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Stable hemiaminals attached to PAMAM dendrimers

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ABSTRACT

Stable hemiaminals (carbinolamines) are formed during the reaction between aromatic aldehydes and amine groups on the surface of polyamidoamino dendrimers in methanol under mild conditions, as monitored by ^{1}H NMR spectroscopy.

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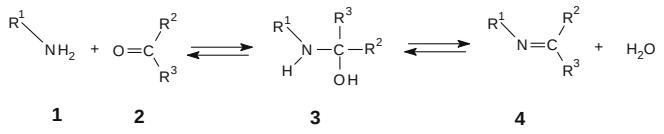
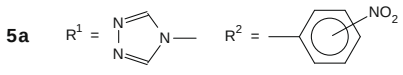
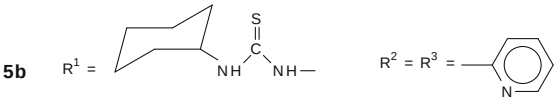
The formation of Schiff bases **4** via condensation of amine **1** with aldehyde or ketone **2** proceeds via a hemiaminal (carbinolamine, **3**) intermediate. The formation of the intermediate was recognized very early,[1] but its presence was confirmed by ^{1}H NMR spectral monitoring in 2007.[2] Recently, stable hemiaminals **5** were obtained from 4-aminotriazole and nitro-derivatives of benzaldehyde and these were characterized structurally **5a**.[3] Elimination of a water molecule from **3** is thermodynamically favored, even in aqueous solution, especially under acidic conditions and is usually faster than the formation of the intermediate **3**.[4] However, when the elimination reaction is slower than the addition of the aldehyde to the amine, the amount of hemiaminal increases and the hemiaminal intermediate can be identified in the solution. Carbinolamine **3** can be stabilized by hydrophobic interactions,[2] by hydrogen bonding involving the hydroxy group of **3**, or electronically by the choice of an appropriate amine, such as 4-amino-1,2,3-triazole[3] or of both precursors, for example, 4-cyclohexyl-3-thiosemicarbazone and di-2-pyridyl ketone (**5b**).[5]



1 **2** **3** **4**

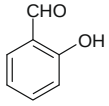


5a



5b

In our current work on dendrimer-attached ligands and their metal ion complexes, we have prepared a series of polyamidoamino dendrimers (PAMAM),[6] and their derivatives by partial protection of the surface amine groups of the third and fourth generations (G3 and G4) of the PAMAM dendrimers by simple alkylation with ethyl- and *iso*-propyl iodides or by acylation with acetyl chloride in order to tune the hydrophilic-hydrophobic balance of the macromolecule.[7] These derivatives were then used as substrates for the synthesis of Schiff bases with aldehydes to generate dendrimers with potential multisite ligands for metal ions. The aldehydes of choice were salicylaldehyde (**6**), pyridoxal (**7**) and imidazole-4-carbaldehyde (**8**). During condensation between the amine groups of PAMAM and the aldehydes we observed the formation of intermediates preceding the formation of Schiff bases as was apparent from ^{1}H NMR spectral monitoring.



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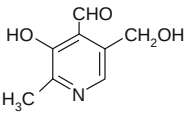

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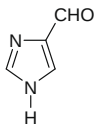

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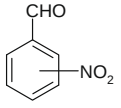

9a (3-NO_2)
9b (4-NO_2)

In these experiments the aldehydes **6–8** in methanol-d_4 solutions were gradually added to the dendrimer G^{nR} (1–3 mg in 0.7 ml methanol-d_4, where n = the percentage of blocked amine groups, R = Et, ^{i}Pr, or Ac). During the course of the reaction we observed a resonance at about 5.3 ppm (singlet) in the ^{1}H NMR spectrum of the reaction mixture, which slowly disappeared after about 0.5 h with the spectrum changing into that typical of a Schiff base. The intermediate was not observed in deuterium oxide nor in DMSO-d_6. Taking into account the reported stability of the hemiaminals obtained from 2-, 3-, and 4-nitrobenzaldehydes,[3] we used 3- and 4-nitrobenzaldehydes (**9**) as precursors to obtain more stable hemiaminals with a series of substituted and unsubstituted G3

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and G4 PAMAM dendrimers. Analogous reaction procedures based on ^{1}H NMR spectral monitoring were applied for these systems. To our surprise, stable hemiaminals were formed in methanol-d_4 solutions in each case. The results are illustrated in Figure 1. For example, the reaction between dendrimer G3 with ten of the 32 surface amine groups substituted with acetyl groups, G^{31Ac} (Fig. 1A) and ca. 10 equiv of **6** at room temperature immediately gave the hemiaminal (HA) with a characteristic singlet resonance at 5.58 ppm and a series of aromatic group proton resonances in the 6.6–7.3 ppm region (Fig. 1B). The free salicylaldehyde protons (labeled as FS) observed in the reaction mixture slowly reacted with G^{31Ac} and after ca. 20 min at room temperature, only the spectrum of HA and the Schiff base (SB) with an aldimine proton resonance at 8.46 ppm was observed. Finally, the equilibrated solution consisted of G3 with ten acetyl-protected amine groups, six amine groups converted into the HA and four amine groups converted into the SB (Fig. 1C).

Similar results were obtained with **9a** and **9b** and the spectrum of the equilibrated solution containing G^{31Ac} and 5 equiv of **9b** is shown in Figure 1D. When this sample was heated for 10 min at 50 °C, the SB dominated in solution (9:1 SB:HA, spectrum not shown). In order to evaluate the stabilizing role of the acetyl substituents of G3, unprotected G3 containing 32 surface amine groups (the ^{1}H NMR spectrum is shown in Fig. 1E) was subjected to a series of experiments with aromatic aldehydes. The formation of a stable intermediate was observed in each case, particularly so in the case of aldehyde **9b**. The hemiacetal was obtained almost quantitatively upon addition of 32 equiv of **9b** together with small amounts of the SB and free aldehyde. Attempts to isolate the major species by washing the product with chloroform or by dialysis with methanol were partially successful; however, the spectra of isolated HA in DMSO-d_6 showed decomposition of HA into SB and the aldehyde. These studies were performed in order to record the ^{1}H NMR spectrum of the HA in DMSO-d_6 for comparison with the spectrum of **5a** (2,4-dinitrobenzaldehyde). In the latter, the HO–C–*H* resonance was observed as a doublet at 7.38 ppm in DMSO-d_6, while in the case of the in situ observed HA obtained from 9-anthraldehyde tethered to a cavitand hydrophobic pocket and isobutylamine, the HO–C–*H* resonance appeared at 4.6 ppm in mesitylene-d_{12}. Thus, the chemical shift of this proton depends strongly on the solvent used and the structure of the HA. In our hands the chemical shift of the HO–C–*H* proton in methanol-d_4 always appeared at about 5.5 ppm (in the $G4^{75Et}$ or $G4^{85Et}$ + **6**, $G4^{85Et}$ and $G4^{72iPr}$ + **8** and $G4^{85Et}$ + **7**, and in all the systems with **9a** and **9b**), while in the case of the $G4^{72iPr}$ + **6** system in DMSO-d_6, a doublet at 6.04 ppm was observed. The characteristic feature of the ^{1}H NMR spectra of Schiff bases attached to G3 or G4 dendrimers, or their partially blocked derivatives, was a resonance at 3.8 ppm with an intensity corresponding to two protons of the SB, attributed to the C=N–CH_2-dendrimer protons. In the case of the G3 + **9b** system, two resonances due to the diastereotopic methylene protons were observed (Fig. 1F). The HA species were easily converted into Schiff bases by prolonged heating of the samples. The SB could also be converted back into the HA and further to the aldehyde and PAMAM substrates by controlled addition of water during NMR-scale experiments. The rate of formation of the HA and SB was dependent on the structures of the dendrimers and the aldehyde used. All the phenyl-substituted aldehydes reacted at room temperature within 1 h, except pyridoxal, which required a slightly longer time (4 h), while formation of the SB using imidazole-4-carbaldehyde was achieved upon heating the sample at 50 °C for 3 h. Therefore, and especially with acetyl-protected G3 and G4, formation of a HA was not observed, as it was converted into the SB.

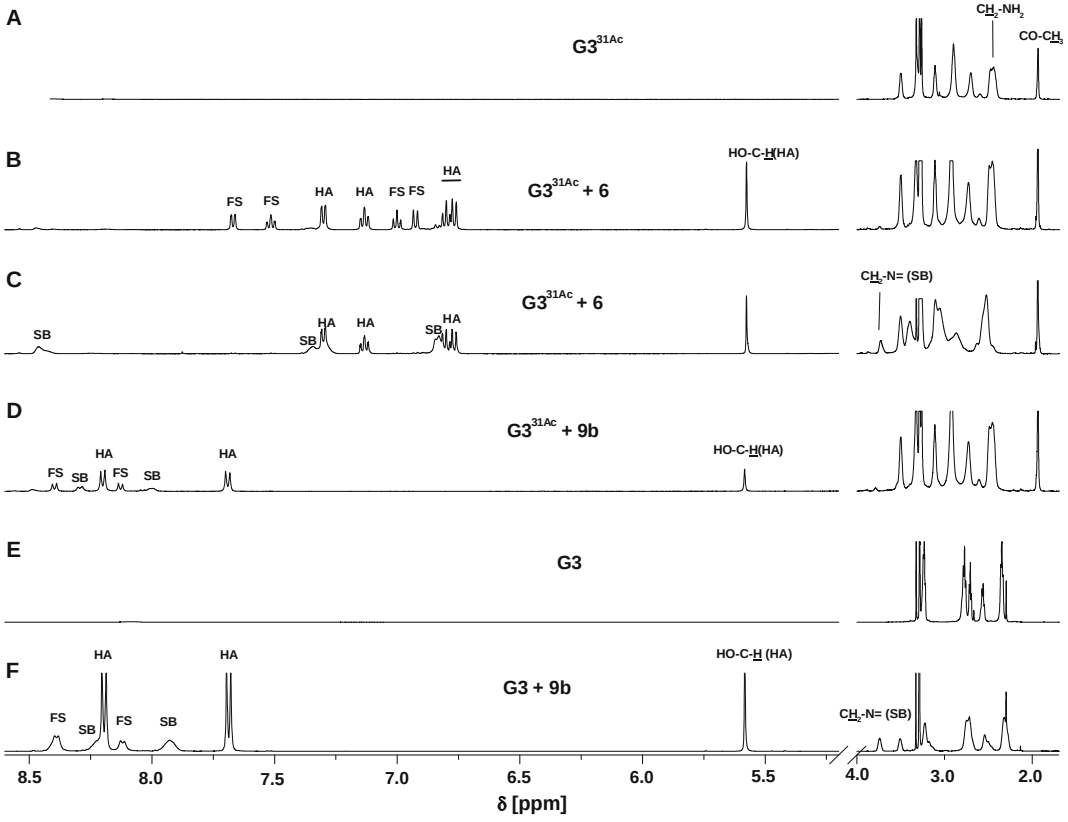

Figure 1. The relevant fragments of the ^{1}H NMR spectra of solutions of: $G3^{31Ac}$ (A), $G3^{31Ac}$ and 10 equiv of **6** immediately after addition (B), and after 20 min (C), $G3^{31Ac}$ and 5 equiv of **9b** (D), G3 (E), and G3 and 32 equiv of **9b** (F) in methanol-d_4.

Generally speaking the synthetic work described here was aimed at the formation of Schiff bases attached to dendrimers in order to create potential multisites to bind transition metal ions of catalytic activity. Such catalytic molecules can be easily separated by dialysis from post-reaction mixtures due to their large size. Pyridoxal bioconjugates with PAMAM dendrimers, which are transdermal agents, may find application as dermatological vehicles for providing vitamin B_6 to skin cells. These applications are of our current interest. PAMAM dendrimers have been studied extensively as water-insoluble drug carriers.[10] In some cases the covalent attachment of drug give the conjugates, which are also transdermal.[11]

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7. In a typical protocol G4[8] (0.125 g) (containing 64 surface amine groups corresponding to 0.56 mmol of NH_2) and of ethyl iodide (1.53 mmol) (EtI) or *iso*-propyl iodide (14.1 mmol) (*i*PrI) in methanol (5 cm^3) were kept at rt for 48 h (EtI) or heated at 50 °C for 2 h (*i*PrI). The G4 dendrimers were substituted at an average level of 85% with Et groups ($G4^{85Et}$) and 72% with *i*Pr groups ($G4^{72iPr}$) based upon the integral intensity of the methyl group proton resonances in the ^1H NMR spectra of the derivatives in methanol-d_4. Later the level of substitution was confirmed by quantitative conversion of $G4^{85Et}$ and $G4^{72iPr}$ into Schiff bases by reaction with the aldehydes used throughout these studies. The acetyl derivative $G4^{35Ac}$ was obtained by the reaction of G4 (0.075 mmol) (5.44 mmol of surface amine groups) with acetyl chloride (3.1 mmol) at rt for 24 h. The excess alkylating and acylating reagents were removed by vacuum evaporation, while the modified dendrimers were further purified by dialysis (12 h) of their methanolic solutions against MeOH through a cellulose membrane (*ZelluTrans* Roth 3.5; molecular weight cut-off 4–6 kD) to remove traces of HI. In analogous procedures, a series of GI^{nEt}, GI^{miPr}, and GI^{kAc} derivatives were obtained (*n*, *m*, or *k* are variable within 30–85%, and *I* = 3 or 4).
8. The G3 and G4 PAMAM dendrimers were synthesized on an ethylenediamine core according to a divergent strategy by alternate addition of methyl acrylate and condensation with ethylenediamine.[9] The current knowledge on the subject is widely described in 'Dendrimers and Other Dendritic Polymers', Tomalia, D. A.; Fréchet, J. M. J., Ed.; J. Wiley & Sons Ltd.: Chichester, 2001.
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