Reactivity at the Interface of Chiral Amphiphilic Dendrimers. High Asymmetric Reduction by $NaBH_4$ of Various Prochiral Ketones

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Abstract: New amphiphilic dendrimers derived from PAMAM and D-gluconolactone were found to induce chirality in the reduction of prochiral ketones by $NaBH_4$, in heterogeneous (THF) and homogeneous (water) conditions. The third generation of these amphiphilic dendrimers, G(3)G, was found to be a good chiral ligand for the reduction of various prochiral ketones in heterogeneous conditions. Even with substrates well-known to give poor results (especially linear ketones), good enantioselectivities were obtained. It is also important to notice that under heterogeneous conditions (THF) the dendrimer could be recovered by filtration, regenerated, and recycled (up to 10 times), leading to reproducible results in asymmetric reduction of ketones. We have also discussed the reduction of acetophenone in water. Evidence is presented that the selectivity is dominated by the architecture of the dendrimer and some supramolecular ordering in the position of the ketone at the chiral solvating interface. The results obtained showed a correlation between stereoselectivity of the reduction and the compact character of the dendritic particles.

Introduction

Dendrimers[1] are highly branched, fractal macromolecules of defined three-dimensional size, shape, and topology which can be prepared with extremely narrow molecular weight distribution. Dendrimer chemistry is now occupying a unique position, not only in polymer and material chemistry but also in other areas of chemistry.

The introduction of chirality into a dendritic structure will create an asymmetric macromolecule having a chiral surface environment with internal cavities.[2] Chiral dendrimers are therefore potentially useful materials in mediating chiral recognition and enantioselective binding of guest molecules. Furthermore, the use of chiral dendrimers as promoters or catalysts in asymmetric synthesis is also one of the prime objectives in dendrimer chemistry.[3−7]

We described recently new chiral amphiphilic dendrimers prepared from polyamidoamine (PAMAM) and gluconolactone (generations 1−4)[8] (Figure 1). These dendrimers can act as chiral rigid unimolecular micelles. We recently reported[9] that sodium borohydride reduces prochiral aromatic ketones at the chiral interface of these amphiphilic dendrimers, to the corresponding chiral alcohols, with both high yields and high enantioselectivities in heterogeneous conditions.

The purpose of this paper is to understand in greater detail the mechanism of this chiral induction and to show the generality of the phenomenon with various ketones.

Experimental Section

^{1}H NMR spectra were recorded on either a Bruker AC200 (200 MHz) spectrometer or a Bruker AC400WB (400 MHz) spectrometer with either the solvent reference or TMS as internal standard.

^{13}C NMR spectra were recorded on a Bruker AC200 (50 MHz) spectrometer or a Bruker AC400WB (100.6 MHz) spectrometer.

Molecular Simulation. Simulations were carried out using the CVFF force field as implemented in the Discover program running on a Silicon Graphics Indigo 2 Workstation. We evaluated the multitude of conformations available for the molecule by refining the energy of a model-built structure and evaluated configurations of the system. The whole assembly was minimized using the conjugated gradients method and a water layer of 0.5 nm. Dendrimer structures were first minimized for 10 000 iterations. To obtain a global minimum, molecular dynamics simulations were used. Dynamics were performed at constant 500 K temperature. The lowest energy conformer obtained in the molecular dynamics simulation was further minimized by 10 000 iterations.

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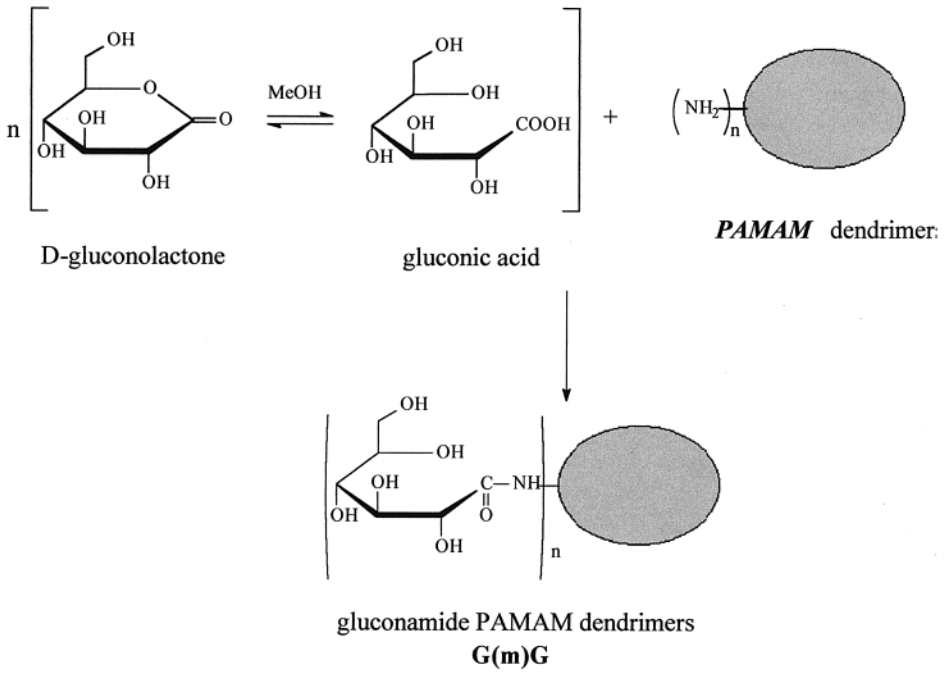


Figure 1. Synthesis and structure of the chiral amphiphilic dendrimers G(*m*)G.

Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with Kieselgel 60 F_{254} (Merck).

All rotations were measured on a Perkin-Elmer 241 polarimeter (at 589.3 nm).

Gas chromatography was performed on a DELSI NERMAG DN200 chromatograph and a VARIAN Chrompack CP 3800 gas chromatograph.

Circular Dichroism. All measurements were performed at 25 °C using a Jobin Yvon Mark VI Dichrograph in the 190−350 nm spectral range. The scan speed was 0.2 nm/s. All the solutions, either in pure water or in sugar−dendrimer aqueous solutions, were prepared by allowing the solvent to remain overnight undisturbed and in contact with the solute (the ketone) at 40 °C. The dendrimer concentration we used for the spectra was always 2.5×10^{-6} M in a 0.1 cm path length quartz cell. Results were normalized in molar ellipticity [θ] based on a unit molecular mass of 110 Da.

Methods for the Characterization of Alcohols. The isolated alcohols were identified by comparing their ^{1}H and ^{13}C NMR spectra with the spectra of authentic samples.

The enantiomeric excess (ee) of the obtained alcohols was determined by gas chromatography with a chiral separation column (SUPELCO α DEX 120, β DEX 110 fused silica capillary column with a 30 m × 0.25 mm × 0.25 μm film thickness and a VARIAN β DEX 2,3,6-M-19 column with a 50 m × 0.25 mm × 0.39 μm film thickness). The isotherm temperature program with N_2 as the gas vector (0.5 to 1.2 mL/mn depending of the compounds) was used. For 1-phenylethan-1-ol: β-DEX 110, 110 °C, t_R for the S isomer is 13.1 min, t_R for the R isomer is 13.4 min. For 1-phenylcyclohexan-1-ol: α-DEX 120, 160 °C, t_R for the S isomer is 10.2 min, t_R for the R isomer is 10.4 min. For 1-phenylbutan-1-ol: α-DEX 120, 130 °C, t_R for the S isomer is 18.2 min, t_R for the R isomer is 18.5 min. For 1-phenylpropan-1-ol: β-DEX 110, 100 °C, t_R for the S isomer is 9.2 min, t_R for the R isomer is 9.5 min. For pBr-1-phenylethan-1-ol: β-DEX 110, 110 °C, t_R for the S isomer is 14.4 min, t_R for the R isomer is 14.6 min. For pentan-2-ol: β DEX 2,3,6-M-19, 110 °C, t_R for the R isomer is 23.6 min, t_R for the S isomer is 25.8 min. For heptan-2-ol: β DEX 2,3,6-M-19, 130 °C, t_R for the R isomer is9.9 min, t_R for the S isomer 1 is 1.5 min. For octan-2-ol: β DEX 2,3,6-M-19, 130 °C, t_R for the R isomer is 7.9 min, t_R for the S isomer is 9.5 min. For 1-(2-pyridyl)-ethan-1-ol: β DEX 110, 110 °C, t_R for the S isomer is 14.9 min, t_R for the R isomer is 15.2 min. For 1-(3-pyridyl)-ethan-1-ol: β DEX 110, 110 °C, t_R for the S isomer is 14.5 min, t_R for the R isomer is 14.9 min. For 1-(4-pyridyl)-ethan-1-ol: β DEX 110, 110 °C, t_R for the S isomer is 14.8 min, t_R for the R isomer is 15.1 min.

Comparison with the racemic and optically pure alcohols (aromatic compounds) purchased from Aldrich was realized under the same chromatographic conditions. By this technique, the purity of the alcohols was also ascertained, confirming the ^{1}H and ^{13}C NMR data. For linear alkyl and pyridyl alcohols, optically pure alcohols are not commercially available: their absolute configurations were determined by optical rotation, by comparison with the reported values in the literature.

General Procedure for Coupling the Poly(amidoamine) Dendrimers (PAMAM Dendrimers) with the D-Glucono-1,5-lactone. Chemicals, including D-glucono-1,5-lactone and PAMAM dendrimers (generations 1−4), were purchased from Aldrich. The PAMAM dendrimers samples used in this report were stored in methanol solution. All solvents were obtained from Aldrich and used without further purification. The solvents were preserved with molecular sieves (4 Å).

In a two-necked, round-bottomed flask equipped with a thermometer and a magnetic stir bar were introduced 7.25×10^{-4} mol of PAMAM dendrimers (generation $n = 1$, 2, 3, and 4) in 5 mL of dry CH_3OH, under argon. A 10% molar excess of **4**, **8**, **16**, or **32** $\times$ 7.25×10^{-4} mol of d-glucono-1,5-lactone in 3 mL of DMSO was added to the solution by a syringe with stirring. The mixture was stirred at 40 °C for 24 h under argon atmosphere. The reaction was followed by TLC using $CHCl_3/CH_3OH$ (80/20, v/v) as eluent.

The solution was poured into an amount of propan-2-ol (IPA). The azeotrope formed by DMSO with IPA was removed under vacuum.

Gluconamidopoly(amidoamine) dendrimer was isolated after vigorous washing of the reaction mixtures with methanol (these compounds showed hydrophilic properties and were soluble in water and DMSO; they were insoluble in methanol and chloroform which dissolved the D-glucono-1.5-lactone). The precipitate was lyophilized to yield a white powder.

The linking of the sugars is achieved by amide bond formation, provided that the reaction proceeds quantitatively or nearly so (G(1)G yield 95%, G(2)G yield 93%, G(3)G yield 96%, G(4)G yield 94%,). The compounds exhibited high hygroscopic behavior, which increased with each subsequent generation.

The isolated dendrimers were characterized by specific physicochemical methods, similar to our previous work.[8]

For the chiral supports (gluconamidopolynorbornene and gluconamidoalkanes), the procedures were similar to previous work.[10,11]

General Procedure for Reduction of Prochiral Ketones in Organic Medium. A stoichiometric quantity of sodium borohydride ($NaBH_4$) (32 mol equiv, 96 mg; 2.5×10^{-3} mol) was added to a solution of glucose-persubstituted PAMAM dendrimers (8×10^{-5} mol) in 25 mL of THF. The mixture was stirred under reflux for 10 h. Then the mixture was cooled to room temperature and the ketone (2.5×10^{-3} mol) was added to it with stirring. After complete reduction (12 h), the THF was evaporated to dryness. A large amount of CH_3OH was added to the resulting solid. After filtration of the dendrimer, a 1 M HCl solution was added to the CH_3OH layer. Evaporation of CH_3OH led to the alcohol. All compounds were obtained in high chemical yields and showed satisfactory NMR characteristics. The ee of products were determined by gas chromatography with a chiral separation column (SUPELCO α DEX 120, β DEX 110 fused silica capillary column with a 30 m × 0.25 mm × 0.25 μm film thickness and a VARIAN CP-Cyclodextrin-β-2,3,6-M-19 column with a 50 m × 0.25 mm × 0.39 μm film thickness) (see below).

The procedure for the reduction of prochiral ketones in the presence of the gluconamidopolynorbornane and bis-gluconamido alkanes was the same.

General Procedure for Reduction of Prochiral Ketones in Aqueous Medium. Glucose-dendrimer aqueous solution with methyl phenyl ketone in excess was allowed to remain for 12 h undisturbed at 40 °C. The maximum concentration of ketone in a 10^{-3} M aqueous solution of glucose-persubstituted PAMAM dendrimers was equal to 2×10^{-5} M for generation 3 and 10^{-4}M for generation 4. Sodium borohydride was added to 10 mL of this saturated solution. The mixture was stirred for 2 h, followed by two successive extractions with CCl_4. After evaporation of the solvent, the methylphenylcarbinol was obtained and analyzed**.**

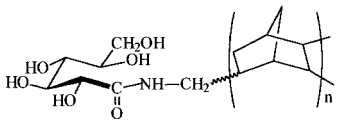
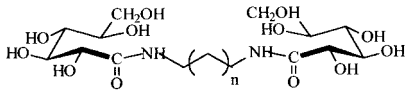
General Procedure for the Regeneration of the Dendrimer. The boron-modified dendrimer (5 g; 3.96×10^{-4} mol) was stirred at room temperature in 0.1 N HCl aqueous solution. The mixture was neutralized with an aqueous solution of 0.1 N NaOH and ultrafiltered on a Millipore microporous membrane system. The complete system consisted of a Millipore filter holder, torque wrench, low shear peristaltic pump and appropriate filter packets, and retentate separators (polysulfone 10 000 NMWL).

No significant difference was observed on conversion and enantioselectivity between the initial and regenerated dendrimer (even with 10 cycles).

Results and Discussion

Asymmetric Reduction of Acetophenone by $NaBH_4$ in THF, at the Solid−Liquid Interface of Amphiphilic Chiral Supports. Reduction of acetophenone by $NaBH_4$ was carried out in THF, which is usually a solvent used for this type of reaction.[12] The reaction was carried out in the presence of various chiral supports with the same sugar group (gluconamido) and structural modulations summarized in Figure 2. This gluconamido group was selected since it allowed us to obtain various chiral objects such as fibers, helices,[13] and the supramolecular expression of chirality, which is directly linked to the headgroup organization.

Table 1. Enantioselective Reduction of Acetophenone in THF at 0 °C by $NaBH_4$ in the Presence of Different Chiral Supports

Chiral support	Chemical yield	% ee[a]
	75	0
 n = 6, 12	90	0
G(1)G	95	0
G(2)G	98	0
G(3)G	92	99(S)
G(4)G	91	3(S)

[a] Determined by GC using a β DEX 110 column (see the Experimental Section).

The results for the reduction in the presence of these different chiral supports are summarized in Table 1.

Under these heterogeneous conditions, good results were only obtained with the third-generation dendrimer G(3)G. All the other dendrimer generations (G(1)G, G(2)G, and G(4)G), linear polymer, or even bolaform chiral auxiliaries were not able to selectively induce chirality.

According to molecular simulations (Figure 2), low generations of gluconamido-persubstituted PAMAM (generations 1 and 2) possess a highly asymmetric, open "starfish-like" shape. Similarly, bolaform structures and even gluconamidopolynorbornene are open structures. In contrast, the G(3)G dendrimer has a spherical symmetry and presents a more closed and densely packed structure which is effectively the most stable form of the dendrimer as shown in the different steps of the modelization (Figure 3). Moreover this compactness is confirmed by ^{13}C NMR relaxation times showing rigidity of the branches of G(3)G.[14] Therefore, this compactness of the surface seems to play a key role in an asymmetric induction. The dendrimer G(4)G became too highly sterically hindered at its periphery, leading to difficulties for the gluconamido end groups in adopting a favorable conformation for chiral induction.

In summary, the results obtained showed a correlation between stereoselectivity of the reduction and the isotropic and compact character of the external surface of the molecule. It seems that better selectivities are obtained as a result of the compromise between the steric clutter and the global compactness of the surface. It is also important to notice that under heterogeneous conditions (THF) the dendrimer could be recovered by filtration, regenerated in HCl/MeOH, and recycled (up to 10 times), leading every time to the same results in asymmetric reduction of ketones.

Asymmetric Reduction of Acetophenone by $NaBH_4$ at the Interface of Amphiphilic Chiral Supports in Water. The

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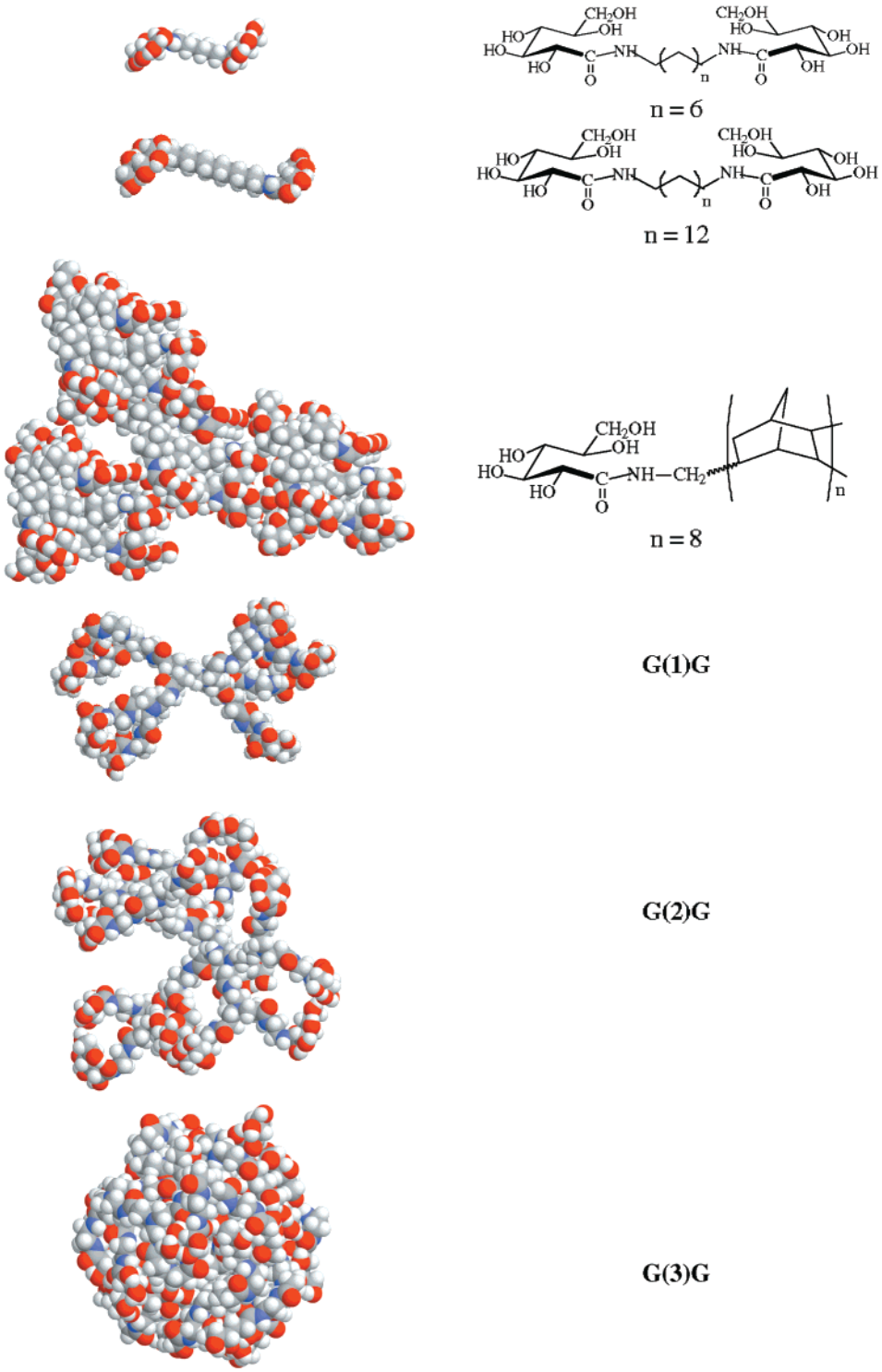

Figure 2. Structures of different chiral supports.

topology of the chiral surface could be also influenced by hydrogen bonding and solvation of the sugar heads. To investigate the influence of these two parameters, we performed the reduction of acetophenone in the presence of these amphiphilic dendrimers in water. In this case the reaction takes place under homogeneous conditions.

As above, the reaction was carried out with various chiral supports and the results are summarized in Table 2.

In these homogeneous conditions, only G(4)G gave high enantioselectivity; all the other chiral supports lead to poor results.

The aim of this study was as well to obtain evidence of the formation of complex inclusion in our dendrimers in water and thereby to understand how the acetophenone is positioned to affect the face selectivity. For this purpose, NMR ^{13}C in water was used to obtain details of the structure and dynamics of the inclusion complex.

The first information obtained from a comparison of the spectra in Figure 4a,b concerns the formation of the dendrimer−AcPh complex by hydrogen bonds. A simple observation of the signals from the dendrimer moiety (32 to 176 ppm) shows that no important variations are produced indicating that the

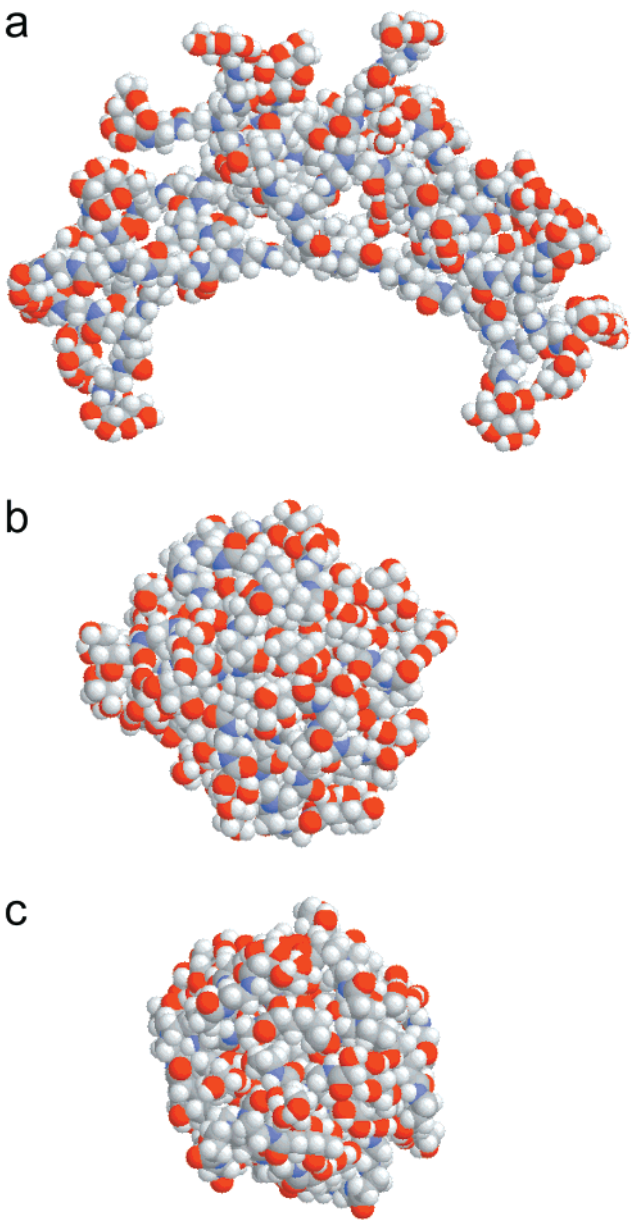

Figure 3. (a) G(3)G after the first energy minimization (fist step), (b) G(3)G at $T = 37.2$ ps of the dynamic simulation (second step), and (c) final conformation of G(3)G. Dynamic modelization of G(3)G.

complex between the dendrimer and AcPh is not affected significantly, at least as far as the stability is concerned. However, a very important observation can be made concerning the signal of the carbonyl and methyl groups of AcPh. The carbonyl group normally appears at 185 ppm and the methyl group appears at 24.5 ppm. In the present case, they disappeared. The possible explanation is to consider that the carbonyl group is strongly immobilized by a hydrogen bond.

Stimulated by the observation of induced chirality of chromophores dissolved into chiral bilayers and micelles[15] and to get direct proof of the effect of the dendrimer in the process, the induced circular dichroism (ICD) spectra of the acetophenone encapsulated in the dendritic cavities were recorded. ICD spectroscopy is based on the transfer of chirality from the environment to an achiral ketone (the carbonyl chromophore displays an intramolecular ICD in the first allowed n → π^* transition around 190 to 300 nm due to perturbation from the surrounding chiral environment). In Figure 5 the results are described for the acetophenone in the presence of all chiral dendrimer generations.

Although four samples show identical UV spectra, a significant difference is observed in their induced CD spectra. The generations 0−2 did not exhibit an induced CD spectrum. However, an exciton-coupled spectrum is observed when acetophenone is encapsulated in G(3)G and G(4)G. Moreover, this exciton coupling indicates the closer proximity of chromophores with a certain fixed orientation, in the case of G(4)G, due to hydrogen-bonded coordination with the chiral dendrimer

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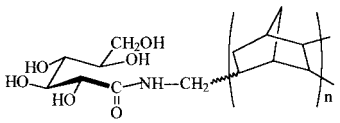
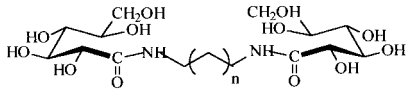
Table 2. Enantioselective Reduction of Acetophenone in Water at 25 °C by $NaBH_4$ in the Presence of Different Chiral Supports

Chiral support	Chemical yield	% ee[a]
	80	0
 n = 6, 12	30	0
G(1)G	95	0
G(2)G	98	0
G(3)G	95	50(S)
G(4)G	92	98(S)

[a] Determined by GC using a β DEX 110 column (see the Experimental Section).

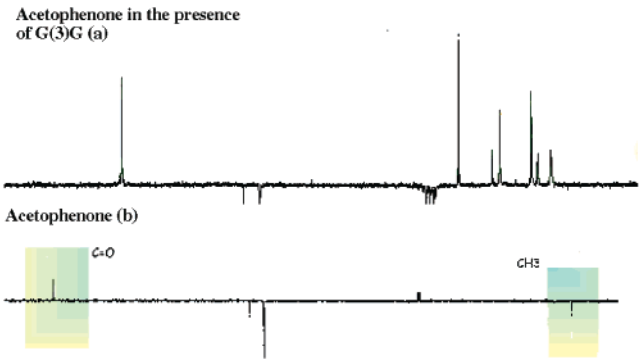


Figure 4. (a) NMR spectra of acetophenone in D_2O, in the presence of G(3)G dendrimer. (b) NMR spectra of acetophenone in D_2O.

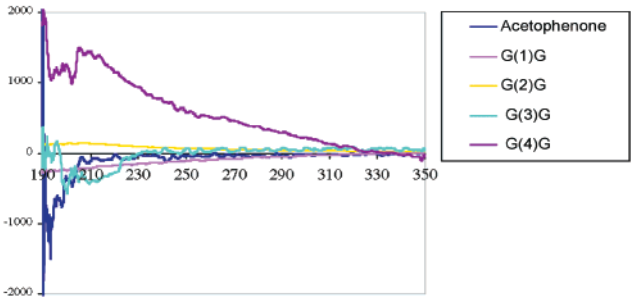


Figure 5. Induced circular dichroism of acetophenone in the presence of chiral amphiphilic dendrimers.

Table 3. Enantioselective Reduction of Prochiral Ketones in THF by $NaBH_4$ in the Presence of G(3)G

ketone	*T*, °C	chemical yield (%)	% ee[a]
cyclohexyl phenyl	25	97	97 (S)
butyl phenyl	25	96	100 (S)
propyl phenyl	25	90	100 (S)
methyl phenyl	25	82	82 (S)
methyl phenyl	0	94	99 (S)
methyl p-Br phenyl	25	94	78 (S)
2-pentanone	0	94	55 (S)
2-pentanone	−20	88	85 (S)
2-heptanone	−20	94	28 (S)
2-heptanone	−80	96	96 (S)
2-octanone	−20	92	25 (S)
2-octanone	−80	85	50 (S)
2-acetylpyridine	0	90	90 (S)
3-acetylpyridine	0	60	59 (S)
4-acetylpyridine	0	45	25 (S)

[a] Determined by GC using α DEX 120, β DEX 110, or β DEX 2,3,6-M-19 columns depending of the compounds (see the Experimental Section).

interface. These ICD effects have been exploited to assess the relatively well-ordered structures of the ketone at the dendrimer hydrophilic chiral interface**.** These results suggest that the procedure employed here with dendrimers produces unimolecular structure (direct "micelle-like") in which guest molecules can be encapsulated and for which the orientation in the dendritic cavity is directly linked to the external dendrimer surface. The ketones are more highly orientated and better fixed in the G(4)G dendrimer because its periphery is more compact and the presence of H-bonds between sugar moieties greatly enhances the rigidity of the system. Therefore G(4)G seems to act in water as G(3)G in THF. As in THF, all the other chiral supports are not compact enough to give high enantioselectivities.

In THF, the heterogeneous conditions allowing the recovery and its regeneration, we investigated the efficiency of the procedure with other ketones.

Asymmetric Reduction of Various Ketones by $NaBH_4$, in THF, at the Solid−Liquid Interface of Amphiphilic Chiral Dendrimer G(3)G. In previous work, we were able to reduce aromatic prokiral ketones [9] with high enantioselectivities. We show here that the process is also efficient with linear ketones and also with some functionalized ketones. The results are summarized in Table 3.

The examination of Table 3 leads to the following comments: (a) Rigidity of the chiral complex is a factor controlling the topology of the reducing reagent, so decreasing temperature resulted in a significant improvement in the chiral induction. (b) The optical induction is larger for aromatic and short linear substrates than for ketones where the carbonyl is attached to a long paraffinic chain. In this last case, the steric hindrance at the chiral interface of the dendrimer is probably the limiting effect.

Nevertheless the high asymmetric inductions obtained with linear alkyl ketones are, to our knowledge, the best result presented in the literature for this type of ketones.[16]

Finally, the enantioselectivity depends on the variation of the position of the carbonyl group on the pyridine moiety. We noticed that better results were obtained through the 2-acetylpyridine. This is probably due to the competition of the complexation of the $NaBH_4$ on the N of pyridine and the hydroxyl dendrimer groups.

Conclusion

New amphiphilic dendrimers derived from PAMAM and D-gluconolactone have been found to induce chirality in the reduction of prochiral ketones by $NaBH_4$. The enantioselectivities obtained appear to be directly influenced by the external surface of the structure.

The third generation of these amphiphilic dendrimers, G(3)G, was found to be a good chiral ligand for the reduction of various prochiral ketones in heterogeneous conditions. Even with substrates well-known to give poor results (specially linear ketones), good enantioselectivities are obtained. It is also important to notice that under heterogeneous conditions (THF) the dendrimer could be recovered by filtration, regenerated in HCl/MeOH, and recycled, leading every time to the same results in asymmetric reduction of ketones.

We have also discussed the reduction of acetophenone in water. It appears that the selectivity is dominated by the architecture of the dendrimer and some supramolecular ordering in the position of the ketone at the chiral solvating interface.

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