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Amphiphilic Polymers Based on Poly(2-oxazoline)s - From ABC-Triblock Copolymers to Micellar Catalysis

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Summary: In this presentation we give an overview on our results in the field of poly(2-oxazolines). By means of living cationic polymerization in combination with the initiation and termination method, functionalized poly(2-oxazoline)s have been prepared, that were used as (i) macromonomers to form graft copolymers, (ii) lipopolymers to prepare stealth liposomes, (iii) ABC like polymers to form two compartment micellar networks and (iv) macroligand for micellar catalysis application. Within this report, we will discuss in detail the synthesis and characterization of various poly(2-oxazoline)s for the above mentioned research areas.

Keywords: amphiphiles; block copolymers; cationic polymerization; micellar catalysis; poly(oxazoline)s

Introduction

2-Substituted-2-oxazolines represent a very versatile monomer system, that can be polymerized or copolymerized via a living, ring-opening cationic polymerization mechanism.[1] During the past two decades there has been a tremendous increase in the application of these monomers in the field of block and graft copolymer synthesis and hyperbranched and star-like polymers with a broad field of different applications.[2] In this report we aim to give an overview on our activities in the area of poly(2-oxazoline)s, (1) studying the mechanism of termination and its usage for macromonomer synthesis, (2) investigating the preparation of lipopolymers and their interaction with bilayer model membranes, (3) the synthesis of amphiphilic telechelic poly(2-methyl-2-oxazoline)s with fluorocarbon and hydrocarbon endgroups and their aggregation behavior in aqueous solution and (4) studying the potential use of functionalized diblock copolymers as macroligands in the field of micellar catalysis.

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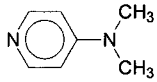
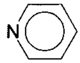
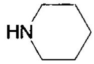
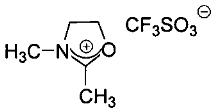
Termination Studies and Macromonomer Synthesis

In our initial studies, we were interested in the preparation of new polymers with different architecture and composition. A suitable approach is the so called macromonomer route, where a polymer precursor is functionalized with a monomer moiety, that can be polymerized in a second step. The living polymerization mechanism of 2-oxazolines made them a very interesting system to incorporate the monomer via a functionalized termination reagent. Thus, different nucleophiles were studied in the termination reaction of 2-alkyl-2-oxazoline polymerization with respect to efficiency. Based on our results (see Table 1) secondary amines were most efficient termination agents.[3]

Table 1. Termination of a living polymerization of 2-alkyl-2-oxazoline, studied via ^1H NMR[a)]

Nu	conversion in % after 10 min	time needed for 100 % conversion
	67	60 min
	5	22 h
	100	< 10 min
H_2O	0	> 8 d

[a)] model studies with **1**:



1

Based on these results, a mono-functionalized piperazine derivative **3** as termination reagent was prepared bearing a styrene unit for subsequent polymerization reactions. Macromonomer synthesis via termination is described in the following scheme:[4]

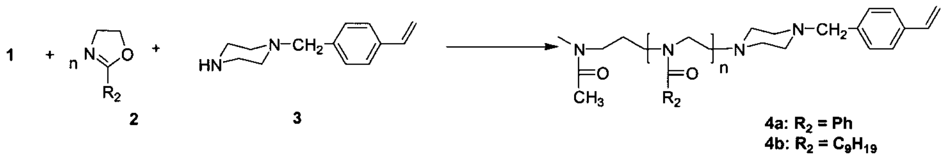
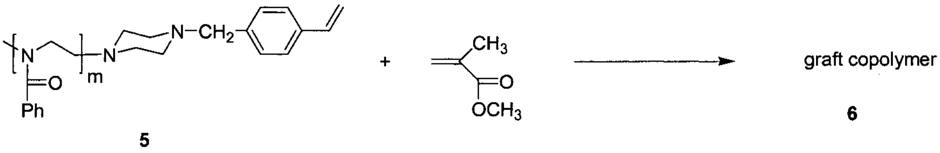


Table 2. Results of the macromonomer synthesis via termination route

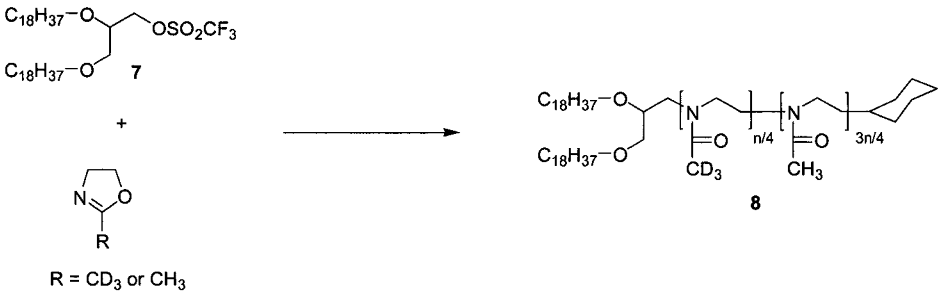
R_2	solvent	T / °C	t / h	n_{th}	n_{NMR}	M_n	M_w/M_n
Ph	acetonitrile	70	72	10.5	10.1	1390	1.13
Ph	acetonitrile	70	72	9.7	9.3	1260	1.15
C_9H_{19}	1,2-dichlorobenzene / nitrobenzene (1 : 1)	70	48	10.0	10.4	2550	1.05

The good agreement between nth and nNMR (table 2) and the low PDI's < 1.15 show clearly, that this synthetic route is applicable for the preparation of macromonomers with controlled molar masses and perfect functionality. These macromonomers were afterwards successfully applied for the synthesis of graft copolymers with methyl methacrylate as monomer.



Lipopolymers with Segmented Deuterated Blocks

A second area of interest was concerned with the preparation of lipopolymers.[5] Such polymeric structures are interesting candidates to prepare so called *stealth liposome*, that can be potentially used as controlled release systems for therapeutics. A question still under debate within this research is concerned with the limited understanding how polymer structure and chain conformation affect the long term stability of such liposomes *in vivo* and its accumulation in specific organs whereas other tissues are not affected at all. A possibility to get better insights in chain conformations is neutron scattering of partly deuterated lipopolymers. For that purpose block copolymers with different positions of the deuterated block became available via sequential polymerization of 2-methyl-2-oxazoline (H) with 2-trideuteromethyl-2-oxazoline (D) using 2,3-distearylglyceryltriflate **7** (L) as a initiator.[5,6] Piperidine was used for termination. By using this approach polymers with the following composition L-DHHH, L-HDHH, L-HHDH and L-HHHD were prepared.



The increase of molecular weight was followed via GPC for L-HDHH and is shown in figure 1.

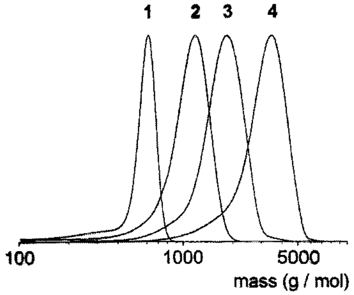


Figure 1. GPC of L (1), L-H (2), L-HD (3) and L-HDHH (4) with L = distearylglyceryltriflate, H = poly(2-methyl-oxazoline) block and D = poly(2-trideuteromethyl-2-oxazoline) block (see **8**).

These polymers were applied for neutron scattering of bilayers composed of lipopolymer **8** (25 mol%) and distearoylphosphatidylcholine (DSPC, 75 mol%). These measurements indicated clearly that brush conformation is favored over pancake and mushroom (Fig. 2), since the periodical length, which depends on the distance between D and the phosphorous atom of the DSCP, becomes significantly smaller with decreasing distance between D and P, which would make no difference in case of pancake and mushroom conformation.

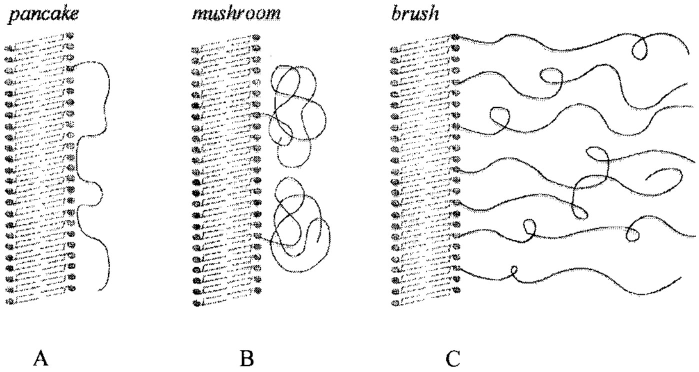


Figure 2. Idealized polymer conformation at the interface of a lipid bilayer and water: (A) pancake, (B) mushroom and (C) brush conformation.

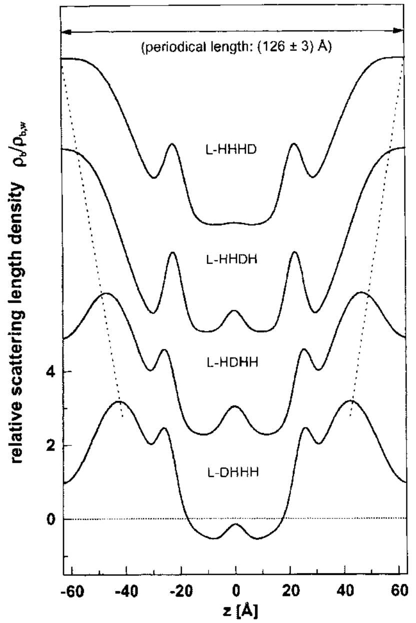
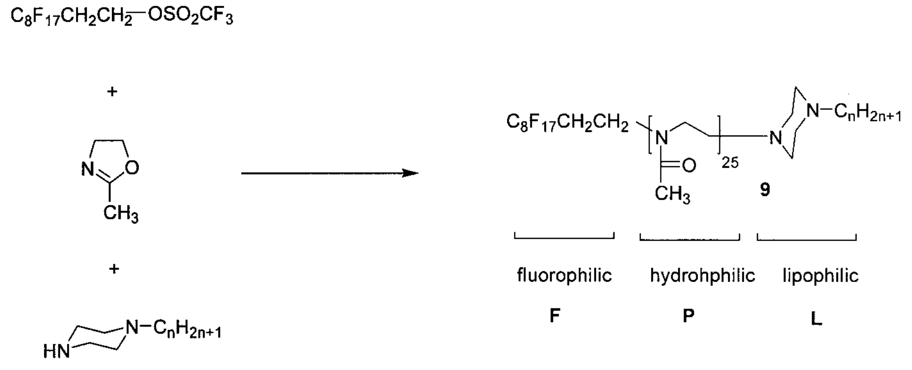


Figure 3. Scattering length density profiles of bilayer from a pospholipid (75 %) and **8** (25 %).

ABC-type Block Copolymers and Micellar Networks

Another area of interest was concerned with the preparation of multifunctional micelles, that would allow to provide compartments, different in their size, shape and physical or chemical properties.[7] Such structures could be potentially useful as drug carrier systems for two or even more therapeutics, that can be selectively solubilized in specific micellar compartments, or might serve as a scaffold for cascade reactions in catalysis, that would resemble the activity of multienzyme complexes in nature. The major goal of this research was therefore to create two micelles in a distinct environment, that show significant differences in their physical properties. Our approach was based on the self-organization behavior of telechelic polymers, that were composed of a fluorocarbon endgroup ($C_8F_{17}CH_2CH_2$) covalently bound to poly(2-methyl-2-oxazoline) and a hydrocarbon (C) segment of various length (C_6 to C_{18}) as the second endgroup. The fluorinated segment was introduced into the polymer via the initiation method whereas monoalkylated piperazine derivatives were used as termination reagents.[7,8]



Polymers with m = 25, 50 and n = 6, 8, 10, 12, 14, 16, 18 were synthesized and characterized. In addition model polymers of the LP-type and FP-type, composed of either a hydrocarbon end group (LP, $C_{16}H_{33}$- PMeOx$_n$, n = 10, 25, 30, 50, MeOx = 2-methyl-2-oxazoline) or a fluorocarbon one (FP, $C_8F_{17}CH_2CH_2$-PMeOx$_n$, n = 10, 20, 35, 50), respectively, were prepared. Both, LP- and FP-type polymers aggregate above a certain concentration and form micelles. The cmc values increase for the LP and FP polymers with increasing length of the hydrophilic block length. Dynamic and static light scattering measurements of $C_8F_{17}CH_2CH_2$-PMeOx$_{35}$ gave aggregation numbers of 22 ± 2 and a hydrodynamic radius of 5.6 nm above the cmc up to 10 g/L. Only at rather high concentrations (c > 50 g $\cdot$ L^{-1}) a strong scattering angle dependency was observed, indicating that the aggregates change their shape most likely by the formation of extended, rod-like micellar structures (Fig. 4).

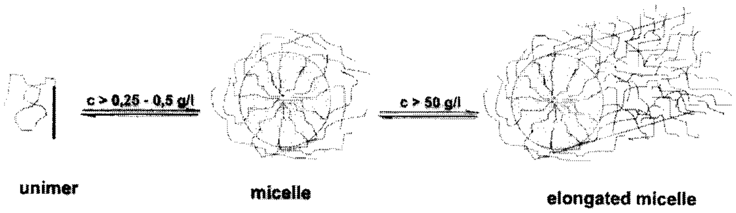


Figure 4. From unimers via micelles to higher aggregates for LP- and FP-type polymers.

Afterwards polymer FPL_{16} was investigated by dynamic light scattering measurements at 0.25 g/L, 5.0 g/L and 20.0 g/L in aqueous solution. The results showed clearly that within this concentration range aggregates were formed with a hydrodynamic radius of 5.7 nm, that slightly increased to 6.7 nm at 20 g/L. This result suggested that at very low concentrations above the first critical aggregation concentration, micelles are formed in solution, which will most likely form network structures at very high amphiphile concentrations. In the following studies ^{19}F NMR measurements and the pyrene Ham effect were used to quantify the aggregation of fluorocarbon endgroups within the micellar networks, and to figure out, if fluorocarbon and hydrocarbon endgroups in such micellar networks form mixed micelle or pure fluorocarbon and hydrocarbon-like aggregates. In the first set of experiments we studied the Ham effect of our model compounds LP and FP in order to see the effect of pyrene fluorescence in the presence of micelles with either pure fluorocarbon and hydocarbon-like micellar core. The values I_1/I_3 were 1.28 in the presence of a hydrocarbon-like micelle, which is in good accordance with literature values, whereas in the presence of micelles with a fluorocarbon-like core, the change was much less pronounced compared to pure water with I_1/I_3 found to be 1.56 (pyrene in water $I_1/I_3 \approx 1.80$). Moreover, by using an excess of pyrene, we found pyrene excimer formation in the presence of micelles with a hydrocarbon interior but no pyrene excimer formation in the presence of micelles with a fluorocarbon-like core, suggesting significant differences in the solubilization behavior of pyrene in the presence of these two types hydrophobic core environment. In the next set of experiments, we studied the ABC type polymers with fluorocarbon and hydrocarbon chain ends by fluorescence spectroscopy. As can be seen from Fig. 5, formation of the first aggregate is predominantly determined by the length of the most hydrophobic endgroup. In the case of short alkyl chain with hexyl, octyl, and decyl chain length, the fluorocarbon endgroup $C_8F_{17}CH_2CH_2$ is more hydrophobic and aggregates first. I_1/I_3 values but also excimer formation (I_1/I_E) resembles the results found with micelles composed of a pure fluorocarbon core (FP). In the case of longer alkyl endgroups (C_{14}, C_{16} and C_{18}), the hydrocarbon endgroups start to aggregate before the fluorocarbon do so, and the micellar aggregates show behavior similar to that of micelles based on LP amphiphiles. In addition, it became clear that at higher concentrations of the latter mentioned FPL amphiphiles, pyrene is only able to detect the hydrocarbon like environment and it is not possible to analyze the formation of fluorocarbon-like aggregates at the same time.

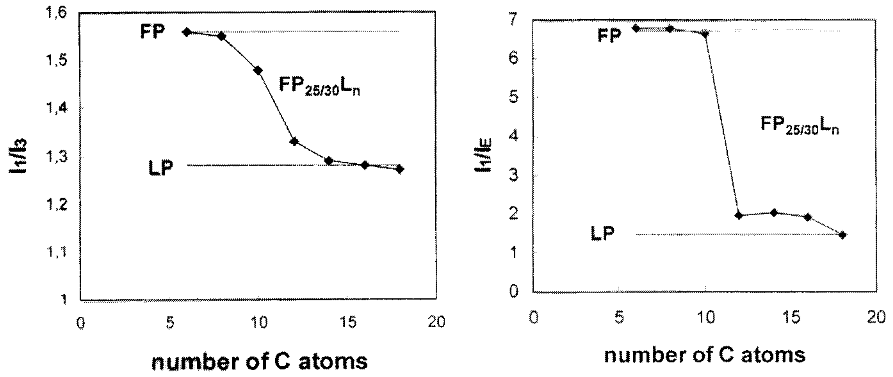


Figure 5. Ham effect of pyrene, lipophilic core (LP): $I_1/I_3 = 1.28$, $I_1/I_E = 1.47$; fluorophilic core (FP): $I_1/I_3 = 1.56$, $I_1/I_E = 6.7$.

In order to overcome this limitation, we applied a second methodology to study the aggregation behavior of the fluorocarbon chain of $FP_{25}L_{16}$ as a function of amphiphile concentration by ^{19}F NMR spectroscopy. Micelles composed of FP were again used as a model compound to study the transverse relaxation of the terminal CF_3-group, that can be described with a biexponential equation.[8]

$$\underbrace{A_{short} \cdot e^{-\frac{\tau}{T_{short}}}}_{A*} + \underbrace{B_{long} \cdot e^{-\frac{\tau}{T_{long}}}}_{B*} = 1$$

The short relaxation time corresponds herein to the fraction of FP dissolved in solution and not aggregates in micelles, whereas the long relaxation time is typical for almost solid-state like behavior of the CF_3-group in the micellar core. Based on these findings it was possible to quantify the amount of aggregated fluorocarbon chains versus free one in aqueous solution as a function of amphiphilie concentration. The results are shown in Table 3 for $FP_{25}L_{16}$.

Table 3. Transverse Relaxation times T_{short} and T_{long} and the fractions A_{short} and B_{long} from ^{19}F NMR for $FP_{25}L_{16}$[a)] in aqueous solution

c_{pol} wt-%	A^*_{short}	B^*_{long}	T_{short} µs	T_{long} µs
0.05	0.12	0.88	292	2120
2.5	0.16	0.84	164	2829
5.0	0.20	0.80	217	1986
10	0.35	0.65	198	2089
20	0.69	0.31	210	2909

a) Polymer 9 with 8 CF_2 groups 25 P units and 16 CH_2 groups.

The results show clearly that the fluorinated endgroups aggregate linearly with increasing amphiphile concentration. The complete aggregation behavior based on our results found by dynamic light scattering, fluorescence measurements and ^{19}F NMR spectroscopy is summarized in the following picture.

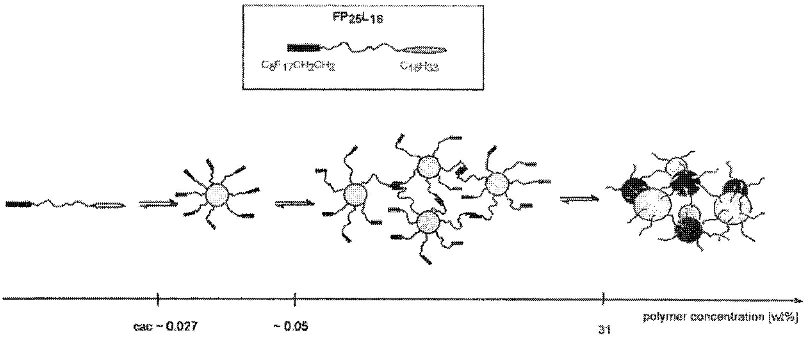


Figure 6. Aggregation diagram of $FP_{25}L_{16}$ versus concentration in aqueous solution.[8]

Amphiphilic AB-block Copolymers for Micellar Catalysis

Homogeneous and heterogeneous catalysis compete in industrial scale. Although homogeneous catalysis has many advantages over its heterogeneous counterpart, such as high reactivity, mild reaction conditions, high selectivity and no diffusion problem, the disadvantages include recycling of the catalyst and product separation. A possibility to combine the benefits of both homogeneous and heterogeneous are liquid-liquid two-phase systems, but also microheterogenization via colloidal assemblies.[9-15]

Limitations for the two-phase catalysis are the large amount of organic solvent which is needed and poor solubility of many starting compounds in water. The idea of micellar catalysis is that the hydrophobic core of a micelle functions as organic phase. Starting compounds are highly soluble in the unpolar phase and the catalyst is immobilized (covalently connected) in this phase, too (Fig. 7).[12]

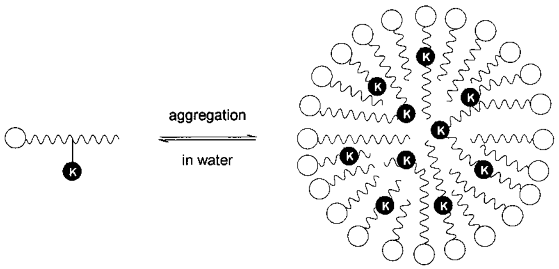
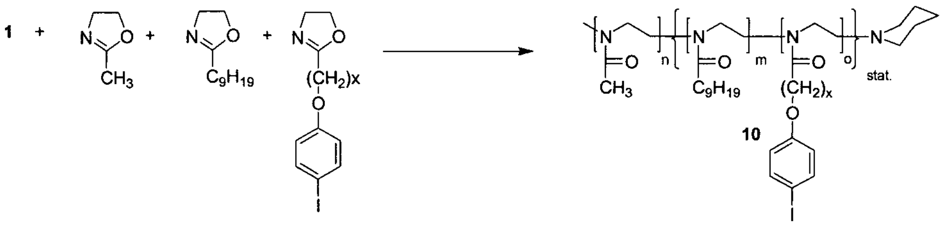
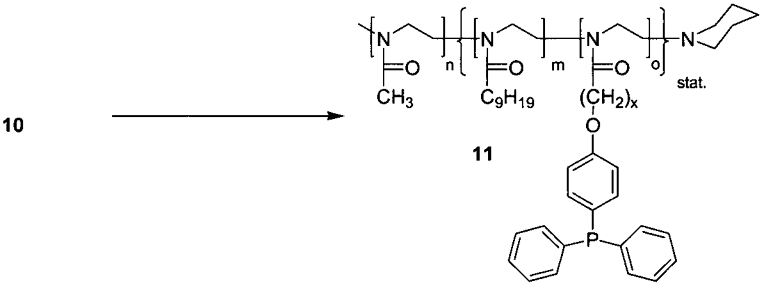
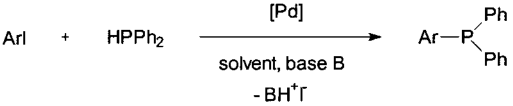


Figure 7. Tentative picture of the aggregation of functionalized ampihpihlies in aqueous solution.

Ideal for such an application are amphiphilic block copolymers from 2-methyl-2-oxazoline (water soluble) and 2-nonyl-2-oxazoline (water insoluble). The hydrophobic part should contain few units with ligands which allow immobilization of interesting transition metals. These ligands can either be introduced via initiation, termination, copolymerization or polymer modification. In principle, all these strategies are possible. For the introduction of triphenylphosphane ligands the polymer modification is favorable. In our case, blockcopolymer **10** was synthesized by sequential addition of suitable monomers. The aryliodide function of **10** was subsequently converted into the triphenylphosphine unit by a palladium catalyzed P-C coupling reaction almost quantitatively, resulting in **11**.



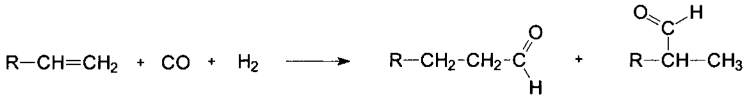




$$ArI + HPPh_2 \xrightarrow[\text{solvent, base B} \; - BH^+I^-]{[Pd]} Ar{-}PPh_2$$

base = NEt_3, KOAc
solvent = DMAc, CH_3CN

As already mentioned for industrial applications of two-phase catalysis it is essential that the solubility of the starting compound is sufficient in water. Therefore, usually higher olefins can not be converted into the corresponding aldehydes by a common two-phase hydroformylation process due to their poor solubility in water. Alternatively, polymer **11** was used for the hydroformylation of 1-octene ($R = C_6H_{13}$).



$$R-CH=CH_2 + CO + H_2 \longrightarrow R-CH_2-CH_2-\overset{O}{\overset{\|}{C}}-H + R-\overset{O=C-H}{\overset{|}{C}H}-CH_3$$

Above the critical micelle concentration, polymer **11** starts to form micelles in water, which have hydrophobic cores with the triphenylphosphane in the core. Consequently, the transition metal ions are immobilized therein. A hydrophilic shell guarantees the water solubility of **11**. One can consider these polymers as nanoreactors with high local concentration of catalyst and starting compound. For comparison experiments were carried out as classical two-phase reactions with Rh-TPPTS (Rh / $P(m\text{-}C_6H_4\text{-}SO_3^-)_3$), with Rh-TPPTS in the presence of sodium dodecylsulfonate (SDS), and finally in the presence of polymer **11**, containing immobilized rhodium. Table 4 summarizes some results.[13,14]

Table 4. Hydroformylation of 1-octene [a)]

ligand	c_{PPh_3}	P : Rh	octene : Rh	t / h	conversion / %	n : iso	TON	TOF / h^{-1}
TPPTS	10^{-3}	25	2000	10	< 5	73 : 27	20	2
TPPTS / SDS	10^{-3}	25	2100	10	< 6	72 : 28	64	2
11[b)]	10^{-3}	18	8500	3	95.5	76 : 24	7400	2480

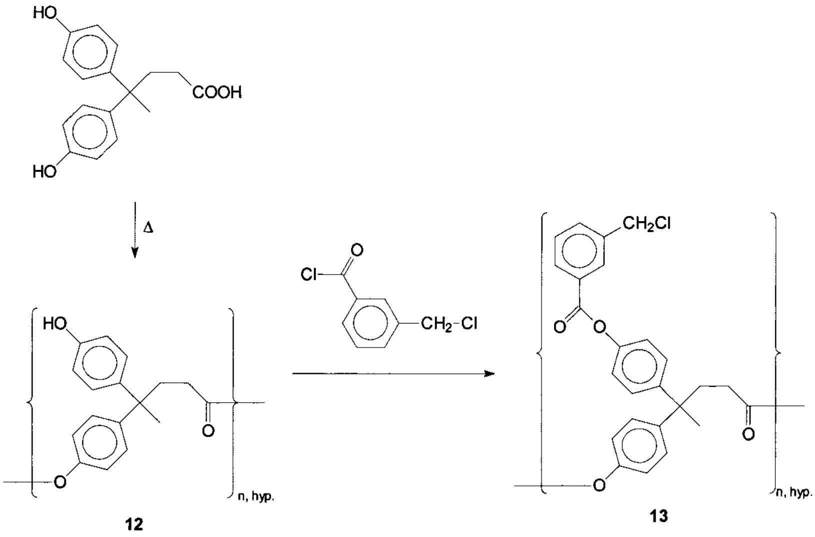
[a)] reaction conditions: V = 50 mL, T = 125 °C, p_0 = 51 bar, $H_2 : CO = 1 : 1$.

[b)] n = 30, p = 4, q = 2.

The polymer **11** containing the valuable transition metal can be recycled and used again.

Star-like Polymers as "Unimolecular Micelles"

Another polymer support material currently under investigation in our group are star-like polymers with a hyperbranched core and amphiphilic, water-soluble graft arms. Such materials can be easily synthesized in a size from 20 to 50 nm, which allow for easy separation via ultrafiltration techniques. In addition, the amphiphilic structure of such polymers is very similar to micellar aggregates with the advantage that one molecule shows already many features of micellar aggregates with respect so their amphiphilicity and are thus called "uni-molecular micelles". The synthetic procedure is shown in the following scheme.[15]



The hyperbranched polymer **12** is soluble in many common solvents – its modification yields **13**, a multifunctional macroinitiator which was applied for the living cationic polymerization of 2-alkyl-2-oxazolines. The following reaction sequence yields the desired unimolecular micelle:[16]

1. copolymerization of 2-(*p*-iodophenoxyalkyl)-2-oxazoline and 2-nonyl-2-oxazoline
2. 2-methyl-2-oxazoline
3. termination with piperidine
4. polymer analogous conversion of the iodophenyl-groups into triphenylphosphane-groups

These star-like polymers are currently under investigation as support materials in the Heck reaction of iodobenzene with styrene and the hydroformylation of 1-octene. From our experiment it is still not clear which of the two methods (classical micelle or unimolecular micelle) gives better results. In long term the unimolecular micelle concept looks promising because of the great variety in the choice of cores.

Summary and Outlook

In summary we have shown the various applications of 2-oxazoline polymerization in the field of macromonomer synthesis, lipopolymers for stealth liposomes, micellar networks and micellar catalysis. Especially the latter field of research provides enormous opportunities to develop new amphiphilic polymer supported catalysts due to the increasing number of transition-metal catalyzed reactions in synthetic organic chemistry as well as polymer synthesis. And within this research we believe, that poly(2-oxazoline)s can take up a key position to evaluate new synthetic approaches in polymer supported catalysis due to their structural versatility and easy accessibility.[17,18]

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