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Supramolecular Polymeric Macrocyclic Receptors – Hybrid Carrier *versus* Channel Transporters in Bulk Liquid Membranes

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Abstract

The synthesis of heteroditopic macrocyclic ureido-receptors is described. NMR studies show the formation of self-organized oligomeric superstructures. Membrane transport experiments show a direct relation between the self-assembling and the transport properties of these molecular information transfer devices. The self-organization of these receptors may provide the first evidence for the possible hybrid transport carrier *versus* channel mechanisms in liquid membranes.

Introduction

Molecular self-organization and the self-assembly to supramolecular structures is the basis for the construction of new functional nano-materials in a bottom-up strategy [1]. The way from molecular to nano(micro)scale devices depends both on the nature of its constituents and on the interactions between them [1, 2]. The chemistry of membrane transport systems of interest for molecular information transfer, has been extensively developed during the last 20 years [1–6]. The membrane selectivity may be induced either by carrier molecules or by transmembrane channels [3]. Different artificial systems, functioning as carriers or as channels-forming superstructures like crown-ethers [2–4], calixarenes [3], cyclic peptides [5] barrel-stave [6] and other host molecules have all been used in this context.

The supramolecular polymers represent an emerging area of supramolecular chemistry [7, 8]. They result from reversible noncovalent interactions of the monomeric components, so that they spontaneously undergo dynamic self-assembly and disassembly processes. These feature confers dynamic character on these materials and in a broader perspective their properties can be of a molecular or supramolecular nature depending on the ability to exchange their constituents. Looking to the important amount of the papers concerning the transport mechanism in membranes the concept of carrier was every time associated with liquid membranes and the term of channel with bilayers membranes (see for example Ref. [3]). From the mechanistic point of view, we use carriers which self-assemble in polymeric crown-ether aggregates which would present combined (hybrid) intermediate features between the former carrier-monomers and the resulted channel-forming poly-associated superstructures [9]. Thus, we therefore decided to synthesise and to study the membrane transport properties of such supramolecular polymeric systems resulted by the dynamic self-assembly of the hydrogen-bonded urea–crown ethers **1**–**3** (Figure 1).

The synthesis of the heteroditopic macrocyclic ureido-receptor **1** and of their NaX complexes was described by us in a recent paper [9]. NMR studies and determination of the crystal structure show the formation of self-organized dimeric or polymeric superstructures by a cooperative macrocyclic cation-complexation, anion–hydrogen bonding and π–π stacking interactions. Membrane transport experiments showed a direct relation between the synergetic ion-pair recognition and the transport properties of **1** as molecular information transfer device.

Experimental

Materials and methods

All reagents were obtained from Aldrich and used without further purification. All organic solutions were routinely dried by using sodium sulfate (Na_2SO_4).

^1H and ^{13}C NMR spectra were recorded on an ARX 250 MHz Bruker spectrometer in $CDCl_3$ with the use of the residual solvent peak as reference. The assignments were made on the base of the COSY and NOESY spectra. Equilibration between hydrogen-bonded and non-hydrogen bonded states for a given N—H proton is

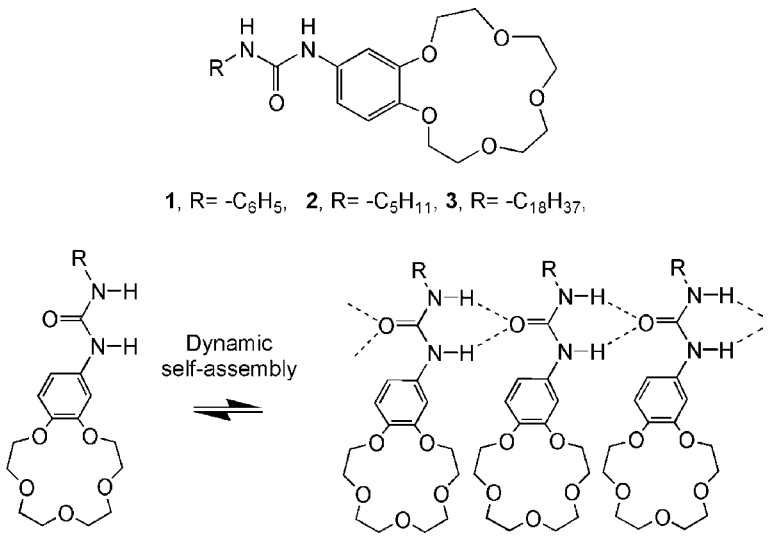

Figure 1. Dynamic self-organization in solution of the heteroditopic receptors **1**–**3**.

almost always fast on the NMR time scale and observed proton chemical shifts are weighted averages of the chemical shifts of contributing states. Variable temperature NMR experiments were performed for the compounds **1**–**3** in the range of 253–298 K. Mass spectrometric studies were performed in the positive ion mode using a quadrupole mass spectrometer (Micromass, Platform II). Samples were dissolved in acetonitrile and were continuously introduced into the mass spectrometer through a Waters 616HPLC pump. The temperature (60 °C), the extraction cone voltage ($V_c = 5$–10 V) was usually set to avoid fragmentations. The self-organization of **1**–**3** has been confirmed by positive ion ESI mass spectroscopy using the Ph_4PCl [10] as soluble charge carrier: a solution of 2.5 M of **1**–**3** in $CHCl_3$ with 5 mM Ph_4PCl was analysed by positive ESI mass spectrometry. The microanalyses were carried out at Service Central de Microanalyses, CNRS Lyon.

Experimental procedure and full characterization for compounds **1**–**3**

1–**3** were prepared by refluxing corresponding isocyanate and 4′-aminobenzo-15-crown-5 (1.5/1 mol/mol) in $CHCl_3$ (5 h). After removal of the solvent, the residue was recrystallized in CH_3CN to afford **1**–**3**.

4-Phenylurea-benzo-15-crown-5, **1** (yield = 93%) the full characterization of this derivative was reported previously [9].

4-Pentylurea-benzo-15-crown-5, **2** (yield = 88%). ^{1}H NMR ($CDCl_3$) $\delta = 0.86$ (t, 6H), 1.26 (m, 8H) 1.49 (t, 4H), 3.19 (t, 4H), 3.72 (m, 8H), 3.89 (m, 4H), 4.09 (m, 4H), 5.62 (s, 1H), 6.56 (d, 1H), 6.68 (d, 1H), 7.00 (s, 1H), 7.40 (s, 1H); ^{13}C NMR ($CDCl_3$) $\delta = 15.77$, 24.59, 28.84, 31.26, 31.29, 31.55, 31.60, 32.08, 42.22, 70.39, 71.08, 71.29, 72.04, 72.49, 110.42, 114.80, 132.77, 146.17, 149.79, 156.44; ES-MS: m/z (%): 397.5 (100) MH^+. $C_{20}H_{32}N_2O_6$ (396.5 g/mol): calcd C, 60.59; H, 8.14; N, 7.07. Found: C, 60.89; H, 8.33, N, 7.10.

4-Octadecylurea-benzo-15-crown-5, **3** (yield = 86%). ^{1}H NMR ($CDCl_3$) $\delta = 0.86$ (t, 6H), 1.26 (m, 28H), 1.49 (t, 4H), 3.19 (t, 4H), 3.75 (m, 8H), 3.89 (m, 4H), 4.09 (m, 4H), 6.16 (s, 1H), 6.67 (d, 1H), 6.78 (d, 1H), 6.93 (s, 1H), 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$) $\delta = 15.45$, 24.79, 28.84, 31.26, 31.29, 31.55, 31.60, 31.67, 31.78, 31.87, 31.99, 32.80, 43.12, 70.90, 71.08, 71.29, 72.04, 72.49, 110.42, 114.80, 133.77, 145.34, 149.89, 158.34; ES-MS: m/z (%): 579.9 (100) MH^+. $C_{33}H_{58}N_2O_6$ (578.8 g/mol): calcd. C, 68.48, H, 10.10; N, 4.84. Found: C, 68.39; H, 10.33; N, 5.10.

Cooperative association model for calculation of dimerization (K_2) and association (K_a) constants of ***1–3***

The association dynamic equilibria of **1**–**3** = **A** were treated with the previously described cooperative association model [11–13]. Namely, one assumes that all association constants K_a are the same and the first dimerization constant K_2 is different

$$\begin{array}{l}\mathbf{A}+\mathbf{A} \overset{K_2}{\Longleftrightarrow} \mathbf{A}_2 \\ \mathbf{A}+\mathbf{A}_{i-1} \overset{K_i=K_a}{\Longleftrightarrow} \mathbf{A}_i\end{array} \quad \text{with } K_2 \neq K_3 = K_4 = \cdots K_i = K_a.$$

The concentration dependency of the chemical shifts presented in Figure 2, can now be described with Equation (1) [12, 13] and gives the association constants K_2 and K_a.

$$\frac{(1-P_f)^{1/2}}{(2P_f-1)c^{1/2}} = K_2^{1/2} + K_a \frac{P_f[(1-P_f)c]^{1/2}}{2P_f-1}$$
$$\text{with } P_f = \frac{\delta_a - \delta_{obs}}{\delta_a - \delta_m}, \qquad (1)$$

where P_f is the population fraction of free N—H protons; c the molar concentration of **1**–**3**; δ_a the

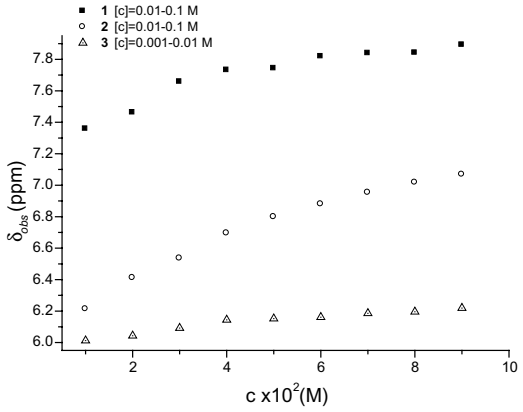

Figure 2. Chemical shifts of the N—H_{ArCE} proton plotted against total concentration of **1**–**3** in $CDCl_3$ at 298 K.

limiting chemical shift for the fully H-bond state, determined by extrapolation from $\delta = f(1/X_1)$ dependency, X_1 = molar ratio of **1**–**3**; δ_m the limiting chemical shift for the non-H-bond state, determined by extrapolation from $\delta = f(X_1)$ dependency, X_1 = molar ratio of **1**–**3**; δ_{obs}: observed chemical shift.

Membrane transport procedure

Membrane transport experiments were performed with magnetic stirring in a conventional U-tube glass cell, at room temperature. The feed phase was a 25 mL of 10^{-3}–10^{-1} M NaCl, the membrane phase consisted of 5×10^{-2} M $CHCl_3$ solution (25 mL) of **1**–**3** in chloroform and the strip phase consisted of 25 mL of distilled water. The concentration of **1**–**3** in the membrane was established in correlation with the NMR results, in the range of fully H-bonded receptors in $CHCl_3$. Aliquots (0.01 mL) of both aqueous solution were withdrawn at appropriate intervals. The sodium and chloride ions concentrations in the feed phase and in the strip phase were determined by atomic absorption spectrometry and anion liquid chromatography, respectively. The diffusion coefficient of NaCl, D_m has been determined using the initial fluxes method by plotting initial flux value J_0 against $C_{0,NaCl,\ feed\ phase}$ [14].

Results and discussion

Synthesis and ^1H NMR studies of association dynamic equilibria in solution of heteroditopic receptors 1–3

Three receptors **1**–**3** were prepared for the studies described here (Figure 1). The corresponding isocyanate was added to a chloroformic solution of commercially available 4′-aminobenzo-15-crown-5 **4** and refluxed 5 h. The self-assembling properties of **1**–**3** in the aprotic solvents were determined, revealing the formation of supramolecular oligomers. They generate organogels in chloroform ($C > 0.2$ M).

All products have been characterized by IR, ^1H and ^{13}C spectroscopies, COSY and NOESY NMR experiments, mass spectroscopy, elemental analysis (see Experimental).

First evidence for H-bond formation upon concentration was obtained from the FTIR spectra: in organogels ($C > 0.2$ M) and in the solid state the H-bond urea vibration shifts were detected at 3289–3322 cm^{-1} instead the vibrations of free N—H at 3410–3546 cm^{-1}, initially observed for the diluted chloroformic solutions.

The oligomer formation was further studied in mixtures of $CDCl_3$ and [D_6]DMSO as a strong H-bond acceptor. While adding [D6]DMSO to a solution of **1**–**3** in $CDCl_3$ did give rise to broad downfield singlets of N—H protons, non-identical to those recorded in pure DMSO (Table 1). Detailed analyses reveals these changes were due to the formation of DMSO–oligomer-adducts rather than dissociation to monomeric form existing in pure DMSO.

^1H NMR dilutions experiments on $CDCl_3$ solutions of **1**–**3** showed a strong downfield shift of both NH protons (Figure 2) upon increasing the concentration, which is indicative of self-association through intermolecular hydrogen bonding.

The association dynamic equilibria of **1**–**3** could be described with a cooperative association model [11–13] and indicates that higher aggregates were formed. This method assume that all association constants but the first equilibrium dimerization constant K_2 are the same K_a and gives the constants shown in Table 2.

The previous studies showed that monosubstituted amides [11, 12] and ureas [13] are highly self-associated

Table 1. Chemical shifts of both N—H protons of **1**–**3** in $CDCl_3$, [D_6DMSO] and in deuterated solvents mixture at 298 K

Compound	$CDCl_3$		85% [D_6DMSO] in $CDCl_3$		[D_6]DMSO	
	δ_{NHR}[a]	δ_{NHArCE}[b]	δ_{NHR}[a]	δ_{NHArCE}[b]	δ_{NHR}[a]	δ_{NHArCE}[b]
1	6.89	7.34	7.65	7.71	8.57	8.48
2	4.77	6.29	5.21	7.40	6.01	8.20
3	4.67	6.15	5.28	7.48	[c]	[c]

[a] NH protons adjacent to crown-ether moiety.
[b] NH protons adjacent to R moiety.
[c] **3** is not soluble in DMSO.

Table 2. Calculated dimerization K_2 and association K_a constants and downfields shifts of NH protons from ^{1}H NMR experiments ($CDCl_3$, $T = 298$ K)

Compound	K_2 (M^{-1})	K_a (M^{-1})	$\Delta\delta_{obs}$ (ppm)[a]	C_{max} (M)[b]
1	96 ± 2	36 ± 5	2.07	0.1
2	157 ± 8	71 ± 6	0.23	0.1
3	19 ± 1	5.5 ± 1	0.67	0.01

[a] $\Delta\delta_{obs} = \delta_{obs}(C_{max}) - \delta_{obs}(4\,mM)$ for the NH protons adjacent to crown-ether moiety,
[b] C_{max} = maximal solubility in $CDCl_3$.

in inert solvents ($K_2 < K_a$). In our case the dimerization constant K_2 is larger that the association constant K_a and it seems that the self-association of **1**–**3** is not a cooperative process.

It was found by variable temperature ^{1}H NMR experiments, that the association process of **1** is driven by enthalpy ($\Delta H_2 = -14.3$ KJ/mol, $\Delta H_a = -27.4$ KJ/mol). The formation of larger aggregates is probably hindered by the bulky macrocyclic moiety. However, the hydrogen bond and π–π stacking enthalpy [9] is enough sufficient to overcome an important amount of an increasing entropic barrier ($\Delta S_2 = -9.1$ J/mol/K, $\Delta S_a = -27.4$ J/mol/K). This enthalpically driven phenomenon is related to similar amides [11, 12] and ureas [13] self-organization processes previously reported. This correspond to the loss of conformational freedom of the macrocyclic moieties motions of which must be restricted when internal hydrogen bonds form. The self-organization of **1**–**3** has been confirmed by positive ion ESI mass spectroscopy using the Ph_4PCl [14] as soluble charge carrier (CC): the resulted spectra shown peaks of the poly-associated oligomers: $[\mathbf{1}\text{–}\mathbf{3}_n(CC)_nCl_{n-1}^+]$, $n = 1$–6 in $CHCl_3$ solutions.

Based of all these spectroscopic results the systems described here represent a prototype for a new hybrid dynamic device displaying self-organized superstructures held together by hydrogen bonds and by van der Waals interactions.

Membrane transport experiments

U-tube transport experiments showed a direct relation between the self-assembly properties of the macrocyclic receptors **1**–**3**, the extractability and the transport rate of NaCl by chloroformic liquid membranes (Figure 3a, b).

At high initial concentration of NaCl the transport by the ditopic receptors **1**–**3** levels off to give a maximum transport rate (*saturation behavior*), reaching a maximum flux J_0 (Figure 3a). This indicate that all receptors at source phase interface of the membrane are present as complex [14, 15]. The extractability of NaCl in the membrane which could be correlated with maximal transport rate J_0 increases with the oligomerization degree of the receptors, **2** < **1** < **3** (Figure 3a, b). This is consistent with the development of higher hybrid aggregates in the membrane phase. The transport of NaCl by the non-associative monotopic 4′-aminobenzo-15-crown-5, **4** receptor used as reference, linearly increase with concentration of NaCl in the feed phase and can be described as diffusion-limited transport of the macrocycle–cation complex in the membrane. One

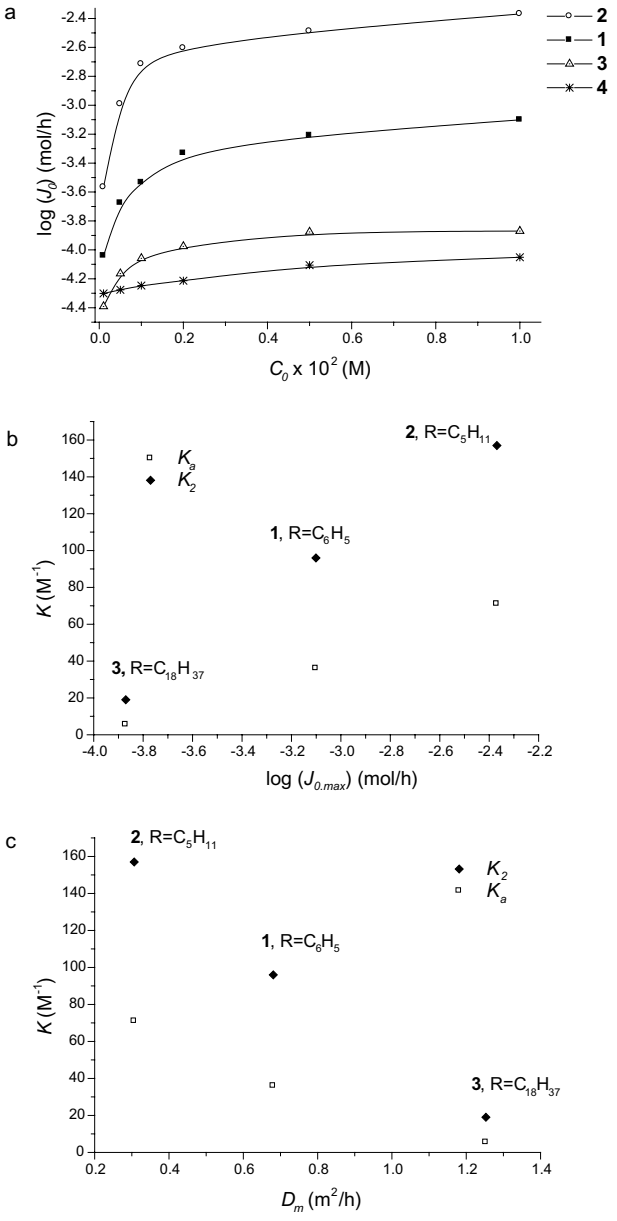

Figure 3. (a) NaCl transport by receptors **1**–**4** as function of initial NaCl concentration C_0 in the feed phase. Dimerization K_2 and association K_a constants plotted against (b) the maximal transport rate J_0 and (c) the diffusion coefficient D_m of NaCl by the liquid membranes using **1**–**3** as transporters.

may point out that the role of the both cation and anion binding in the present superstructures [**1**–**3**—NaCl] is related to that in the previously bifunctional receptors described as heteroditopic carriers [14, 15].

Although the extraction of salt into the membrane phase increases in a direct relation with the self-assembly properties of **1**–**3**, the diffusion of resulted highly associated superstructures decreases (Figure 3c). These experiments showed a relatively fast rate for NaCl transport when a non-associative 4′-aminobenzo-15-crown-5, **4** receptor is used ($D_m = 2.6 \pm 0.1\,m^3/h$ [14]). The diffusion of the salt is reduced by using heteroditopic receptors **1**–**3**. The NaCl diffusion linearly decreases with the association constants value of the self-assembled receptors **2** < **1** < **3**, which is consistent with the development of higher low-diffusive self-assembled supramolecular macrocyclic oligomers [**1**–**3**–NaCl]$_n$ in the membrane (Figure 3b).

From experiments above, it is clear that the simultaneous complexation of both cation and anion by heterotopic receptors **1**–**3** and their self-assembly increases the extractability of salts in organic phase. However, the salt transport rate is less effective; this is caused by the lower rate of diffusion of higher supramolecular hybrid aggregates, which result in a direct relation with the self-assembly properties of the former receptors.

Conclusions

The heteroditopic systems described here represent a prototype for the new dynamic devices displaying self-organized superstructures. These superstructures are held together by hydrogen bonds and offer an intriguing potential for the design of potential hybrid devices of interest for molecular information transfer. The present results show that the self-organization properties in the membrane phase may provide the first evidence for the possible hybrid transport carrier *versus* channel mechanisms in correlation with self-assembly properties of the heteroditopic receptors. It results an increase of the extractability of salts in organic phase due a synergetic extraction of cations and anions, but the salt transport rate is less effective due the lower rate of diffusion of higher supramolecular aggregates. Furthermore these dynamic self-organized systems could be "frozen" in a polymeric hybrid matrix by sol–gel process, opening the door to the design of a novel class of solid nanomembranes.

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