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First example of high asymmetric induction at the "pseudo-micellar" interface of a chiral amphiphilic dendrimer

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Abstract : Sodium borohydride reduced, at the chiral interface of an amphiphilic dendrimer, prochiral ketones to the corresponding chiral alcohols in high yields (>90%) with enantioselectivities over 95% in THF (ex: ee of 99.4% was obtained in reduction of acetophenone). © 1999 Published by Elsevier Science Ltd. All rights reserved.

Chiral direct (or reverse) micelles have focussed a great interest during the last twenty years since they can be used as the simplest analogues to mimic the stereochemistry of enzymatic reactions[1]. Therefore hydrolysis of enantiomeric p-nitrophenylesters was catalyzed enantioselectively by chiral micelles[2]. In contrast, only few examples of asymmetric induction were described in literature. Moreover, in all cases- with various chiral surfactants, in direct or reverse micelles- asymmetric induction was not good enough (the ee varying from 1.7% to 27% for reduction of aromatic ketones[3,4], with enantioselectivity no more than 10% for oxidation of sulfides[5]).

One important reason of all these failures is the dynamic of the micelles leading to a chiral interface not enough rigid to provide stable asymmetric complexes.

Recently, we described new amphiphilic dendrimers derived from PAMAM involving the multiple attachment of polyhydroxylated groups derived from glucose[6]. The structures of these dendrimers are represented in Figure 1. These new amphiphilic dendrimers could therefore be considered **as rigid unimolecular micelles**, being able in solution in water to solubilizate hydrophobic compounds such pyrene or aromatic ketones in dendritic cavities[6a].

In this work, we present first results concerning the reduction of prochiral ketones by sodium borohydride at the chiral interface of these dendrimers. In a first time, we have chosen the third generation dendrimer G(3)G (see figure 1) which is the first generation G(n)G leading to nearly spherical shape similar to a micelle and presenting more closed and densely packed structure than previous generations G(0)G to G(2)G[6a].

According to literature, reduction was performed in water[3,4] and in THF in which chiral modifications of borohydride were also performed by chiral auxiliaries derived from sugars[7]. Results are summarized in Table 1.

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Figure 1: Structures of amphiphilic dendrimers G(n)G[6]

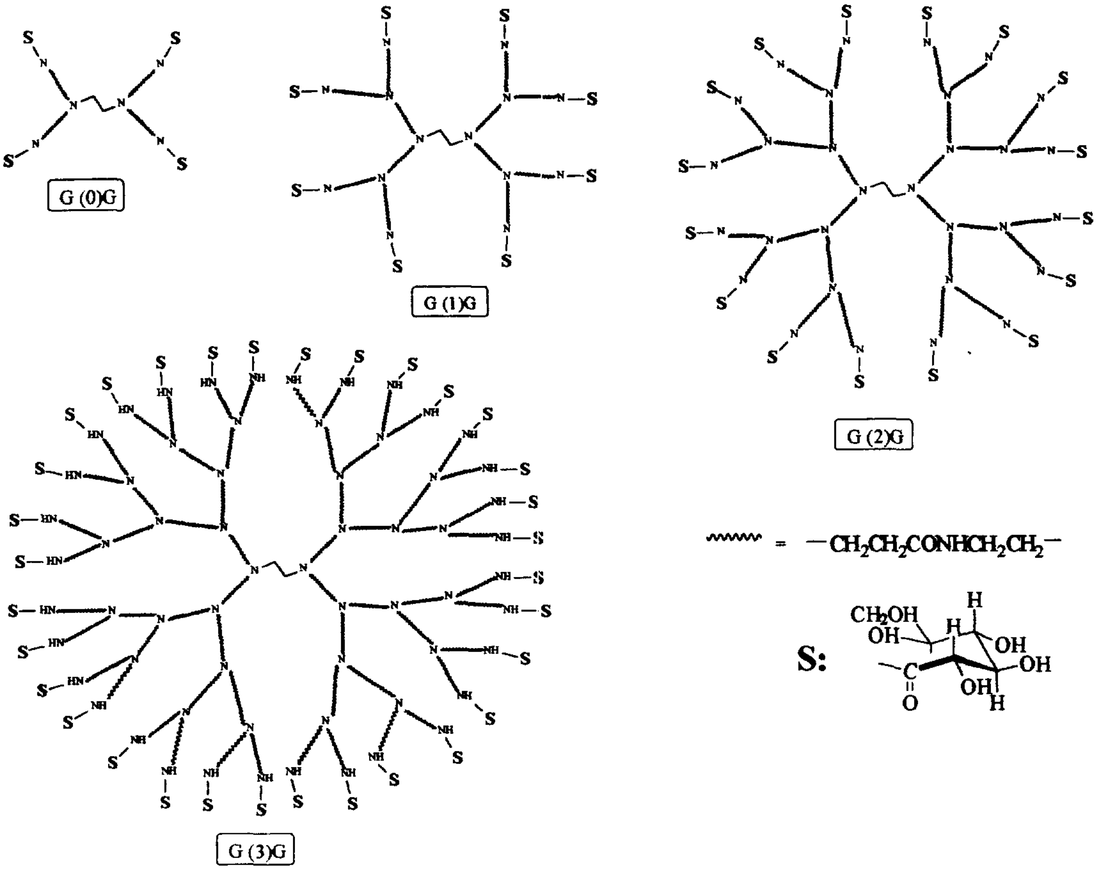

Table 1: Enantioselective reduction of prochiral ketones by $NaBH_4$ in presence of G(3)G[8]

Ketones	Solvent	T(°C)	Chemical yield (%)	Ee (%)[a]	Abs. Conf. of alcohol
Cyclohexyl phenyl	Water	25	95	50	*S*
Cyclohexyl phenyl	THF	25	97	97	*S*
Butyl phenyl	THF	25	96	100	*S*
Propyl phenyl	THF	25	90	99.9	*S*
Methyl phenyl	THF	25	92	82	*S*
Methyl phenyl	THF	0	94	99.4	*S*

a- determined by GC analysis using a chiral column (β dex 110 for methyl phenyl ketone and propyl phenyl ketone, α dex 120 for butyl phenyl ketone and cyclohexyl phenyl ketone).

The examination of these results leads to the following comments:

(i) **For the first time, really high asymmetric induction is obtained in presence of a chiral dendrimer** leading to very good enantioselectivities in reduction of various aromatic ketones (even with acetophenone well known to give often poor results in asymmetric reduction in homogenous[9] or heterogeneous[10] conditions).

(ii) The best results are obtained in THF, which is usually the solvent used for asymmetric reduction of prochiral ketones by boranes or modified borohydride[7,9]. In THF, the reaction is performed in heterogeneous conditions : the complex between $NaBH_4$ and the dendrimer being not soluble in THF. **It is also the first time – at our knowledge- that dendrimers are used in asymmetric synthesis in heterogeneous conditions**: in such conditions, the dendrimer could be recovered by filtration and recycled.

(iii) It is finally important to notice that the spherical structure of the dendrimer G(3)G is the same in solution in water or in suspension in THF.

Indeed, in THF, G(3)G acts as a "pseudodirect" micelle with a pseudo-micellar chiral interface in contrast with linear polymers which conformation depends of their heterogeneous or homogeneous state in solution[6b].

In conclusion, amphiphilic dendrimer G(3)G acts as an highly pseudo-micellar enantioselective chiral ligand for the reduction of prochiral ketones. Work is now in course to develop this new concept in asymmetric synthesis with reduction of other ketones (particularly aliphatic ketones) and with other reactions (oxidations, for example).

References and notes

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b) the procedure to prepare the dendrimers G(n)G is similar to previous work to prepare glycopolymers derived from norbornene (see Puech, L.; Perez, E.; Rico-Lattes, I.; Bon, M.; Lattes, A. *New J. Chem.*, **1997**, *21*, 1229)

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(8) Typical procedures are the following:

Reduction in organic medium: A stoechiometric quantity of sodium borohydride ($NaBH_4$) (32 mol equiv, 96 mg; 2.5 10^{-4} moles) is added to a solution of glucose persubstituted PAMAM dendrimers (generation 3; 1 g ; 8 10^{-5} moles) in 25 ml THF. The mixture was stirred under reflux for 10 h. Then the mixture was cooled at room temperature and the ketone (2.6 10^{-3} moles) (1:3 mol equiv to the sodium borohydride) was added to it with stirring. After the completion of 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 1M HCl solution was added to the methanol layer. Evaporation of CH_3OH leads to the alcohol. All compounds were obtained in high chemical yields and showed satisfactory NMR characteristics. The enantiomeric excesses of products were determined by the optical rotation and by gas chromatography with a chiral separation column (SUPELCO α DEX 120 or β DEX 110 fused Silica Capillary Column 30m x 0.25 mm x 0.25 µm film thickness).

Reduction in aqueous medium: As described previously (6a), glucose-dendrimer aqueous solution with cyclohexyl phenyl ketone in excess is allowed to stay for 12 h undisturbed at 40 °C. The maximum concentration of ketone in a 10^{-2}M aqueous solution of glucose - persubstituted PAMAM dendrimers (generation 3) was found equal to 10^{-4}M. Sodium borohydride (22 mg ;3 mol equiv. to the ketone) 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 cyclohexyl phenyl carbinol is obtained in 95% chemical yield and analyzed as described above.

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