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Chiroptical Induction and Molecular Recognition in Optically Active Hyperbranched Polyethers with Inherently Chiral Benzophenone Core

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Molecular recognition plays a crucial role for the biological function of natural polymers in receptors, enzymes, antibodies, and DNA.[1] Therefore, numerous synthetic pathways mimicking such receptors have been developed to generate models for understanding recognition processes and in general to realize molecular recognition for catalysis, chiral separation, and information storage.[2] Optically active, highly branched three-dimensional macromolecules, such as dendrimers and hyperbranched polymers, can be considered to be particularly interesting compounds in this context, since they can be designed to contain peripheral or internal chiral units or may possess an optically active core.[3] However, only few precisely constructed optically active dendrimers, particularly with chiral core, have been reported and used for enantioselective recognition of chiral molecules. ^{1}H NMR and circular dichroism (CD) spectroscopy or fluorescence spectroscopy have been used for the related studies.[4] The respective chiral recognition processes were due to repulsive (steric effects) or attractive interactions (hydrogen bonding, van der Waals forces). Large contact areas, a multiplicity of interaction sites, and strength of the interaction aid recognition in the case of optically active dendrimer receptors by a substrate.

While there are only limited examples of perfect, optically active dendrimers suitable to achieve chiral recognition,[3] hyperbranched polymers based on chiral building units, prepared in a one-pot polymerization process, have neither been reported to date nor considered as chiral receptors for enantioselective molecular recognition.[4] This Communication describes a rapid approach for the preparation of chiral, nonracemic hyperbranched polyethers, initiating the polymerization of enantiomerically pure glycidol monomer from the racemic mixture of an inherently chiral benzophenone core. Further developing the concept, optically active hyperbranched polymers consisting of merely a small inner shell of enantiomerically pure units followed by an outer shell of racemic glycerol have also been studied in view of the global chirality of the hyperbranched macromolecules. Recognition of the enantiomers of naproxen [2-(6-methoxynaphth-2-yl)propionic acid, NPX], a non-steroidal anti-inflammatory drug, has been investigated.

In order to obtain well-defined hyperbranched polyether polyols, we relied on the ring-opening multibranching polymerization (ROMBP) of glycidol as an AB_2 type monomer, using slow monomer addition.[5] This method has been successfully used to obtain hyperbranched polyglycerols with moderate to narrow polydispersity ($M_w/M_n < 1.8$) and a large number of hydroxyl end groups.[6] Recently, we reported covalent incorporation of a photoactive core, namely a 2,2′,4,4′-tetrahydroxybenzophenone (THBP) within a racemic hyperbranched polyglycerol corona (TGBP-(rac)-PG).[7] Benzophenone, a well-known C_2-symmetry photoactive chromophore, is intrinsically chiral due to its inability to adopt a planar conformation (Scheme 1 and Chart 1S, Supporting Information).[8] The conformer with minimum energy adopts a helical geometry, with the phenyl rings twisted out of the central carbonyl plane in opposite directions by the same torsion angle (ca. 30°).[9] However, benzophenone is configurationally labile in solution due to rapid interconversion between both conformational enantiomers (*M*) and (*P*). Similarly, THBP exhibits fast interconversion equilibrium between structures I and II at room temperature (Scheme 1).

Both enantiomerically pure and racemic glycidol monomers (Gly* and *rac*-Gly, respectively) were used to covalently incorporate THBP into the hyperbranched structure of polyglycerol. The phenolic nature of the hydroxyl groups of the THBP permits facile deprotonation and results in incorporation of the benzophenone chromophore within the hyperbranched shell. In view of obtaining both optically active and photoactive functional hyperbranched macromolecules, it is an intriguing issue whether this polymerization in the presence of enantiomerically pure glycidol[10] could lead to a preferential sense of twist of the conformationally flexible benzophenone in the first stages of the polymerization reaction, resulting in a preferred diastereoisomer.

Chiral, nonracemic polymers TGBP-(*R*)-PG_{34}, TGBP-(*S*)-PG_{50}, and TGBP-(*S*)-PG_{62} with different average molecular weights (M_n) of 2600, 3600, and 4200 g/mol, respectively, moderate polydispersity ($1.3 < M_w/M_n < 1.8$), and different optical activity derived from the use of (*R*)- or (*S*)-glycidol have been prepared, employing a Gly*/THBP molar ratio of 63 (Scheme 1 and Table 1S in Supporting Information).[11,12] The UV/vis spectra of the polymers in methanol were compared with a parent model compound, namely 2,2′,4,4′-tetramethoxybenzophenone (TMBP) (Figure 1A). We had previously reported that the UV/vis absorption spectra of the TGBP-(*rac*)-PG polymers are similar to that of TMBP, with a weak n,π^* band close to 350 nm and two strong bands with maxima at $\lambda = 278$ nm ($\log \varepsilon = 4.45$) and 312 nm ($\log \varepsilon = 4.42$).[7]

In marked contrast, an unexpected and drastic change in the UV-absorption shape in the 250−375 nm range was observed for the structurally analogous chiral, nonracemic polymers (Figure 1A). In particular, the band at 278 nm increases at the expense of that at 312 nm, which is due to a π,π^* transition and assigned to the 2,4-dimethoxybenzoyl chromophore.[13] Besides, the band at 278 nm can be attributed to the 2,4-dimethoxyphenyl chromophore.[14] Therefore, the change observed in the UV/vis spectrum of benzophenone upon covalent encapsulation within the chiral hyperbranched polymer shell can only be interpreted in terms of a decreasing number of conformers. This permits to conclude that a "loss" of 2,4-dimethoxybenzoyl dipoles took place.

CD spectra of all the polymers in methanol recorded at the same concentration (10^{-4} M) showed intense, bisignate curves (Figure 1B), indicating dipole−dipole coupling between locally excited states that belong to two chromophores with similar energies and intensities, having a chiral, oblique orientation (exciton coupling).[15] Since the bisignate signal is centered at 310 nm, it has to be assigned to the 2,4-dimethoxybenzoyl chromophore. The sign of the couplet (defined by the sign of its longer wavelength

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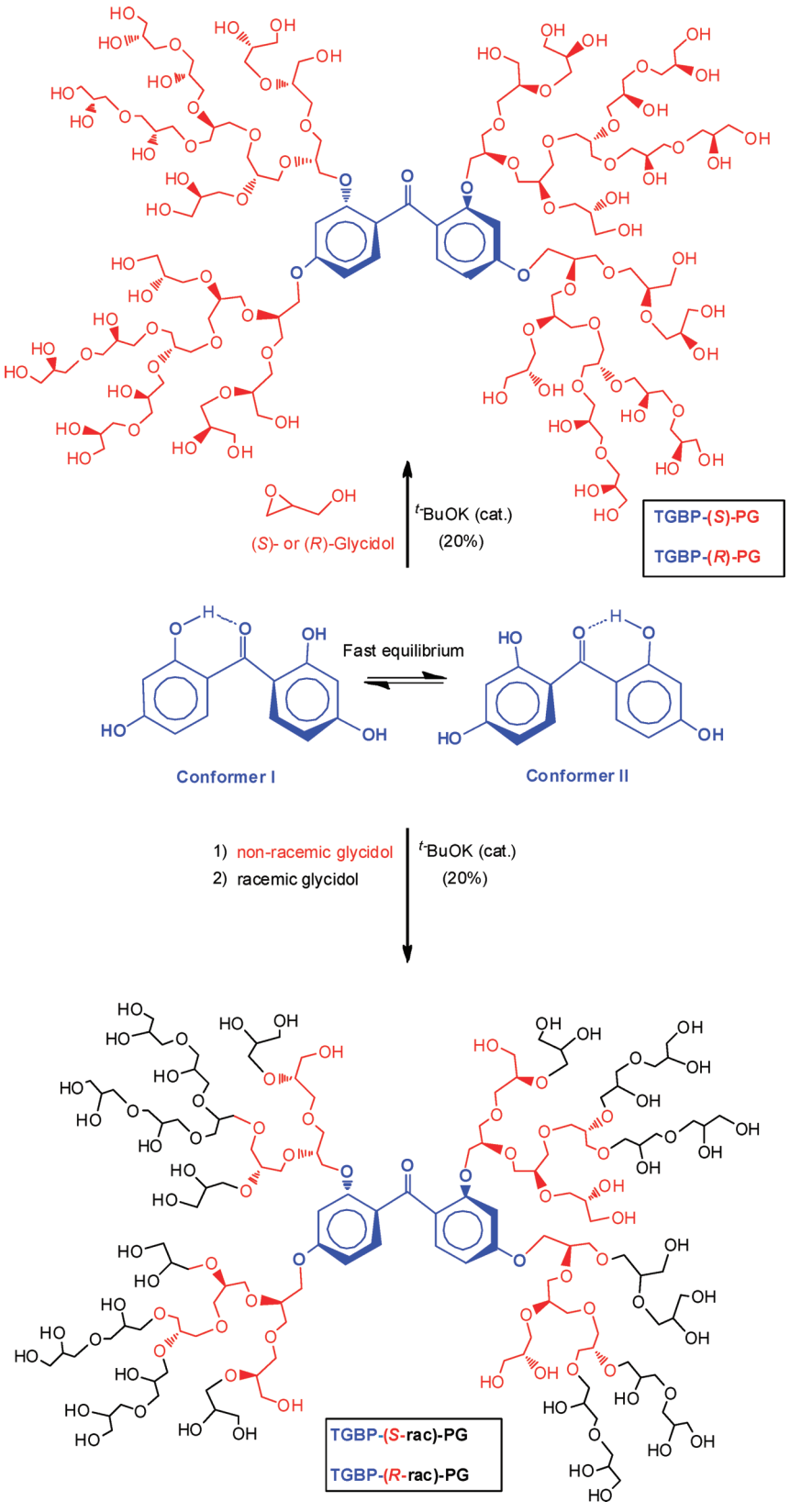
Scheme 1. Synthesis of Chiral Hyperbranched Polyglycerols Starting from the Racemic Mixture of Inherently Chiral 2,2′,4,4′-Tetrahydroxybenzophenone (THBP)[a]



[a] Polymers with enantiomerically pure glycerol units (top) and polymers with a small enantiomeric excess of the glycerol units (bottom) were studied.

component) was negative for polymers with (*R*)-Gly, while (*S*)-Gly showed positive exciton chirality. This is the consequence of a predominant one-handed helical configuration of the benzophenone core inside the chiral, nonracemic hyperbranched structure.[16] Thus, there is a change in the equilibrium between the *P* and *M* conformers in the presence of the chiral glycerol units in the first

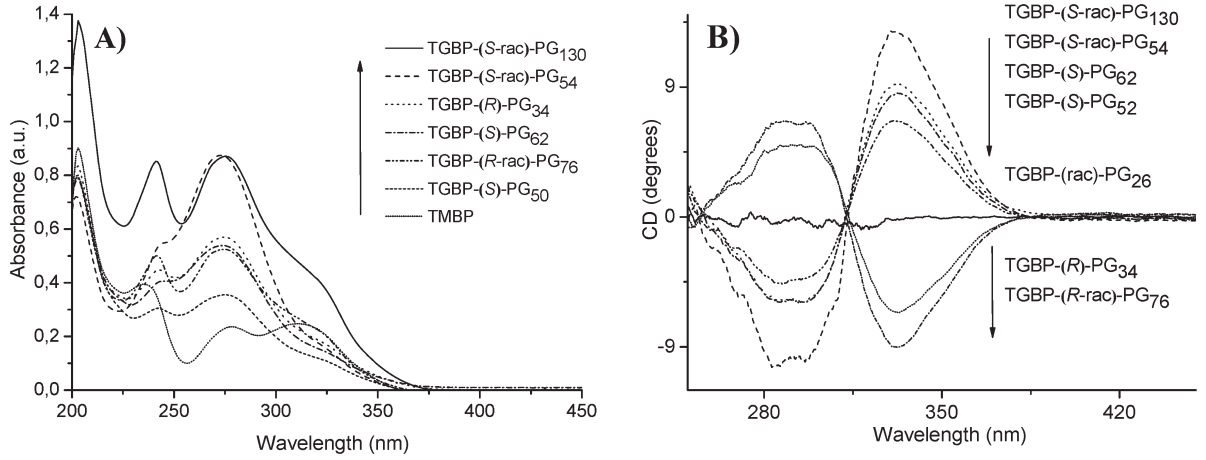


Figure 1. UV−vis (A) and CD spectra (B) for TGBP-PGs polymers in methanol at 25 °C.

Table 1. Characterization Data for the Chiral, Nonracemic TGBP-Core Hyperbranched Polyglycerols

	[Gly]/[THBP]							
polymer	Gly*	*rac*-Gly	M_w/M_n [b]	M_n [b] (SEC) (g/mol)	M_n [c] (NMR) (g/mol)	DP_n [c]	OH [c,d]	$[\alpha]_D^{20}$ [e] (deg)
TGBP-(*R*)-PG_{34}	63 (+)[a]		1.7	2560	2570	30	34	−2.60
TGBP-(*S*)-PG_{50}	63 (−)[a]		1.8	3560	3730	46	50	1.70
TGBP-(*S*-rac)-PG_{54}	14 (−)[a]	49	1.3	3130	3950	50	54	2.95
TGBP-(*S*)-PG_{62}	63 (−)[a]		1.8	4220	4540	58	62	1.60
TGBP-(*R-rac*)-PG_{76}	14 (+)[a]	49	1.6	4650	5620	72	76	−0.05
TGBP-(*S-rac*)-PG_{130}	14 (−)[a]	49	1.5	9090	9580	126	130	1.70

[a] Optical rotation sign of the enantiomerically pure glycidol (Gly*) used as the starting material is given in parentheses. [b] Determined by SEC in dimethylformamide with polystyrene standards. [c] Calculated from ^{1}H NMR spectra. [d] Number of hydroxyl groups. [e] The specific optical rotation [α] sign of (*R*)-Gly and (*S*)-Gly are +15° and −15°, respectively.

stages of the polymerization when using the Gly* monomer. According to the CD exciton chirality method,[17] the configuration was assigned as *P* and *M* for polymers TGBP-(*R*)-PG and TGBP-(*S*)-PG, respectively.

Variable temperature CD spectra have also been recorded at 10, 25, and 50 °C. Temperature-dependent CD spectra (Figure 1S) demonstrate surprisingly high stability of the helical configuration of the TGBP core in all hyperbranched polymers at increased temperature. The CD signal maxima are not shifted, and only a slight increase of the intensities was observed when decreasing the temperature. Moreover, when the solution is cooled to room temperature from 50 °C, the CD spectrum exhibits a similar intensity to that initially obtained at 25 °C.

The sign of $[\alpha]_D$ of the chiral polymers is opposed to that of the glycidol monomers used in the polymerization process, showing a "Pfeiffer effect" (Table 1).[18] This evidences the induction of a preferred sense of twist in the benzophenone core, whose optical rotation sign appears to be opposed to that of the polyglycerol corona. In addition, the values indicate that the optical rotation caused by the core for TGBP-(*R*)-PG_{34}, TGBP-(*S*)-PG_{50}, and TGBP-(*S*)-PG_{62} exceeds that of the polyglycerol shell.

On the basis of these unexpected observations, the following question appeared to be intriguing: will an inherently chiral core with only a small amount of enantiomerically pure glycerol units in an otherwise racemic hyperbranched polyglycerol lead to the same chiroptical properties? To answer this question, a series of polymers, namely TGBP-(*S-rac*)-PG_{54}, TGBP-(*R-rac*)-PG_{76}, and TGBP-(*S-rac*)-PG_{130}, were prepared by addition of racemic glycidol subsequent to the polymerization of a defined, small fraction of Gly* monomer (Gly*/THBP, molar ratio of 14). The respective polymers were prepared with varied molecular weights (M_n ranging from 3000 to 9100 g/mol) and low polydispersities (< 1.8). Most remarkably, all copolymers of this type showed strong CD signals. The CD spectra (Figure 1B) reveal that the polymer with the highest molecular weight, which should also contain the highest fraction of racemic glycerol (i.e., TGBP-(*S-rac*)-Gly_{130}), exhibits the highest CD signal intensity. This indicates an increase in diastereoselectivity in the interaction of plane polarized (racemic) light and the nonracemic hyperbranched polymer, which is even higher than that found in materials containing exclusively enantiomerically pure glycerol units.

Overall, the intensities of the induced CD spectra showed little variation within the series of polymers, although some of the samples contain a rather small enantiomeric excess of chiral glycerol units. In addition, the $[\alpha]_D$ values indicate that the resulting optical rotation of the core for TGBP-(*S-rac*)-PG_{54} and TGBP-(*S-rac*)-PG_{130} exceeds and for TGBP-(*R-rac*)-PG_{76} counterbalances that of the corona (Table 1).

These results show some analogy to the optical properties of linear polyisocyanates composed of randomly distributed (*R*) and (*S*) units. These polymers show disproportionally high optical activities compared to the enantiomeric excess of the monomers. This phenomenon arises from a "majority-rule effect" among the units on the helical sense of the backbone.[19] We suggest that the phenomena observed for our system do not fit in this concept, since we first polymerize enantiomerically pure glycidol in the presence of the racemic benzophenone; subsequently, racemic glycidol is added.[20]

We decided to take a closer look at the intriguing question: why do the chiral TGBP-polyglycerols with low proportions of enantiomeric excess of the glycerol units exhibit a disproportionally high optical activity? At first, we suspected that hydrogen-bonding interactions largely present throughout the polymer architecture might play an important role due to the large number of hydroxyl groups in close proximity. This guarantees a highly dynamic nature of the cooperation process between the few nonracemic units surrounding the benzophenone core and the large number of racemic glycerol units. However, this hypothesis was contradicted by the CD spectra recorded at different temperatures (vide supra), where CD intensities were similar at low

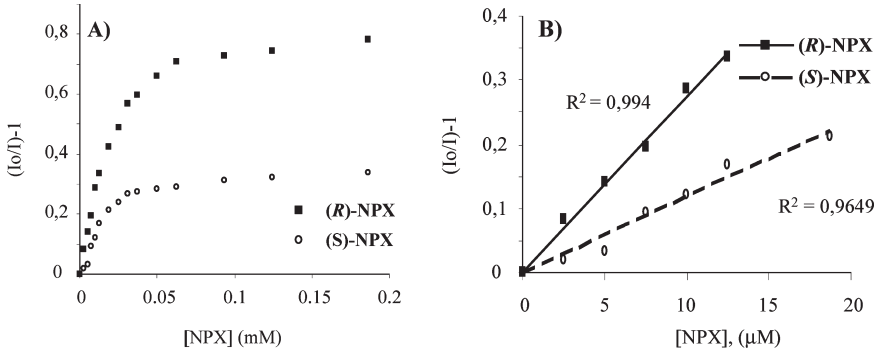


Figure 2. Stern−Volmer graphs of the fluorescence quenching of TGBP-(*R-rac*)-PG_{76} in deoxygenated methanol solutions at room temperature, upon addition of increasing quantities of (*R*)- or (*S*)-NPX guests (λ_{exc} = 355 nm).

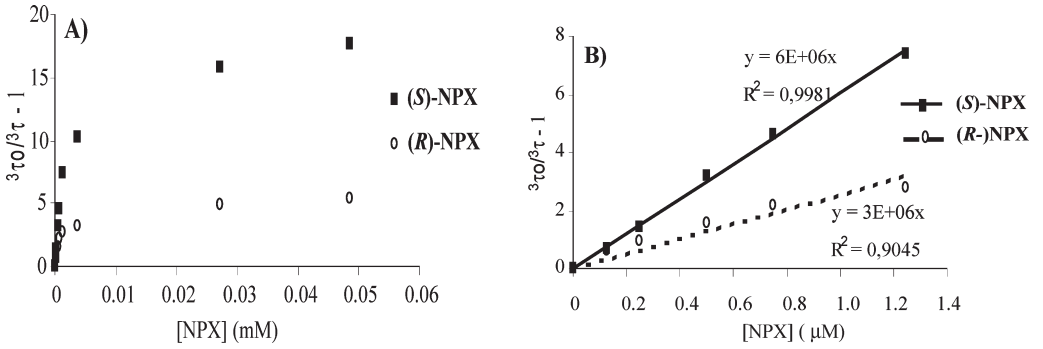


Figure 3. Stern−Volmer graphs of the triplet quenching of TGBP-(*S-rac*)-PG_{130} in deoxygenated methanol solutions at room temperature upon addition of increasing quantities of the naproxen guest (λ_{exc} = 355 nm).

temperature (ca. 10 °C), where hydrogen bonding is more pronounced and at elevated temperature (ca. 50 °C), where this type of interaction is less pronounced.

This observation has been further underlined by full permethylation of all hydroxyl groups of TGBP-(*S-rac*)-PG_{54}. Unexpectedly, the CD effect in the permethylated chiral polymer TGBP-(*S-rac*)-PG_{54} C_{54} was similar to its parent polyol precursor (Figure 2S, Supporting Information). This indicates most probably that the cooperation between the chiral units is driven by the hydrophobic character of the building units. Hydrophobicity provides stability to the chiral polymer structure because it causes a collapse of the nonpolar side chains, permitting to avoid contact with a polar solvent such as MeOH. This leads to intimate cooperation between the chiral units, which restricts rotations of both phenyls of the benzophenone core and induces chiral amplification at the core level.

To study the molecular recognition properties of the chiral, nonracemic photoactive hyperbranched polyglycerols, we used fluorescence and transient absorption spectroscopic methods to investigate chiral recognition. The fluorescence spectra of polymers TGBP-(*R*)-PG_{34}, TGBP-(*S*)-PG_{50}, TGBP-(*R-rac*)-PG_{76}, and TGBP-(*S-rac*)-PG_{130} in methanol have been recorded and were found to be similar to those of their racemic analogues. The respective excitation spectra confirmed that the emission band is related to the n,π* transition (Figure 3S, Supporting Information).[7] Steady-state fluorescence quenching studies were performed in the presence of both enantiomers of naproxen [(*R*)- and (*S*)-NPX], acting as guests, to determine the chiral recognition capacity of the receptor polymers. The data were analyzed using the Stern−Volmer equation.

Time-resolved fluorescence measurements confirmed that the fluorescence lifetime is not influenced by the quencher concentration, which indicates a static process of fluorescence quenching. Therefore, the saturation behavior detected for the fluorescence quenching of the polymer receptor must be caused by NPX molecules closer to the core, leading to an intimate ground-state complex {(TGBP---NPX)} in the nonracemic domain of the polymer corona into the environment of the nonracemic photoactive core (Figure 2A,B).

Further investigation of chiral recognition of NPX using the optically active polymers was performed by laser flash photolysis (LFP) experiments (Nd:YAG, 10 ns laser pulse, λ_{exc} = 355 nm), monitoring the triplet excited state of the benzophenone, which is similar to that of TMBP (π,π* character, two bands located at λ_{max} = 470 and 680 nm);[21] see Figure 4S for TGBP-(*S*)-PG_{50} and Table 4S. The triplet quantum yield of the polymer, measured as transient absorption (ΔA) at 690 nm, immediately after the laser pulse decreased with the concentration of NPX. A plot of $\Delta A/\Delta A_0 - 1$ vs [NPX] showed a nonlinear relationship between both magnitudes (Figure 5S in Supporting Information for TGBP-(*S-rac*)-PG_{130}), which evidences once again the formation of a complex between NPX and the benzophenone core. The chiral recognition capacity of the studied chiral, nonracemic hyperbranched polymers is clearly evident, when following the decrease of triplet formation in the presence of the enantiomerically pure quenchers, mainly when the plot approaches the plateau.

Additional measurements of the effect of [NPX] on triplet lifetime of the polymers ($^3\tau_0$) have also been carried out. A plot of ($^3\tau_0/^3\tau - 1$) vs [NP] leads to a graph which passes through the origin but deviates from linearity at [NP] exceeding 1.5 μM, as shown in Figure 3 for TGBP-(*S-rac*)-PG_{130}. Stern−Volmer constant (K'_{sv}) values were estimated from the slope of the plots at concentrations of NPX lower than 1.5 μM (Table 3S). The fact that at [NPX] exceeding 50 μM the plot approaches a plateau indicates the existence of a pre-equilibrium intermediate regarded as a ^{3}TGBP---NPX complex.

In summary, we have developed an approach to optically active hyperbranched polyether polyols, covalently incorporating a racemic, yet inherently chiral photoactive core. The ring-opening polymerization of the enantiomerically pure glycidol

monomer preserves the stereochemistry and induces a preferred helical sense at the core level. Subsequent addition of racemic glycerol units leads to an unexpected amplification of the chirality of the resulting polymers. This phenomena fits neither in the "sergeants-and-soldiers" principle nor in "majority rules" effects. The use of fluorescence and transient triplet state spectroscopic methods permitted to investigate the chiral recognition properties of the hyperbranched macromolecules, using both enantiomers of naproxen, a non-steroidal anti-inflammatory drug, as a model guest. Such chiral, nonracemic hyperbranched polymer receptors are potentially useful for asymmetric photochemistry. Studies to address these issues are in progress.

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Supporting Information Available: Synthesis procedure, UV−vis, CD, and emission spectra, and tables containing further fluorescence data. This material is available free of charge via the Internet at http://pubs.acs.org.

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