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Mechanistic study of the enantioselective reduction of ketones in the presence of glycodendrimers

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Abstract—Prochiral ketones were sodium borohydride reduced at the chiral interface of amphiphilic dendrimers bearing sugar moieties at their ends. In water, stereoselectivities were improved by using the fourth generation of these amphiphilic dendrimers [G(4)G]. Under heterogeneous conditions (THF) the third generation [G(3)G] gave the best enantioselectivities. Mechanistic studies of such asymmetric induction were performed by molecular modeling, ^{13}C NMR spectroscopy, Induced Circular Dichroism, as well as reaction parameters: influence of the temperature, cations, molecular structure of the sugar ends and of dendrimer links with the sugars:
– in homogeneous conditions (water), the main factor is the ordering and specific orientation of the ketone at the chiral interface;
– in heterogeneous conditions (THF) enantioselectivities are due to a chiral intermediate with the C(3) and C(4) sites of the sugar part, and to the C(2) site whose structure is important for ketone positioning.

1. Introduction

Dendrimers are chemically well-defined, highly branched molecules which are constructed in a generation-wise manner starting from a central core molecule.[1] They can be designed to form unimolecular micelles (when they are amphiphilic) possessing cavities able to accommodate guest molecules.[2] Dendrimers can also be functionalized, for example with sugars giving glycodendrimers mimicking the multi-antennary carbohydrate moieties of the glycoconjugates exposed on the surface of mammalian cells.[3]

Recently we described new glycodendrimers prepared from polyamidoamine (PAMAM) and gluconolactone (generations [G(n)G], $n=1$–4).[4] These glycodendrimers have a chiral surface environment with internal cavities, and can act as rigid chiral unimolecular micelles. Sodium borohydride reduces prochiral ketones in the presence of these amphiphilic dendrimers, to give the corresponding chiral alcohols with both high yields and high enantioselectivities:[5]

(i) under heterogeneous conditions (THF) good results were only obtained with the third-generation dendrimer: [G(3)G];
(ii) under homogeneous conditions (water), good results were only obtained with the fourth-generation dendrimer: [G(4)G];

This indicated a correlation between the stereoselectivity of the reduction and the confinement of the prochiral molecule in a chiral environment. To explain this behavior we postulated two hypotheses:

– in THF, the third generation dendrimer is relatively open, and allows substrate molecules to reside at the solid-liquid interface,
– in water, with generation four, the maximum enhancement in enantioselectivity is dominated by the position of the ketone at the chiral solvating interface.[6]

Herein we describe different physicochemical methods to gain a better understanding of the mechanisms of these reactions.

2. Results and discussion

Figure 1 shows the synthesis and structure of amphiphilic dendrimer [G(3)G].

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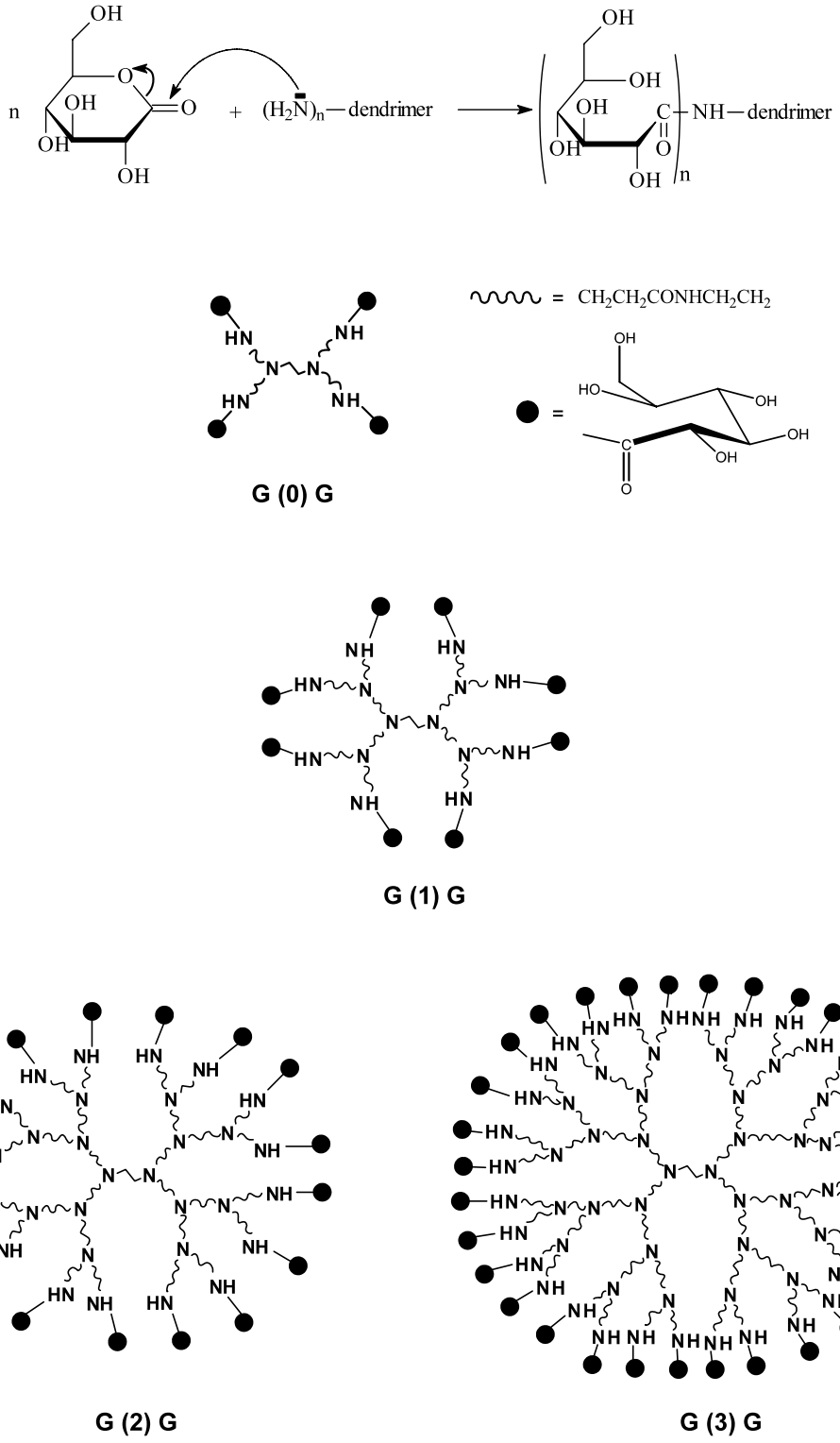


Figure 1. Synthesis and structure of amphiphilic dendrimers [G(*n*)G]. The G(*n*) symbol is applied to all the PAMAM dendrimer and the letter after indicates the nature of the sugar: G in the case of glucose. Ex.: [G(1)G] points out the first PAMAM generation functionalized with glucose.

2.1. Asymmetric reduction of acetophenone by $NaBH_4$ at the interface of amphiphilic chiral supports in water

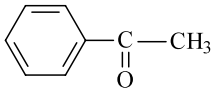
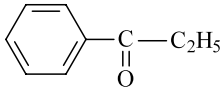
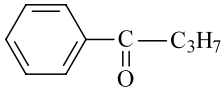
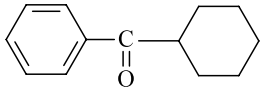
2.1.1. Capping of prochiral ketones. In a previous study the physicochemical properties of glucose-persubstituted poly(amidoamine) dendrimers were investigated in water.[6] This study showed that these new amphiphilic dendrimers were able to dissolve or encapsulate increasing quantities of hydrophobic compounds (pyrene or aromatic ketones) in water, depending on the number of microcavities in each dendrimer.[4] To investigate the effect related to the hydrophobicity of

the compounds, we studied the incorporation of different ketones having different hydrophobicities. To do so, we used the partition coefficient between water and 1-octanol, expressed by its logarithm: log *P*, calculated with the atomic increment method (Table 1).

We have shown before that dendrimer generation 3 provided the best water protection to the dissolved pyrene molecules indicating that this structure allowed large amounts of pyrene to gain access to the hydrophobic core. We chose this dendrimer to study the solubility of ketones in aqueous solution. The concentration of the dissolved ketones was found to increase linearly with the concentration of dendrimer (Fig. 2).

Besides, the more hydrophobic the ketone, the greater the solubility. These results agree with the accessibility of the ketones to the hydrophobic core.

Table 1. Ketones log *P* lipophilicity parameters

Ketone	Formule	logP
Methyl phenyl		**1,822**
Ethyl phenyl		**1,983**
Propyl phenyl		**2,380**
Cyclohexyl phenyl		**3,569**

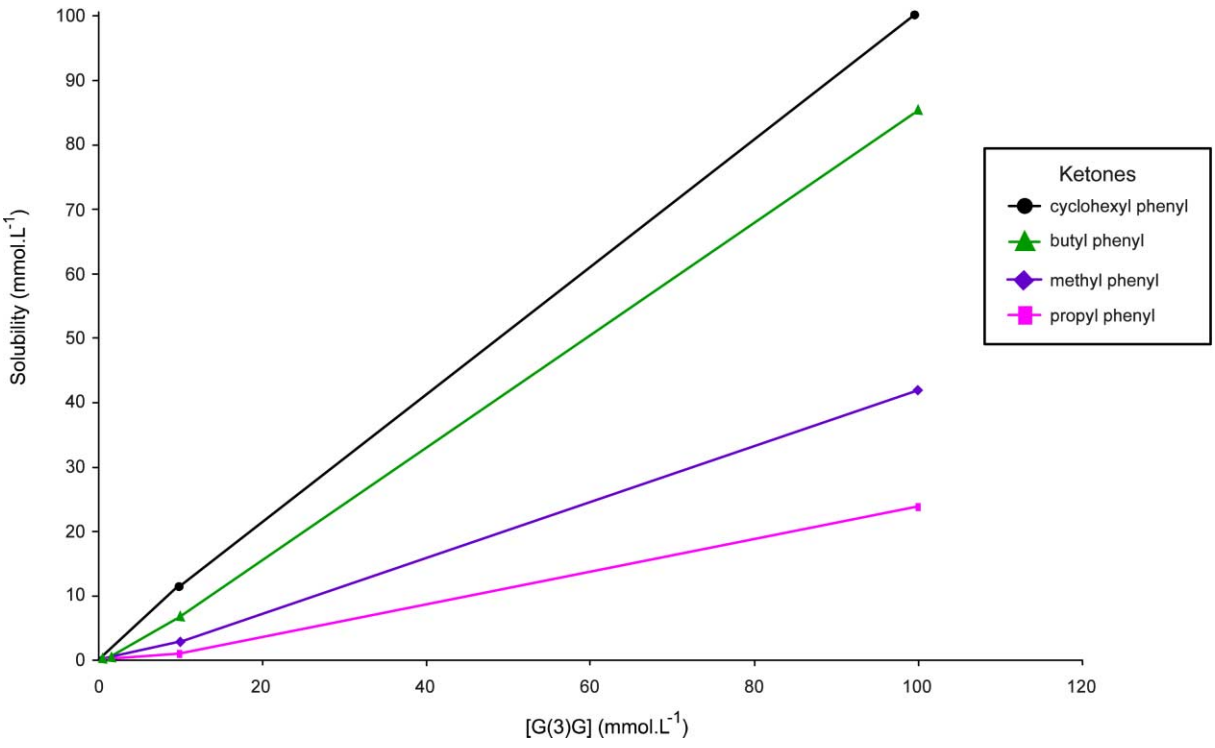


Figure 2. Ketones solubility in water versus the [G(3)G] concentration (24.00 h at 40°C; UV analysis at 25°C).

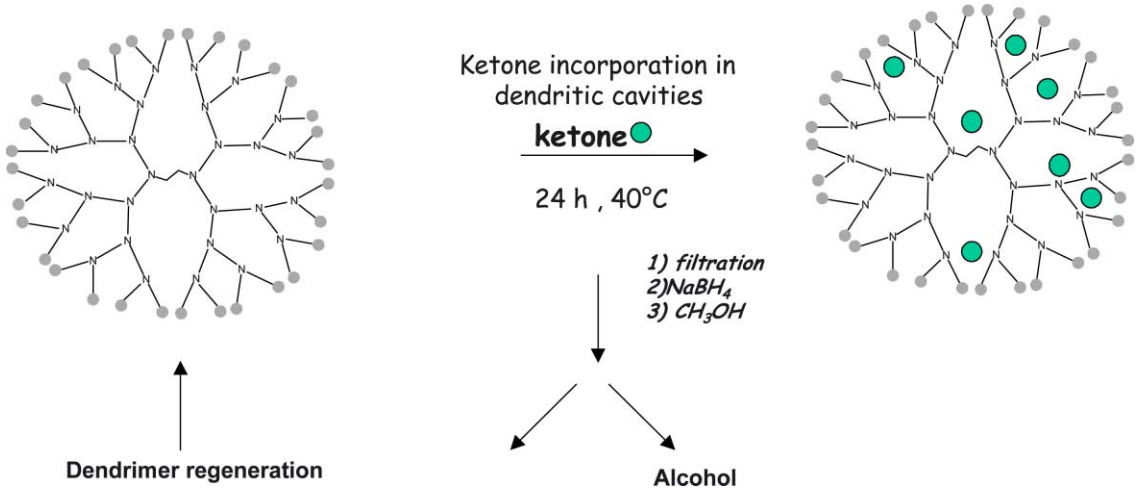
2.1.2. Reduction of prochiral ketones. Scheme 1 summarizes the general procedure for reduction of prochiral ketones in aqueous media the dendrimer being insoluble in methanol, it was very easy to recover it by filtration.

2.1.2.1. Reduction of acetophenone in water, in the presence of [G(*n*)G] dendrimers. We chose acetophenone, because of its strong hydrophobic character, with a concentration of 10^{-2} M in aqueous dendrimer solution, to achieve a good arrangement between both components: the reaction then takes place under homogeneous conditions. Under these conditions, the enantioselectivity depends on the dendrimer generation. With the highest generation tested,[G(4)G], giving 98% enantiomeric excess in the favor of (*S*), two important parameters have to be considered:

– better insertion of the hydrophobic molecule into the cavity, with a better orientation,
– a diminution of the quantity of ketone dissolved due to the external surface compactness.

In our opinion, another parameter should be considered: the aggregation of the dendrimers. In an earlier work we investigated these aggregation properties in water by Transmission Electron Microscopy[4] when Molecular simulation was essential to gain insight into the nature of the aggregates.

2.1.3. Molecular modeling study. Figure 3 shows the result of the molecular simulation of the aggregation of four [G(3)G] dendrimer molecules, in water, with minimization.



Scheme 1. Reduction of prochiral ketones in water.

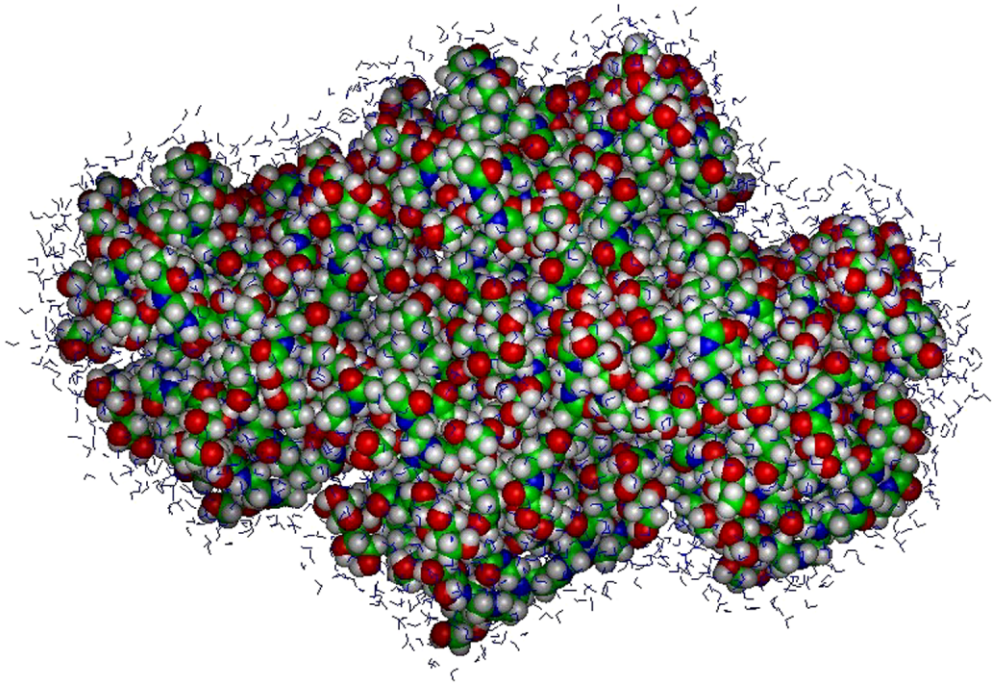


Figure 3. Molecular simulation of the aggregation of four [G(3)G] dendrimer molecules in water.

This study showed:
- the high solvation of hydroxylic groups by water,
- the strong association of [G(3)G] molecules.

The association, due to the intermolecular hydrogen bonding between the sugar moieties which persists in aqueous solutions, could prevent the ketone from penetrating into the hydrophobic cavities: in this case, the actual quantity of encapsulated ketone would be less than theoretical. Another point concerns the compactness of the chiral outer surface which evolves depending on the generation of the dendrimer: high for the third generation (with maximum ketone encapsulation), the denser outer layer of the fourth generation dendrimer leads to steric hindrance accounting for the low quantities of acetophenone penetrating the hydrophobic core.

The ketone encapsulation phenomenon in the dendritic cavities of [G(3)G] was also simulated by the same molecular modeling method. After 'gelling' the dendrimer host, with a water layer 0.5 nm thick, the minimization calculation was carried out only on the guest molecule (ketone) taking into account its macromolecule environment. At the beginning, the ketone is in the water layer, outside of the dendrimer, but during the calculation it penetrates into one of the hydrophobic cavities The lowest energy conformer fits positioning by hydrogen bonding with a hydroxylic group (Fig. 4).

Schematically, the mechanism of the reaction with the hydride ion can be described as in Scheme 2. After inclusion and positioning of the ketone in the cavity, due to the hydrogen bonding with the hydroxylic group in the position of the terminal amide bond, there is a selective attack of the carbonyl group by the hydride anion. This attack occurs from below the double bond and leads to the (*S*)-enantiomer, owing to the steric hindrance on the other side. Taking this model into

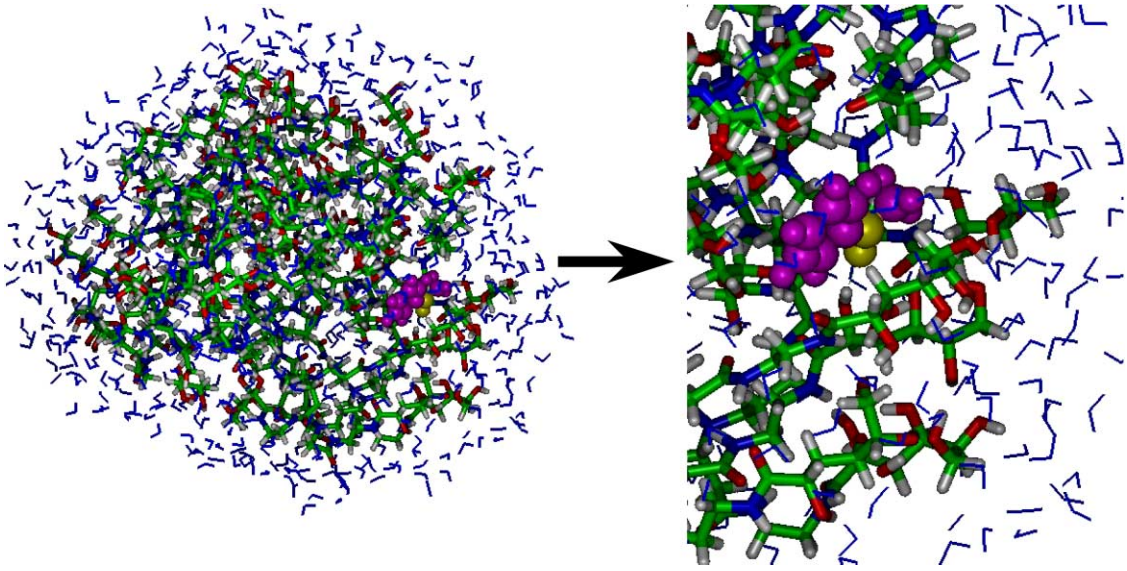
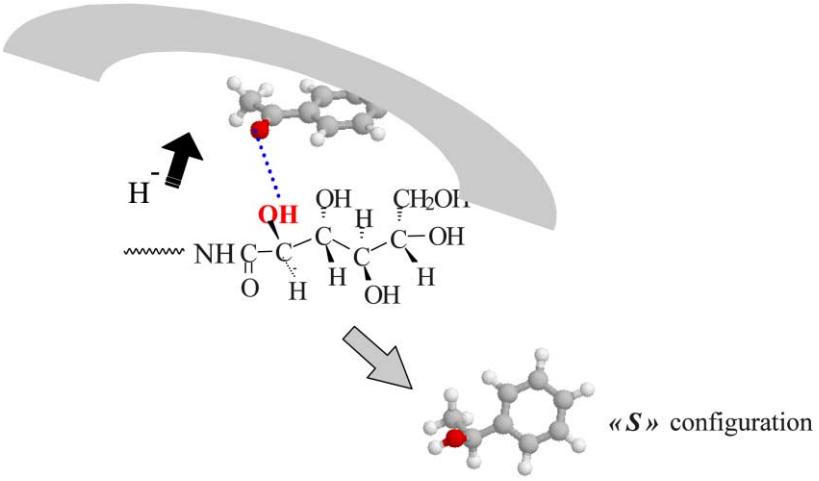


Figure 4. Acetophenone positioning in the dendritic cavity (red: O, grey = H, green: dendrimer C atoms, yellow = carbonyl group of the ketone, magenta: ketone framework, blue: N of the amido group and water molecules).



Scheme 2. Mechanism of the hydride reaction.

account, we can explain the results obtained with the different generations:

– [G(1)G] and [G(2)G] dendrimers possess an open 'starfish-like' shape, not rigid enough to provide stable orientation for the ketone,
– from [G(3)G] to [G(4)], the cavities become more compact forcing the ketone to adopt a favorable orientation, but limiting the quantity of ketone incorporated.

^{13}C NMR was then used to validate the simulation: the change of the environment carbonyl group shifting its resonance.

2.1.4. ^{13}C NMR studies. The ketone ^{13}C NMR spectra in D_2O and in dendrimers solution in D_2O, provide some important data:

– with the generations 0–1, we did not observe any change of the ^{13}C signal with or without dendrimer: it is a mixture of ketone and dendrimer spectra;
– with the second generation, the ^{13}C carbonyl group signal was a slightly deshielded;
– with the third generation, the ^{13}C methyl signal disappeared and the carbonyl group signal shifted downfield.

The last changes can be attributed to the positioning of the ketone in the cavity; the hydrogen bond between C=O and OH groups rigidifies the system generating a change in the relaxation times.

These results agree with the molecular modeling studies corroborating the localization of the ketone at the chiral interface of the dendritic cavity.

2.1.5. Induced circular dichroism spectra. Incorporating acetophenone in dendritic cavities by direct contact with the [G(3)G] dendrimer solution at 40°C for 24 h, we observed a slight shift of circular dichroism of absorption bands in comparison with the UV spectra (Fig. 5). Only with the [G(3)G] did we find an induced CD spectrum indicating closer proximity of chromophores with the chiral dendrimer interface.[8]

All three methods: Molecular modeling, ^{13}C NMR spectra and induced circular dichroism converged to account for our results in water by specific positioning of the ketone inside the dendritic cavities and specific orientation induced by the dendrimer chiral interface.

2.2. Asymmetric reduction of ketones by $NaBH_4$ in THF at the solid–liquid interface of amphiphilic chiral supports

Reduction of ketones by $NaBH_4$ was carried out in THF which is the usual solvent used for this type of reaction in the presence of carbohydrate molecules.[9–11] Scheme 3 shows the general procedure for the reduction of prochiral ketones in THF.

The $NaBH_4$–dendrimer complex formed during the first step of this procedure was not soluble in THF, so the reduction was performed under heterogeneous conditions. These conditions allowed the recovery of the dendrimer by filtration. After recovery it was possible to regenerate this chiral support: the recycled glycodendrimer led to the same asymmetric reduction of ketones.

2.2.1. Reduction of acetophenone. To determine the best stoichiometry for the reduction, we studied the molar ratio: $NaBH_4$/acetophenone; in the presence of [G(3)G], chemical yields decrease to 72% and enantiomeric excess to 16% (S) when we use 1:2 molar ratio.

This result leads to the following comments:

1) two hydrides seem to be involved in the reaction;
2) the asymmetric induction strongly decreases with a 1:2 stoichiometry.

With a 1:1 stoichiometry, which was the one previously used in water, acetophenone reduction at 25°C gave different enantioselectivities depending on the dendrimer generation

As in water solution, low generation dendrimers, but also [G(4)G], were not able to selectively induce chirality (2–5% ee); good results were only obtained with the third generation [G(3)G] (82%):

– with generations 1 and 2, the arrangement is too open;
– with generation 4, the dendrimer becomes too highly sterically hindered at its periphery.

The behavior of the last generation in water and in THF can be explained by competition for hydrogen bonds between intermolecular water solvation and 'intramolecular' sugar moiety hydroxylic groups. The

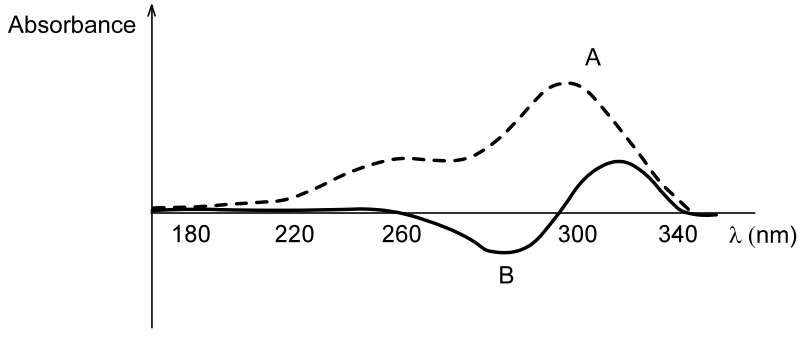
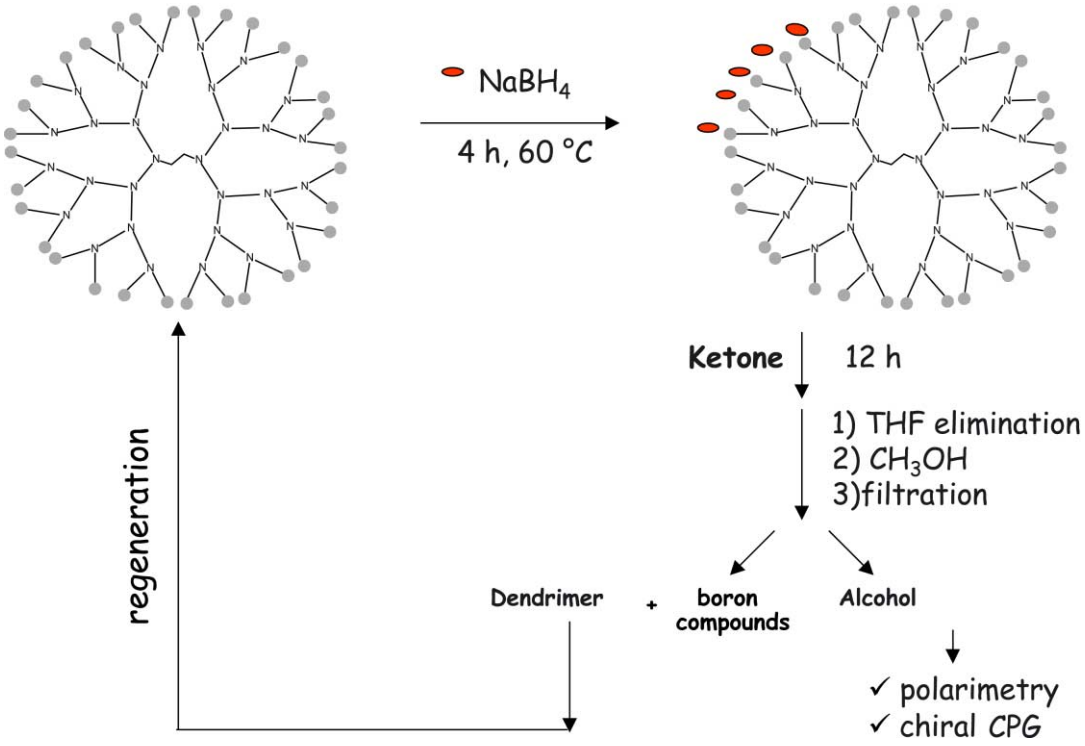


Figure 5. A: Acetophenone UV spectrum in aqueous solution. B: Acetophenone CD spectrum in aqueous solution of [G(3)G].



Scheme 3. Reduction of prochiral ketones in THF.

solvation by water was able to open out the chiral ends, allowing a well-ordered structure of the ketone and enhancing penetration through the interface.

In THF, the [G(4)G] dendrimer became too highly sterically hindered because of the compactness due to the intramolecular H-bonds between the sugar moieties.

2.2.2. Influence of temperature. Decreasing the temperature from 25 to 0°C resulted in a significant improvement in the asymmetric induction: at 0°C the enantiomeric excess was more than 99%. This result can be explained by the slowdown of exchange between the $NaBH_4$ and the sugars, but also by a different partition coefficient of the ketone between THF and dendrimer.

2.2.3. Influence of the solvent. For a better explanation of the influence of the solvent on the enantioselectivity, we performed the reduction in two solvents: THF and dichloromethane (DCM) which were used for both reaction steps: Transformation of the chiral inductor and reduction of the ketone. Examination of the results leads to the following comments: with DCM as solvent for the whole process, the global yield was reduced and the enantiomeric excess was very low (6%); when THF was used in the first step and DCM in the second, the enantiomeric excess was 70%, but only 4% when the solvents were reversed. This shows the importance of the THF during the formation of the chiral reducing agent, which is also important in the second step owing to the lower enantioselectivity in DCM. The mechanism in THF can be explained by different phenomena, by increasing the interaction between sodium borohydride and sugars, favoring the formation of the reducing agent or by solvation of the sodium cation, limiting the electrophilic activation of the ketone.[12]

2.2.4. Cation effect. We compared the effect of the cation by reducing the ketone with KBH_4 and $LiBH_4$ in THF: the decrease of the enantioselectivity is of the same order as ketone electrophilicity enhancement by complexation with the cation: $Li^+ > Na^+ > K^+$. With $LiBH_4$, the reactivity was the best (98% yield) while selectivity decreased (27%S). With KBH_4, the reaction was slower, the cation being less complexed, and the anion reactivity lowered (70% yield; 33%S).

The selectivity of the reduction is strongly influenced by the solvent cation pair. The problem is finding a good compromise between the solvation of the cation and its electrophilic assistance.

2.2.5. Influence of the sugar molecular structure. Owing to this surprising selectivity and to explain the role of the dendrimer structure, it was essential to evaluate the influence of the stereogenic carbon atom configuration on the reaction enantioselectivity. Therefore, we synthesized PAMAM-type dendrimers substituted with epimeric D-mannose and D-galactose moieties. In this way we synthesized third generation PAMAM dendrimers functionalized with galactose [G(3)Gala] and mannose [G(3)M], by direct coupling between dendrimer and D-galactonic-γ-lactone or mannonic-γ-lactone (Fig. 6).

The results obtained for acetophenone reduction at 0°C in THF, in the presence of these dendrimers can be interpreted as following:

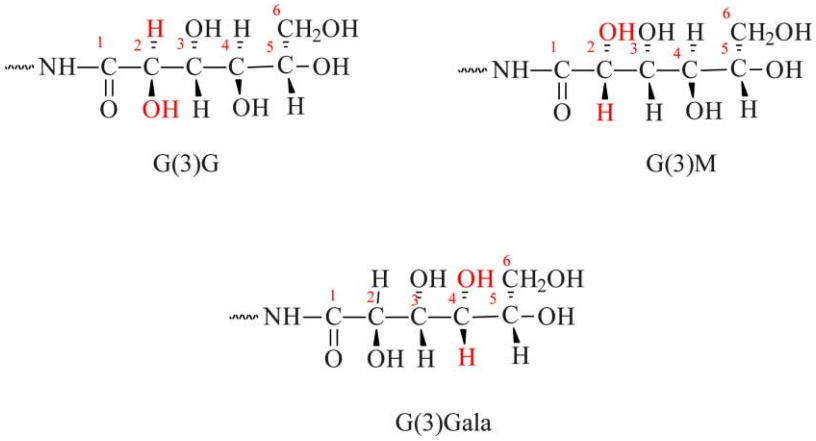


Figure 6. Functionalized PAMAM dendrimer with epimeric sugars.

2.2.5.1. C(2) configuration. On changing the configuration of the C(2) centre, we did not observe asymmetric induction [G(3)M, 3%S]. It seems therefore that this C(2) configuration is of crucial importance for the enantioselectivity. Besides, molecular modeling in water has shown that it was this hydroxylic group on C(2) which was involved in the formation of hydrogen bonds between the ketone and hydrophilic part of the dendrimer.

2.2.5.2. C(4) configuration. We carried out the same reduction in the presence of [G(3)Gala]: in this case the configuration change is located on C(4). With the original C(2) configuration maintained. The enantiomeric excess was 60% showing a slight decrease of selectivity, but this decrease was not as great as with the change of C(2) carbon atom configuration.

2.2.5.3. Amide bond influence. To estimate the contribution of the amide bond, we reduced the amido groups with BH_3 in THF to get the corresponding amines (Fig. 7): When we used the new dendrimer obtained to reduce acetophenone at 0°C, the enantiomeric excess was only 20%: the alcohol being, this time, enhanced in (*R*)-enantiomer, displaying the influence of the amide bond in the proximity of the stereogenic centers. In seems that the pair: amide bond-C(2) configuration as a whole, plays a very significant role in reduction enantioselectivity. We proved this hypothesis using L-gluconolactone as the capping groups of the dendrimer (Fig. 8): Reversing the configurations of all stereogenic carbons, the enantiomeric excess (*S* enantiomer) obtained by reducing acetophenone at 0°C, was only 20%. These results were confirmed by NMR spectroscopy.

2.2.5.4. ^{13}C NMR studies. After studying the influence of the dendrimer chiral moieties, we investigated the structure of the reducing agent formed with [G(3)G] and $NaBH_4$ in THF at 60°C. We separated the complex generated and tested it to verify its activity: The enantioselectivity was maintained during the acetophenone reduction.

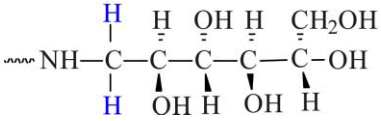


Figure 7. Reduced [G(3)G].

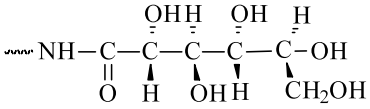


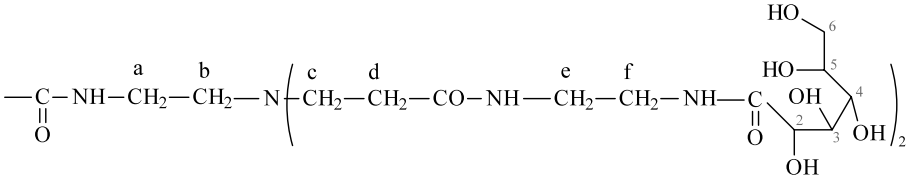
Figure 8. L-Gluconolactone substituted G(3).

^{13}C NMR in DMSO, gave a comparison between the dendrimer structures and the carbon framework motions with those of the complex. Measuring T_1 longitudinal relaxation times provided information on the molecular dynamics of [G(3)G] and its complex with boron; the latter compound being short of reducing agent. Table 2 shows the terminal chiral part of [G(3)G] and the assignment of the signals. All the chemical shifts are the same for [G(3)G] and [G(3)G/8$NaBH_4$] but, with the complex, C(2), C(3), C(4) and C(5) signals are not split unlike [G(3)G]. This splitting can be attributed to two preferential conformers and their disappearance in the presence of the reducing agent supports the involvement of amido groups in the complexation. New signals appear at 75.6, 74.6 and 64.1 ppm, with [G(3)G]/8$NaBH_4$ assigned to the complexation of the dendrimer sugar moiety with borohydride. In Figure 9 both the dendrimer and the complex are visible (new signals in red), the exchange between dendrimer and borohydride being very low at the NMR time scale. The new signals with added boron hydride most probably correspond to carbon atoms of the complexed sites.

This exchange however was underlined by varying the temperature: increasing the temperature speeded up the exchange bringing the signals closer together. From 25 to 90°C it was impossible to observe coalescence of the peaks showing that the exchange was slow in this temperature range. Chemical shift variation of each

Table 2. ^{13}C NMR chemical shifts of [G(3)G] and [G(3)G]/8$NaBH_4$

Carbon atoms	G(3)G δ (ppm)	G(3)G/8$NaBH_4$ δ (ppm)
(a)	**37**	**37**
(b)	**52,2**	**52,2**
(c)	**49,5**	**49,5**
(d)	**33,2**	**33,2**
(e), (f)	**38,4**	**38,4**
(2)	**73,6** **73,1**	**73,6**
(3)	**71,5** **71,6**	**71,5**
(4)	**70,2** **70,5**	**70,2**
(5)	**72,3** **72,5**	**72,3**
(6)	**63,4** **63,5**	**63,4** **63,5**
carbonyles	**175,6** **172,9** **171,7** **171,5**	**173** **171,9** **171,6**



carbon atom of the sugar moiety versus the temperature was greatest for C(3) and C(4) carbon atoms: We can postulate that both corresponding sites are complexed with the borohydride. This result is in agreement with the previous stoichiometric study: the reducing agent seems to have two active hydrides required for the reduction. So, the chiral intermediate formed with [G(3)G] and $NaBH_4$ should be obtained with the C(3) and C(4) sites of the sugar moiety. The reversibility of the complexation was confirmed by going back to room temperature: chemical shifts were then the same as before.

Another hypothesis is the covalent reaction of a very small quantity of $NaBH_4$ with sugar, owing to the presence of traces of water. However, the very small quantity of this compound cannot explain the high enantioselectivity of the reaction.

This ^{13}C NMR study combined with the sugar effects suggests a complexation between the C(2) site and the ketone, while C(3) and C(4) sites are complexed with $NaBH_4$.

2.2.6. Influence of the ketone. We successively studied the reduction in the presence of [G(3)G] of the aromatic, aliphatic, heterocyclic and substituted aromatic ketones. Table 3 shows the results obtained with aromatic ketones at 25°C in THF. In all cases, whatever the nature of the R group, the quantity of (*S*)-alcohol formed is enhanced: the enantioselectivity being better in heterogeneous than in homogeneous media. With substituted aromatic ketones, enantioselectivites were less than with unsubstituted aromatic ketones: the decrease can be explained by an increased total volume of the molecule, hence steric hindrance during contact between the reactants.

This reducing method is general, as shown in Table 4, with a limitation for the linear aliphatic ketones: even at very low temperature (−80°C) it was impossible to obtain ees above 25% with 2-nonanone.

With acetylpyridines, yields and enantioselectivities depended on the position of the carbonyl group relatively to the nitrogen atom. The best result was obtained with 2-acetylpyridine, owing to a possible

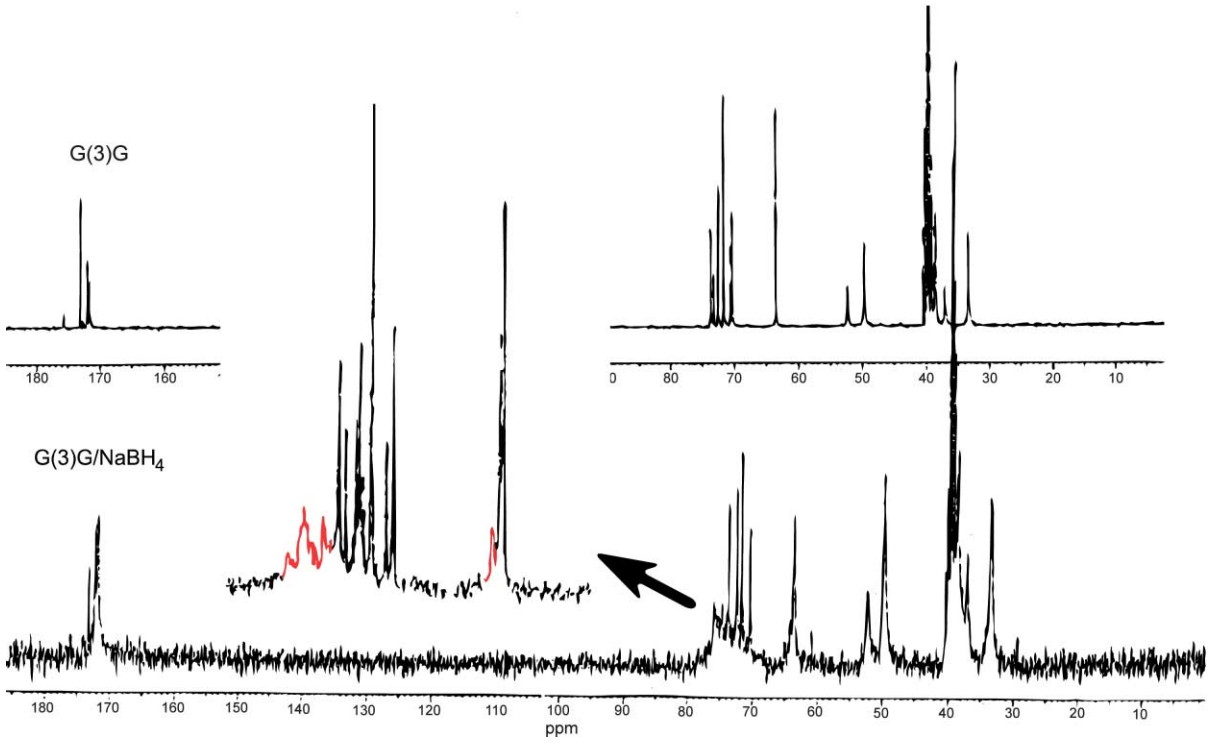
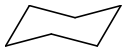


Figure 9. ^{13}C NMR spectra of [G(3)G]/8$NaBH_4$.

Table 3. Prochiral aromatic ketones reduction (THF, 25°C, [G(3)G)]

Ketone C_6H_5-CO-R	R	chemical yields (%)	ee (%)
methyl phenyl	CH_3	92	82 (S)
ethyl phenyl	CH_2CH_3	90	99 (S)
propyl phenyl	$CH_2CH_2CH_3$	96	99 (S)
cyclohexyl phenyl		97	97 (S)

hydrogen bond with hydroxylic group of the dendrimer (Fig. 10).

Another hypothesis is the formation of a cyclic complex where the reactant is at first complexed with both the carbonyl group and the heteroatom[13] (Fig. 11): such complexation is impossible with acetyl in 3 or 4 position.

2.2.7. Dendrimer reconditioning and recycling. The most important advantage of the reaction in heterogeneous phase is the recovery of the dendrimer by filtration at the end of the reaction. To do so it was necessary to transform organic boron compounds by adding acidic aqueous solution. Then we used two methods of reconditioning ultrafiltration, owing to the difference in size between dendrimer and the salt and gel filtration demineralization. In both cases the dendrimer was recycled for further ketone reduction: after ten cycles we observed neither lowering of the activity or stereoselectivity in the reduction of acetophenone.

3. Conclusion

The study of the reduction of ketones in the presence of a new family of glycodendrimers, has shown that it is possible to get very high enantioselectivity:– in homogeneous water solution, with the fourth generation dendrimer, showing that its rigidity and compacity are essential for high stereoselectivity;– in heterogeneous THF medium, with the third generation dendrimer,

Table 4. Enantioselective prochiral ketones reduction (THF, [G(3)G])

Ketone	T(°C)	Chemical yields (%)	ee (%) (S)
2-Pentanone	0	94	55
	-20	88	85
2-Heptanone	0	89	14
	-20	94	28
	-80	96	96
2-Octanone	-20	92	25
	-80	85	50
2-Nonanone	0	80	5
	-80	90	25
2-Acetylpyridine	0	88	90
3-Acetylpyridine	0	69	59
4-Acetylpyridine	0	25	43
p-bromo-acetophenone	0	91	78
	25	94	46
p-nitro-acetophenone	0	76	71
	25	93	65

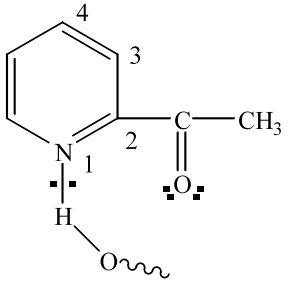


Figure 10. Hydrogen bonding of 2-acetylpyridine with [G(3)G].

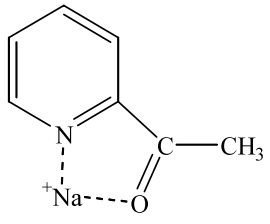


Figure 11. Cation coordination with carbonyl group and nitrogen atom.

giving a very useful system for practical synthesis and recovery of the reactant.

In THF, we showed that enantioselectivity is attributable to a chiral intermediate obtained by reaction between C(3) and C(4) sites of the sugar part, the ketone positioning depending on the structure of the C(2) carbon atom.

4. Experimental

PAMAM dendrimers, lactone, ketones, borohydrides and THF were purchased from ALDRICH; DCM was obtained from NORMAPUR. The general procedure for coupling the PAMAM dendrimers with the D-glucono-1,5-lactone has been previously described as well as the general procedure for the reduction of prochiral-ketones in organic or aqueous media.[6] The general procedure for the regeneration of the boron-modified dendrimer was also described in the same paper.[6] Following reduction in water recovery of the dendrimer was carried out by ultrafiltration. ^{1}H NMR spectra were recorded on either a BRUKER AC 200 (200 MHz) spectrometer, or a BRUKER AC 400 WB (400 MHz) spectrometer with either the solvent as reference or TMS as internal standard. ^{13}C NMR spectra were recorded on a BRUKER AC200 (50 MHz) spectrometer or a BRUKER AC 400 WB (100.6 MHz) spectrometer. Circular dichroism spectra were recorded at 25°C using a Jobin Yvon Mark VI dichrograph. Log *P* values were calculated using the TSAR 2.02 software, Oxford Molecular. 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. Details of the study of

dendrimer structures are described in Ref. 7. General procedures for reduction of prochiral ketones in aqueous or organic media are described in Ref. 7 as well as the methods used for the characterization of the alcohols. UV spectra were recorded with a Hewlett-Packard HP 845LA diode-array UV–vis spectrometer.

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