrophilic character of their linear segments.

The lack of reactivity of compounds **1**, **2**, and **3** under the present conditions can be explained by the marked flexibility of both moieties (central oligoether and end arms) and the highly basic character of the aliphatic amines. These structural features favor the generation of aggregates *via* strong intra- and/or inter-molecular hydrogen bonds,[21] which hinder accessibility and consequently reduce reactivity. These results are consistent with those reported by Dušek and co-workers on jeffamines,[21] and those dealing with self-assembly, aggregation and gelation of dendrimers with hydroxyl and amines groups at the surface.[26-29]

^{1}H NMR is often used to detect and study aggregation processes.[19,20] In this investigation, the broadening of the signals associated with moieties bearing amino groups provided strong evidence that aggregation did take place through the systematic use of ^{1}H-^{1}H 2D and 1D selective NOESY and ROESY experiments in three different solvents. The results pointed to the fact that the end of the dendritic arms were localized at a distance lower than 4-5 Å from the -CH_2- belonging to the central oligoether. This finding may be explained by the formation of hydrogen bonds between the -NH_2 and the oxygen atoms and/or tertiary amines from the central block. Even when it was not possible to determine if the hydrogen bonds were intra- or

inter-molecular or a combination of them, it was clear that the terminal amine groups were involved into such an association, possibly aggregates, and were neither free, nor accessible to react.

Additional evidence supporting the lack of reactivity of tetra-functional jeffamines due to aggregation was the fact that compound **1** did react when conditions were favorable.[12,16] **1** was indeed used as the starting material for the synthesis of a second generation linear-dendritic copolymer (*octa*-amine jeffamine) *via* Michael addition with acrylonitrile, followed by catalytic hydrogenation.[12] The reaction conditions for a Michael addition are in fact very different from with those used to synthesize Schiff's bases or polyureas from aldehydes and isocyanates, respectively. The synthesis of the octa-nitrile jeffamine (precursor for the octa-amine jeffamine) *via* Michael addition could be easily optimized to prevent aggregation, by changing solvents and/or adding different chemical compounds to increase the ionic strength, modify the dielectric constants, shift the equilibrium and/or catalyze the reactions, among others.[30] These strategies were not always applicable to the condensation of amines with aldehydes or isocyanates, due to the chemical nature of the functional groups, the specific reaction mechanisms, the solubility of each reactant, *etc.*. Finally, it was established that changes in the central oligoether segment did not influence significantly the reactivity in these contexts.

Conversely, the presence of aromatic moieties in compound **4** provided higher stiffness to the dendritic arms. Secondly, the aromatic amines (in copolymer **4**) are less basic than its aliphatic counterparts (copolymers **1**, **2**, and **3**). These two effects together caused compound **4** to be less prone to form hydrogen bonding than its aliphatic analogues, thus leaving the amino groups more accessible and available to react. This is in agreement with a) the ^{1}H NMR spectra, where all signals corresponding to compound **4** were well resolved, evidencing that both moieties (linear and dendritic segments) were well solvated by the solvent, thus enhancing a high mobility of the entire molecule in solution, as shown in Figure 4, and b) the NOESY and ROESY experiments, where no correlations were found between the dendritic part and the linear segment.

Conclusions

The four first-generation linear-dendritic block copolymers bearing primary amine end groups synthesized in this study displayed an unusual behavior in that the aromatic tetra-functional jeffamine (**4**) exhibited a much higher reactivity than its aliphatic homologues, in the context of the specific tested reactions. The reason for this difference was that the aliphatic tetra-amine jeffamines underwent aggregation through strong intra- and inter-molecular hydrogen bonds, rendering them inaccessible to the potential reactants. It was shown that their chain length, the hydrophilic/hydrophobic character, as well as the flexibility of their oligoether central blocks, did not modify this lack of reactivity. In contrast, the presence of a stiff moiety in the form of an aromatic ring reduced considerably the occurrence of hydrogen bonds, thus leaving the -NH_2 functional groups accessible to react.

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Supporting Information: Additional 1D and 2D NOESY and ROESY NMR spectra. These materials are available *via* the Internet at http//www.springer.com/13233.

References

(1) C. Román, H. R. Fischer, and E. W. Meijer, *Macromolecules*, **32**, 5525 (1999).
(2) F. Wurm and H. Frey, *Prog. Polym. Sci.*, **36**, 1 (2011).
(3) J. M. J. Fréchet, I. Gitsov, T. Monteil, S. Rochat, J. F. Sassi, C. Vergelati, and D. Yu, *Chem. Mater.*, **11**, 1267 (1999).
(4) G. C. Eastmond, M. Gibas, W. F. Pacynko, and J. Paprotny, *J. Memb. Sci.*, **207**, 29 (2002).
(5) M. Albert, P. Feiertag, G. Hayn, R. Saf, and H. Hönig, *Biomacromolecules*, **4**, 1811 (2003).
(6) M. A. B. Meador, V. A. Cubon, D. A. Scheiman, and W. R. Bennett, *Chem. Mater.*, **15**, 3018 (2003).
(7) M. F. D. Nograro, P. Guerrero, M. A. Corcuera, and I. Mondragón, *J. Appl. Polym. Sci.*, **56**, 177 (1995).
(8) Y. W. Chung, J. K. Lee, W. C. Zin, and B. K. Cho, *J. Am. Chem. Soc.*, **130**, 7139 (2008).
(9) E. Lee, B. I. Lee, S. H. Kim, J. K. Lee, W. C. Zin, and B. K. Cho, *Macromolecules*, **42**, 4134 (2009).
(10) J. L. Mynar, A. P. Goodwin, J. A. Cohen, Y. Ma, G. R. Fleming, and J. M. J. Fréchet, *Chem. Commun.*, 2081 (2007).
(11) H.-I. Lee, J. A. Lee, Z. Poon, and P. T. Hammond, *Chem. Commun.*, 3726 (2008).
(12) P. Froimowicz, A. Gandini, and M. Strumia, *Tetrahedron Lett.*, **46**, 2653 (2005).
(13) A. W. Bosman, H. M. Janssen, and E. W. Meijer, *Chem. Rev.*, **99**, 1665 (1999).
(14) R. Scherrenber, B. Coussens, P. van Vliet, G. Edouard, J. Brackman, E. de Brabander, and K. Mortensen, *Macromolecules*, **31**, 456 (1998).
(15) P. Welch and M. Muthukumar, *Macromolecules*, **31**, 5892 (1998).
(16) P. Froimowicz, J. Paez, A. Gandini, N. Belgacem, and M. Strumia, *Macromol. Symp.*, **245-246**, 51 (2006).
(17) P. Froimowicz, M. N. Belgacem, A. Gandini, and M. C. Strumia, *Eur. Polym. J.*, **44**, 4092 (2008).
(18) A. Halabi, P. Froimowicz, M. Martinelli, M. C. Strumia, and

B. L. Rivas, *ARKIVOC*, **2003**, 566 (2003).
(19) K. Nakamura, R. Endo, and M. Takeda, *J. Polym. Sci. Part B: Polym. Phys.*, **14**, 135 (1976).
(20) I. Gitsov, K. L. Wooley, and J. M. J. Fréchet, *Angew. Chem., Int. Ed. Engl.*, **31**, 1200 (1992).
(21) K. Dušek and L. Matìjka, in *Formation of Epoxy Networks, Including Reactive Liquid Elastomers*, American Chemical Society, Washington, DC, 1989, p 303.
(22) T. D. W. Claridge, in *Tetrahedron Organic Chemistry Series*, Elsevier, New York, 2009, Vol. 27, p 247.
(23) R. M. Silverstein, F. X. Webster, and D. Kiemle, in *Spectrometric Identification of Organic Compounds*, John Wiley & Sons, Hoboken, 2005.
(24) H. Friebolin, *Basic One-and Two-Dimensional NMR Spectroscopy*, Wiley-VCH, Weinheim, 2005.
(25) J. K. M. Sanders and B. K. Hunter, *Modern NMR Spectroscopy, A Guide for Chemists*, Oxford University Press, Oxford, 1993.
(26) A. Halabi, P. Froimowicz, and M. C. Strumia, *Polym. Bull.*, **51**, 119 (2003).
(27) J. M. J. Fréchet and D. A. Tomalial, *Dendrimers and Other Dendritic Polymers*, Wiley, Chichester, 2002.
(28) G. R. Newkome, C. N. Moorefield, and F. Vögtle, *Dendritic Molecules: Concepts, Syntheses, Perspectives,* VCH, Weinheim, 1996.
(29) A. Halabi and M. C. Strumia, *J. Org. Chem.*, **65**, 9210 (2000).
(30) P. Froimowicz, Ph. D. Thesis, National University of Córdoba, 2005.