A Bis-Acridinium Macrocycle as Multi-Responsive Receptor and Selective Phase Transfer Agent of Perylene

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Abstract: A bis-acridinium cyclophane incorporating switchable acridinium moieties linked by a 3,5-dipyridylanisole spacer was studied as a multi-responsive host for polycyclic aromatic hydrocarbon guests. Complexation of perylene was proven to be the most effective and was characterized in particular by a charge transfer band as signal output. Effective catch and release of the guest was triggered by both chemical (proton/hydroxide) and redox stimuli. Moreover, the dicationic host was also easily switched between organic and perfluorocarbon phases for application related to the enrichment of perylene from a mixture of polycyclic aromatic hydrocarbons.

Introduction

The past decades have seen the emergence of numerous covalent artificial receptors.[1] Supramolecular chemistry and self-assembly have also allowed the formation of sophisticated receptors incorporating several recognition units.[2] These receptors have gained in complexity with the integration of switching units allowing a control of the guest-binding properties.[3] However, multi-state systems responsive to different types of stimuli are still scarce in the literature and are based on the combination of molecular switches in either the host or the guests. Such systems were recently reported to control the association/dissociation process in host-guest complexes[4] and the motion in mechanically interlocked molecules.[5] In this context, 9-aryl-acridinium moieties are emerging building blocks[6] for the development of multi-responsive receptors of Polycyclic Aromatic Hydrocarbons (PAHs). Indeed, these building blocks are single components responsive to different stimuli (electron, light and nucleophile) thus avoiding the combination of several switches. Upon redox[7] or acid/nucleophile[8] stimulations, the acridinium fragments experience reversible and profound changes of their electronic properties and/or shape, two key parameters strongly affecting recognition processes (Scheme 1). Among the few studies reporting acridinium based switchable supramolecular systems, a family of [2]rotaxanes incorporating two acridinium stoppers was described by Abraham and coworkers.[9] The photochromic properties of the acridinium stoppers were used to trigger the shuttling of a tetracationic macrocycle. In a seminal work, Yoshizawa and coworkers recently reported the synthesis of the tetrakisacridinium receptor interacting with long hydrophilic molecules (e.g. coumarin and steroid derivatives).[10] Upon addition of nucleophiles, the formation of the corresponding tetrakisacridane macrocycle triggers the decomplexation of the guest molecules as the result of the modulation of the cavity size of the receptor.

Scheme 1. Two possible mesomeric forms of the 9-aryl-N-methyl acridinium subunit highlighting the electronic and 2D to 3D structural changes occurring upon addition of redox and pH stimuli.

An additional interest of acridinium moieties resides in their ionic nature allowing their straightforward confinement in aqueous and organic phases according to the associated counterions.[10,11] This is of primary importance for applications in molecular...
separation/purification processes which mostly exploit aqueous/organic solvents biphasic systems.\textsuperscript{[12]} Perfluorocarbons (PFCs) are the least polar liquids making them non-miscible at room temperature and ambient pressure with both water and organic solvents, hydrocarbons included.\textsuperscript{[13]} In reason of their extremely poor solvation ability, PFCs are appealing phases for receptors confinement.\textsuperscript{[14]} They do not compete with the host-guest interactions, thus increasing their strength.\textsuperscript{[15]} But also potentially limit the number and amount of competing guests or hosts in the recognition phase. These unique properties have been exploited to develop potentiometric ion sensing assays exhibiting unequalled sensitivity and selectivity ranges.\textsuperscript{[15a-b, 16]} As well as a few colorimetric/fluorogenic assays.\textsuperscript{[17]} Rather surprisingly, application of PFCs and fluorous supramolecular receptors to selective separation/transportation processes have been much less explored.\textsuperscript{[18]} It might be ascribed to the difficulty of getting receptors with enough fluorophilicity to impart high partitioning in the fluorous phase.

Herein, the four-step synthesis of the bis-acridinium cyclophane (1\textsuperscript{+}) and its recognition properties towards PAHs is reported. The chemical and redox-controlled encapsulation/release properties of the cyclophane towards perylene (Per) is demonstrated. This dicationic host also showed its ability to switch between CHCl\textsubscript{3} and perfluorocarbon phases using fluorophilic supramolecular anions. In addition, the confinement of the receptor in a fluorous phase was exploited to the selective extraction of Per from a mixture of PAHs.

Results and Discussion

Design and Synthesis. The multi-switchable bis-acridinium cyclophane 1-2PF\textsubscript{6} was designed to target PAH guest molecules that are ubiquitous environmental pollutants, most of them being carcinogenic.\textsuperscript{[19]} It is known that acridinium moieties can act as recognition units in \pi-donor/\pi-acceptor interactions with electron rich guests.\textsuperscript{[20]} The targeted receptor 1-2PF\textsubscript{6} was synthesized in four steps from commercially available 3,5-dibromoanisole (Scheme 2). First, 3,5-dibromoanisole (1 eq.) was borylated under Miyaura conditions using bis(pinacolato)diboron (2 eq.), Pd(dppf)Cl\textsubscript{2} (10 mol%) and KOAc (6 eq.) in DMF. After purification, the corresponding bis(pinacolato)anisole 1 was isolated in 78\% yield. Compound 1 was reacted with 2,6-dibromopyridine (4 eq.) under Suzuki conditions using Pd(PPh\textsubscript{3})\textsubscript{2} (20 mol%) and K\textsubscript{2}CO\textsubscript{3} (2 N) in a toluene/ethanol/water mixture. After column chromatography, the semi-rigid spacer 3 was obtained in 60\% yield. The dibromo derivative 3 underwent a bromo-lithium exchange using a solution of nBuLi (2 eq.) in hexanes (2.5 mol L\textsuperscript{-1}) followed by reaction with dec-1-enzyme-9(10H)-acridone (2 eq.).\textsuperscript{[21]} Aromatization of the bis-acridine intermediate by acidification of the reaction mixture using HCl (37 wt.\%) led to the bis-acridinium tweezer 4-2PF\textsubscript{6} from a 9:1 ratio (Fig. 2a). Crystals of the inclusion complex C\textsubscript{6}H\textsubscript{6}⊂ 1-2PF\textsubscript{6} were grown by vapor diffusion of C\textsubscript{6}H\textsubscript{6} into an CH\textsubscript{3}CN solution of 1-2PF\textsubscript{6}, and its structure was solved by X-ray diffraction analysis (Fig. 1b-c).\textsuperscript{[24]} The preorganization of both acridinium moieties was clearly evidenced by the optimum distance for \pi-stacking interactions (\textit{d}_{\text{C9-C9}} = 7.198 Å and \textit{d}_{\text{N-N}} = 7.767 Å). Overall, the cavity size (7.2 × 15.6 Å) is well-adapted to PAHs such as Per.

Recognition Properties. NMR and UV-vis studies were employed to probe the recognition properties of 1-2PF\textsubscript{6} toward PAHs. 

Figure 1. a) Scheme of the receptor 1-2PF\textsubscript{6}. b) Side view and c) Top view of the crystal structure of C\textsubscript{6}H\textsubscript{6}⊂ 1\textsuperscript{+} showing the inclusion of a benzene molecule (thermal ellipsoids at 50\% probability level; PF\textsubscript{6}\textsuperscript{-} anions and a benzene have been omitted for clarity).

Scheme 2. Synthesis of the cyclophane 1-2PF\textsubscript{6} from 3,5-dibromoanisole as commercially available material.
PAHs, namely Per, anthracene (Ant) and naphthalene (Naph). The $^1$H NMR (CD$_2$CN, 298 K) of the 1:1 mixture ($c = 1.5 \times 10^{-3}$ mol L$^{-1}$) of 1∙2PF$_6$ and Per revealed a chemical shift of all protons in comparison to the individual host and guest (Fig. 2). More especially, upfield shifts of the acridinium protons ($\Delta \delta$(H$_\text{naph}$) = 0.42, $\Delta \delta$(H$_\text{trans}$) = 0.41, and $\Delta \delta$(H$_\text{cis}$) = 0.57 ppm) of 1∙2PF$_6$ for the trans isomer as well as of the Per protons ($\Delta \delta$(H$_\text{trans}$) = 0.58, $\Delta \delta$(H$_\text{naph}$) = −0.52 and $\Delta \delta$(H$_\text{cis}$) = −0.44 ppm) suggested π-π interactions between the guest and the acridinium subunits. The inclusion complex Per $\subset$ 1∙2PF$_6$ was confirmed by the downfield shifts of the inner proton H$_6$ of the 1,3 dipropyliyldiaminyl spacer ($\Delta \delta$(H$_6$) = 0.42 ppm) and the olefin protons ($\Delta \delta$(H$_\text{cis}$) = 0.22 and $\Delta \delta$(H$_\text{trans}$) = 0.08 ppm). In addition, the existence of the inclusion complex was confirmed by control experiments using the 9-pyridyl-N-acridinium moiety as host (see SI, Figure S4.1). Indeed, the $^1$H NMR spectrum (CD$_2$CN, 298 K) of the 1:1 mixture of 9-pyridyl-N-acridinium and Per showed no chemical shifts of any proton signals suggesting a macrocyclic effect and the cooperative assistance between both acridinium moieties in 1∙2PF$_6$.

**Figure 2.** $^1$H NMR (500 MHz, CD$_2$CN, 298 K, $c = 1.5 \times 10^{-3}$ mol L$^{-1}$) spectra of (a) 1∙2PF$_6$, (b) the 1:1 mixture of Per and 1∙2PF$_6$; and (c) Per. The photographs of the solution of 1∙2PF$_6$ and the 1:1 mixture of Per and 1∙2PF$_6$ are shown.

Of particular interest, complex formation gave rise to a new electronic transition in the visible region ($\lambda_{\text{max}} = 606$ nm, $\epsilon_{\text{max}} \approx 670$ L mol$^{-1}$ cm$^{-1}$)[28] attributed to a charge transfer band from Per to the acridinium units of the receptor, responsible for the color change from yellow to green (Fig. 2-3). This optical output was only observed for the complexation of Per and account of its higher π-donor character in comparison to Ant and Naph. The poor solubility of Per did not allow NMR or UV-Vis titration experiments in CH$_2$CN. In order to get higher solubility of both 1$^{2+}$ and Per in a common solvent, namely CH$_2$Cl$_2$, 1∙2PF$_6$ was converted to the corresponding tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BARF) salt, 1∙2BARF (see SI). Monitored by UV-Vis spectroscopy, titration experiments in CH$_2$Cl$_2$ allowed the estimation of an association constant of 1200 ± 38 L mol$^{-1}$ between Per and 1∙2BARF (fitted to a 1:1 binding model, see SI, Fig. S4.3.[29] Remarkably, this binding constant is 18 and 400 times higher than the binding constant determined between 1∙2BARF and Ant ($K_a = 66 \pm 3$ L mol$^{-1}$, see SI Fig. S4.5-6) and Naph ($K_a = 3 \pm 0.08$ L mol$^{-1}$, see SI Fig. S4.7-4.8) respectively.[27]

Classical molecular dynamics simulation shed light on the dynamic behavior of the Per $\subset$ 1$^{2+}$ complex in CH$_2$Cl$_2$. In the course of the calculated trajectory (10 ns), Per exchanges eleven times between the center of the cavity of host 1$^{2+}$ and bulk CH$_2$Cl$_2$ (see SI, Fig. S8.1-2) with an average residence time of about 650 ns (from 23 ns to 2151 ns). The calculated free energy difference of −26.8 kJ mol$^{-1}$ between the associated and dissociated complex is in good agreement with the experimental value of −17.6 kJ mol$^{-1}$.

**Multi-Switching Properties.** To demonstrate the chemical switching from the bis-acridinium macrocycle, the macrocyclic bis-acridinium 5 was prepared in quantitative yield by addition of a solution of KOH (1 mol L$^{-1}$) to a solution of 1∙2PF$_6$ in CH$_2$CN (see structure in Fig. 3).[30] Compound 5 exhibited no binding ability for Per in CD$_2$Cl$_2$ as demonstrated by $^1$H NMR spectroscopy (see SI, Fig. S5.3-S5.4). This behavior can be rationalized by the drastic geometrical change of the acridine units and by the loss of aromaticity of the recognition units in 5 in comparison to its bis-acridinium precursor 1∙2PF$_6$ (see SI).[31] The reversible conversion between 5 and the receptor 1∙2PF$_6$ upon addition of protons (trifluoroacetic acid, TFA) or hydroxides (KOH) was evidenced by $^1$H NMR and UV-vis studies (see SI, Fig. S5.1-2 and S5.6-7).

The chemical switching of macrocycle 5 to 1∙2PF$_6$ to efficiently release/catch Per was then proved by UV-vis spectroscopy following the variation in intensity of the Per to acridinium charge-transfer band (Fig. 3). Quantitative restoration of the Per $\subset$ 1$^{2+}$ complex was achieved upon addition of 4.8 eq. of TFA. In other words, the dihydroxylated macrocycle 5 behaves as a proton-activated latent receptor for Per. In addition, Per was reversibly released upon addition of 9 eq. of tetrabutylammonium hydroxide (TBAOH, Fig. 3 inset).

**Figure 3.** UV-Vis spectra (CH$_2$Cl$_2$, $l = 0.1$ cm, 298 K) of a mixture of 5 ($c = 1.5 \times 10^{-3}$ mol L$^{-1}$) with 5 eq. of Per upon addition of TFA (0.8, 1.6, 2.4, 3.2, 4.0 and 4.8 eq.); Insert: UV-Vis spectra (CH$_2$Cl$_2$, $l = 0.1$ cm, 298 K) of a mixture of 1∙2CF$_3$-COO$^-$ ($c = 1.5 \times 10^{-3}$ mol L$^{-1}$) with 5 eq. of Per upon addition of TBAOH (1.5, 3, 4.5, 6, 7.5 and 9 eq.).
The redox-switchable properties of 1-2PF₆ were investigated by cyclic voltammetry experiments in C₆H₄Cl₂ (Fig. 4). At 100 mV s⁻¹, 1-2PF₆ exhibited a reduction wave at a potential \( E_{1/2} \) of –0.946 V vs Fc+/Fc and a re-oxidation wave at –0.828 V vs Fc+/Fc (Fig. S1). This observation is in agreement with two quasi reversible one-electron injection processes \( (\Delta E_p = 118 \text{ mV}) \) leading to the formation of the diradical 1⁺ at \( E_{1/2} = –0.887 \text{ V vs Fc+/Fc} \). This observation is supported by the scan rate study performed from 50 to 800 mV s⁻¹ (see SI, Fig. S6.1). Indeed, the plot of the cathodic and anodic intensity as a function of the square root of the scan rate \( (i_c = f(V^{1/2})) \) shows a perfect linear relationship (see SI, Fig. S6.2 and S6.4). Noteworthily, the slight shift of the cathodic potential \( (E_c) \) corroborates a process under diffusion control. In addition, spectro-electrochemical experiments were undertaken to provide evidences of the reduction of both acridinium units at the same potential. Upon reduction, the original spectrum of 1-2PF₆ was converted to the spectrum of 1⁺ (see SI, Fig S6.6) revealing four maxima at 357 (20200), 367 (24100), 492 (8400) and 531 nm (8350). Upon re-oxidation, the spectrum of 1-2PF₆ was substantially restored thus demonstrating the clean chemical reversibility of this electrochemical process (see SI, Fig S6.7).

After addition of an excess of Per (10 eq.) corresponding to 74% complex formation, a cathodic shift of the reduction \( \left( E_{1/2} = –0.977 \text{ V vs Fc+/Fc} \right) \) and re-oxidation processes \( \left( E_{1/2} = –0.875 \text{ V vs Fc+/Fc} \right) \) were observed \( (E_{1/2} = –0.926 \text{ V vs Fc+/Fc}) \). This observation corroborates the formation the host-guest complex since the electron rich guest transfers some of its electronic density to the acridinium moieties making them more difficult to reduce. The half-wave potential difference \( (\Delta E_{1/2}) \) was found to be –39 mV and allowed the estimation of a binding constant \( (K_a) \) of 54 L mol⁻¹ between the reduced receptor 1⁺ and Per. This 20 times lower association constant compared to the constant found between 1-2PF₆ and Per \( (K_a = 1 \times 21 \text{ L mol}^{-1} \text{ in C}_6\text{H}_4\text{Cl}_2 \text{ in the presence of } 0.1 \text{ mol L}^{-1} \text{ of TBAPF}_6; \text{see SI, Fig. S4.9}) \) clearly evidences the destabilization of the host-guest complex upon reduction. This binding constant corresponds to 34% complex formation between the 1⁺ and Per showing that the host-guest association-dissociation can be controlled to a different extent using either a redox or a chemical stimulus.[31]

**Phase transfer in perfluorocarbons.** Interested in applying the receptor in selective transportation processes, perfluorocarbons (PFCs) were envisioned as potential liquid phases for the receptor confinement.[32] In 2011, some of us reported the transfer of a [Ru(bipy)₃]²⁺ dication from CH₃Cl₂ to a perfluorodecalin (PFD) phase by a markedly increase of the fluorine content coming from the associated counter-ions (Scheme 3).[33] These counter-ions are heteromeric supramolecular fluoruous carboxylates-carboxylic acid anions easily formed in PFCs by anionic H-bond interaction thus doubling the number of fluoruous chains.[34] The back transfer from the PFD to CH₃Cl₂ was achieved by adding a tiny amount of a H-bond competitor, namely CH₃OH, to the biphasic system thus disrupting the supramolecular anion.

Based on these results, the easy confinement of 1⁺ in a fluoruous phase was hypothesized using highly fluorphilic supramolecular anion (Fig. 5a-b). Accordingly, a stock solution of 1-2(RfCOO-H-OOCR) (c = 0.55 × 10⁻³ mol L⁻¹) in perfluoromethylcyclohexane (PFMC, 6 mL) was conveniently prepared by stirring a solution of bis-acridane 5 (c = 1.88 × 10⁻³ mol L⁻¹) in CH₃Cl₂ (2 mL) with a solution of commercially available perfluoro-2,5,8,11-tetramethyl-3,6,9,12-tetraoxopentadecanoic acid (RfCOOH, Rf = CF₃CF₂CF₂O(CF₂)CF(CF₂O)₂(CF₂)CF(CF₂)₃) in PFMC (c = 7.5 × 10⁻³ mol L⁻¹, 6 mL). The formation of 2⁺(RfCOO-H-OOCR) and its phase transfer were followed by UV-Vis spectroscopy and a transfer of 90% of 1⁺(RfCOO-H-OOCR) into the fluoruous phase was determined (see SI, Fig. S7.1-2).[35] The receptor 1⁺(RfCOO-H-OOCR) proved to be highly fluorophilic as revealed by a back extraction from the PFMC phase to a fresh CH₃Cl₂ solution of only 0.3 % (see SI, Fig. S7.3). Addition of a small amount of CH₃OH (a volume of ~ 4% of CH₃OH compared to that of PFMC) as a H-bond competitor led to the quantitative back transfer of the receptor from the PFMC to the CH₃Cl₂ phase, thus supporting the...
formation of supramolecular H-bonded anions in the fluorous phase.

The reversible extraction/release of Per between both CHCl₃ and PFMC phases was then probed (Fig. 5c and see SI, Fig. S7.4-9). A solution of Per (c = 4 x 10⁻³ mol L⁻¹, 1 mL) in CHCl₃ was stirred with a solution of 1∙2(RCOO-H-OOCR) in PFMC (c = 0.55 x 10⁻² mol L⁻¹, 6 mL, stir bar in the bottom of the tube) and fresh CHCl₃ (3 mL); c) Photographs and schematic representation of the extraction/release of Per using 1∙2(RCOO-H-OOCR); i) magnetic stirring (30 min, 1000 rpm, stir bar present in the bottom of the tube) of an aliquot of the PFMC stock solution (1 mL) and a solution of Per (c = 4 x 10⁻³ mol L⁻¹) in CHCl₃ (1 mL); ii) an aliquot (0.5 mL) of the PFMC solution containing Per c = 1∙2(RCOO-H-OOCR) was taken and fresh CHCl₃ (2 mL) was added; iii) manual shaking for 60 s and decantation.

Figure 5. a) Conversion of the bis-acridine 5 to the highly fluorophilic bis-acridinium 1∙2(RCOO-H-OOCR); b) Photograph of a biphasic system taken after stirring and decantation of a stock solution of 1∙2(RCOO-H-OOCR) in PFMC (c = 0.55 x 10⁻² mol L⁻¹, 6 mL, stir bar in the bottom of the tube) and fresh CHCl₃ (3 mL); c) Photographs and schematic representation of the extraction/release of Per using 1∙2(RCOO-H-OOCR); i) magnetic stirring (30 min, 1000 rpm, stir bar present in the bottom of the tube) of an aliquot of the PFMC stock solution (1 mL) and a solution of Per (c = 4 x 10⁻³ mol L⁻¹) in CHCl₃ (1 mL); ii) an aliquot (0.5 mL) of the PFMC solution containing Per c = 1∙2(RCOO-H-OOCR) was taken and fresh CHCl₃ (2 mL) was added; iii) manual shaking for 60 s and decantation.

The efficient synthesis of a multi-responsive cyclophane incorporating two acridinium moieties as recognition units was described. Its ability to form host-guest complexes with perylene on account of π-donor/π-acceptor interactions was shown in solution. Upon addition of hydroxide anions, the chemical switching properties of this system lead to the formation of the corresponding bis-acridinium derivative. This derivative is unable to interact with perylene thus demonstrating the ability of the cyclophane to work as an ON/OFF switch. The electrochemical switching properties of the bis-acridinium cyclophane clearly evidenced a decrease of the host-guest interactions upon reduction. Finally, the phase switching behavior of the macrocycle between a perfluorocarbon and an organic layer was explored and successfully applied to the straightforward enrichment of perylene from a mixture of polycyclic aromatic hydrocarbons. The multifunctional properties associated to the cyclophane receptor integrating multi-responsive acridinium units are promising and will be further explored in the context of selective transportation processes and functional materials.

Acknowledgements

Conclusion
Keywords: Multi-Responsive Receptor • Phase Transfer • Acridinium • Perfluorocarbons • Host-Guest Chemistry
The free energy profile as a function of the centers of mass (COM) distance of Per and 10 shows that the complexed state is about 8.4 kJ mol\(^{-1}\) higher in energy than the uncomplexed state (see SI, Fig. S8.1). MD simulation indicates that Per can enter the cavity of 10 but they underestimate the stability of the complexed state.

[32] Receptor 10\(^{2+}\) proved to be insoluble in water as a chloride, sulfate and nitrate salt. Consequently, perfluorocarbons (PFCs) were considered as potential orthogonal phase to both water and organic solvents.

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[35] Protonation of the pyridines of the receptor was not observed even in concentrated HCl and pure H\(_2\)SO\(_4\).
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A bis-acridinium cyclophane binds selectively and reversibly perylene upon chemical or redox stimuli in organic media. In addition, its straightforward phase-transfer into a perfluorocarbon was exploited for the enrichment of perylene from a mixture of PAHs.

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