ChemistrySelect

Effect of pH Variations on the Properties of Cyclodextrin-Calixarene Nanosponges
--Manuscript Draft--

Abstract:	The pH-responsive properties of cyclodextrin-calixarene nanosponge co-polymeric materials has been investigated. In particular, ISE-H+ potentiometric titrations were carried out in order to evaluate the acid-base properties and the actual amount of ionizable sites present in the materials. Moreover, the relevant pH-dependent adsorption abilities were evaluated towards a set of selected model organic pollutant molecules by means of adsorption tests and by studying the corresponding adsorption isotherms. The latter ones could be suitably described by means of the Freundlich model. The whole of the experimental results enabled us to clarify some general

	aspects of the microscopic behavior of the nanosponges considered.
Author Comments:	To the Editor of ChemistrySelect Sir, I'm pleased to submit our manuscript entitled "Effect of pH Variations on the Properties of Cyclodextrin-Calixarene Nanosponges", by A. Di Vincenzo, M. Russo, S. Cataldo, D. Milea, A. Pettignano and P. Lo Meo, for publication on ChemistrySelect. The paper deals with an investigation on the protonprotonation equilibria and the consequent pH-responsive abilities of mixed cyclodextrin-calixarene nanosponge materials. The work, based on an integrated analytical and supramolecular chemistry approach, clarifies various aspects of the microscopic behavior of these materials. This, in our opinion, might be helpful in perspective for designing smart pH-switchable selective adsorption/release devices for both organic and inorganic species. Sincerely yours Prof. Paolo LO MEO
Section/Category:	Organic & Supramolecular Chemistry
Additional Information:	
Question	Response
Submitted solely to this journal?	Yes
Has there been a previous version?	No
Do you or any of your co-authors have a conflict of interest to declare?	No. The authors declare no conflict of interest.
Animal/tissue experiments?	No

Effect of pH Variations on the Properties of Cyclodextrin-Calixarene Nanosponges

Antonella Di Vincenzo,[a] Marco Russo,[b] Salvatore Cataldo,[c] Demetrio Milea,[d] Alberto Pettignano*[c] and Paolo Lo Meo*[a]

Abstract: The pH-responsive properties of cyclodextrin-calixarene nanosponge co-polymeric materials has been investigated. In particular, ISE-H+ potentiometric titrations were carried out in order to evaluate the acid-base properties and the actual amount of ionizable sites present in the materials. Moreover, the relevant pH-dependent adsorption abilities were evaluated towards a set of selected model organic pollutant molecules by means of adsorption tests and by studying the corresponding adsorption isotherms. The latter ones could be suitably described by means of the Freundlich model. The whole of the experimental results enabled us to clarify some general aspects of the microscopic behavior of the nanosponges considered.

Introduction

Smart materials with stimuli-responsive properties constitute an interesting and expanding area of research, in view of both their possible applications and the conceptual issues implied. These systems might be profitably employed in various fields, spanning from drug carrier/delivery devices to sensors, environment remediation, active packaging and so on.[1] In this context, we have been particularly interested in the synthesis of nanosponge materials with tunable properties.

Nanosponges (**NS**s)[2] are hyper-reticulated polymers constituted by supramolecular host units as the monomers, joined by suitable linker units. We have recently succeeded in obtaining pH-responsive NSs based on polyamino-cyclodextrin[3] or polyamino-calixarene[4] architectures, able to vary their adsorption properties towards diverse model organic guests, and to support metal nanoparticle catalysts.[5] Moreover, we also synthesized various pre- and post-modified[6] cyclodextrin-calixarene co-polymers (**CyCaNS**s)[7] bearing 1,2,3-triazole

linker units, which appeared interesting materials under several viewpoints. In fact, their adsorption and controlled release properties can be largely varied depending on the molar ratio between the co-monomers, and on the substituent groups present on each co-monomer scaffold as well. Furthermore, the introduction of ionizable groups by chemical post-modification enabled, once again, to obtain materials with remarkable pH-responsive properties.[6,8] On that occasion, we noticed that fair pH-tunability was possessed even by non-modified CyCaNSs, and this behavior was tentatively attributed to the presence of the triazole linkers, which may act as weak bases. However, this hypothesis implies that the triazole units should largely increase their basic strength (up to several orders of magnitude), due to their insertion in the polymeric network.

We were interested in verifying the latter point, and in general in achieving a deeper understanding of the microscopic features implied in the supramolecular behavior of our materials. Therefore, the present work was aimed at performing a systematic study of both their acid-base properties and the dependence of their adsorption abilities towards a set of suitably selected model organic guests on the pH of the solvent medium. In particular, we considered a panel of fifteen different CyCaNSs (**A1**-**A5**, **B1**-**B5**, **C1**-**C5**, Scheme 1), which have been already synthesized and fully characterized (FT-IR, ^{13}C{^{1}H} CP-MAS NMR, TGA, SEM) in previous works.[6-7] The materials are constituted by different cyclodextrin or calixarene co-monomers (as specified on Scheme 1), reacted in various eq/eq ratios by means of the well-known *CuAAC* azide-alkyne coupling process (materials **A1**-**A3**, **B1**-**B3**, **C1**-**C3**), whereas possible post-modification resulted in the insertion of either amine (materials **A4**, **B4**, **C4**) or carboxylic (materials **A5**, **B5**, **C5**) groups. For the sake of clarity, post-modification exploited the presence of unreacted azide or alkyne functional groups present in the resulting pristine material, whenever it is prepared using an excess of either the cyclodextrin (materials **A1**, **B1**, **C1**) or the calixarene (materials **A3**, **B3**, **C3**) component. The acid-base behavior was investigated by means of ISE-H+ potentiometric titrations, whereas the adsorption abilities were tested towards a set of 4-nitroaniline derivatives and diversely structured dyes (Scheme 2), selected in such a way to present significant variations of molecular properties such as molecular shape volume, hydrophobic character and charge status.

Results and Discussion

Potentiometric titrations. Considering the polymeric nature and the negligible water solubility of the materials, the ordinary approach used in the study of the acid-base properties for low molecular weight compounds is unsuitable. Therefore, ISE-H+ potentiometric titrations were carried out on well dispersed suspensions of the polymers (experimental details are reported in the Supporting Information). The ISE-H+ potentiometric data

[a] Dr. A. Di Vincenzo, prof. P. Lo Meo
Department of Biological, Chemical and Pharmaceutical Sciences and Technologies (STEBICEF)
University of Palermo
V.le delle Scienze pad. 17 - 90128 Palermo (Italy)
E-mail: paolo.lomeo@unipa.it
[b] Dr. M. Russo
Istituto per lo Studio dei Materiali Nanostrutturati (ISMN)
CNR Palermo
Via Ugo La Malfa 153 - 90146 Palermo (Italy)
[c] Dr. S. Cataldo, prof. A. Pettignano
Department of Physics and Chemistry
University of Palermo
V.le delle Scienze pad. 17 - 90128 Palermo (Italy)
E-mail: alberto.pettignano@unipa.it
[d] Prof. D. Milea
Dip. di Sc. Chimiche, Biologiche, Farmaceutiche ed Ambientali, University of Messina
Viale Ferdinando Stagno d'Alcontres, 31, 98166 Messina (Italy)

Supporting information for this article is given via a link at the end of the document
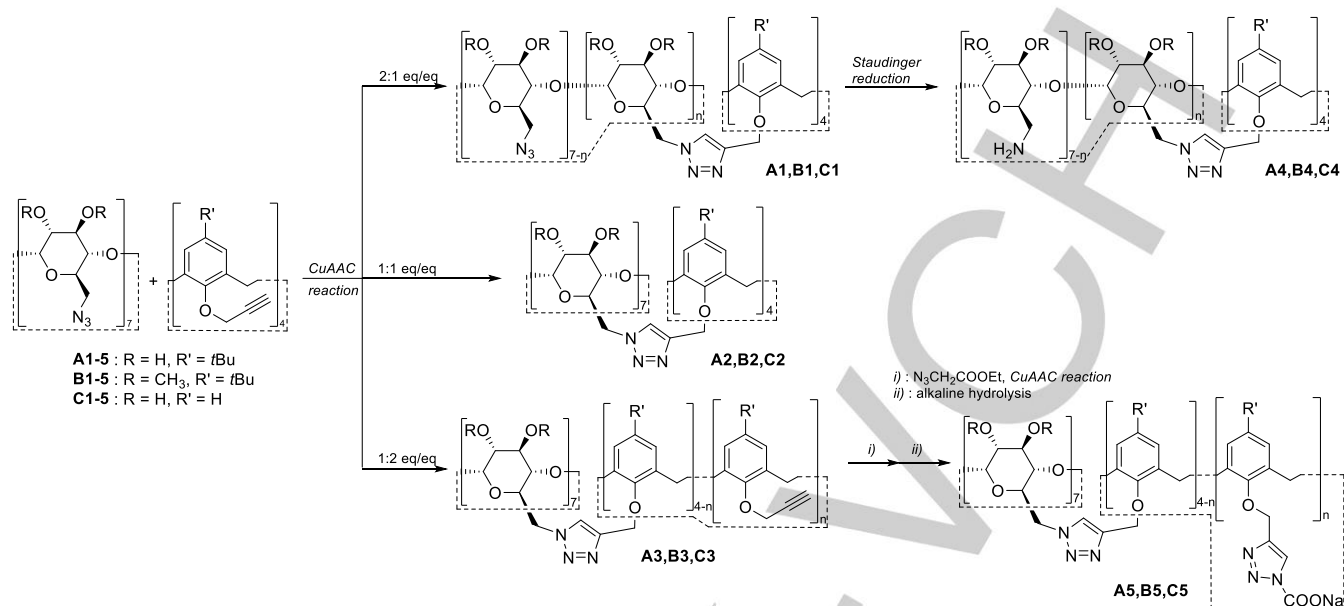
Scheme 1. Synthesis of CyCaNSs.
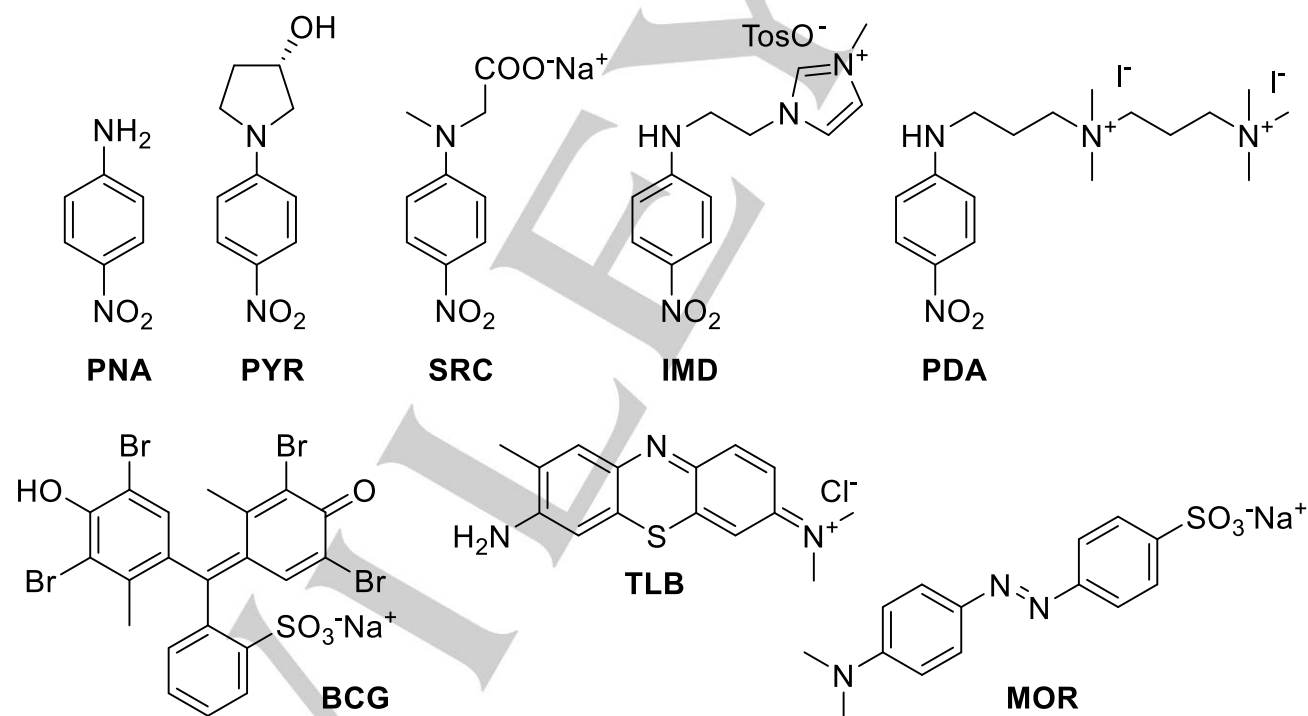
Scheme 2. Structures of the guests.

were analysed assuming the existence of different units, one for each type of functional group in the molecule. Protonation constants of each unit were calculated by using different models (see Supporting Information for mathematical details), namely: *i)* the modified Henderson-Hasselbalch equation;[9] *ii)* the three parameters Högfeldt equation,[10] based on the zeroth approximation;[11] *iii)* the Diprotic-like model,[12] which considers, for each type of functional group, di-functional units with two

protonation constants (K_1 and β_2) independent from the dissociation fraction α. These models take into account the effect of the gradual change of superficial charge of the molecules with protonation or deprotonation of their functional groups; hence, they have been successfully used to process experimental data of polymeric substances.[12-13] In general, the results obtained with the three different models led to similar results as confirmed by the comparable values of the average constant <Log$K$> calculated with the three equations (see Supporting Information); therefore, we will focus herein in detail only on those obtained with the Diprotic-like model, summarized in Table 1 (the complete data collection is reported in the Supporting Information, Table S1).

Data for non-post-modified materials confirm the presence of ionizable groups, which can be identified with the 1,2,3-triazolyl linkers. The relevant Log $\beta_{1/2}$ (average constant according to the diprotic-like model) values, ranging from 6.91 up to 7.43, confirm

the hypothesis that triazolyl units embedded in the polymeric network are much more basic than expected for the free 1,2,3-triazole in solution, for which a pK_b value as large as 12.75 is reported in literature (log$K$ = 1.25).[14] The results obtained for the post modified materials **A4**-**C4** and **A5**-**C5** deserve further considerations. A negligible variation of protonation constants with α was observed for the triazole groups of **A4**-**C4** and the carboxyl groups of **A5**-**C5**. In fact, in both cases one protonation constant only was sufficient to describe the relevant acid-base properties. The amine and carboxyl groups of post modified materials **A4**-**C4** and **A5**-**C5** affect the acid-base properties of triazole groups. In particular, the introduction of carboxyl groups causes an increase of protonation constants of triazole units (Log $\beta_{1/2}$ = 8.25, 8.58 and 8.19 for **A4**, **B4** and **C4**, respectively); on the contrary, the presence of amine groups results in a fair decrease (Log$K$ = 6.63, 6.05 and 6.67 for **A4**, **B4** and **C4**, respectively). Finally, the values of the protonation constants for amine and carboxyl groups are consistent with those for a free amine or carboxylic acid in solution.

It is important to stress here that the amount of ionizable groups per weight unit of material estimated from titration is by far smaller than the one expected on the grounds of the results from solid state NMR determinations reported elsewhere.[6,7] Based on data in Table 1, as long as the non-modified materials are concerned the amount of triazolyl groups estimated by titration is ca. 30 % on average with respect to NMR datum. A similar trend occurs also for post-modified materials; in fact, in comparison with NMR even amine and carboxyl groups of post-modified materials appear underestimated. More in detail, titrimetric data range from 28% (amine groups in **B4**) up to 46% (amine groups in **C4** and carboxyl groups in **A5**). Close inspection of data collected in Table 1 seems to indicate that the discrepancies between titrimetric and NMR data averagely increase on increasing the hydrophobic character of the material. Thus, everything considered, this suggests that the titration method actually underestimates the amount of ionizable groups. We might tentatively justify this peculiar finding by admitting the existence of highly hydrophobic microregions within the material matrix, which are unable to effectively interact with the aqueous medium during the titration experiment, so that ionizable groups possibly present inside these regions are not quantified.

Effect of pH on the adsorption abilities. The pH-dependent adsorption abilities of **CyCaNS**s were then studied. A systematic investigation on the sequestration abilities towards *p*-nitroaniline (**PNA**) and Bromocresol Green (**BCG**) had been performed in a previous work.[6] In the present study we considered six further guests that can be viewed as typical model organic pollutants, and show significant variations in their molecular properties, namely *N*-(*p*-nitrophenyl)-*3S*-hydroxy-pyrrolidine (**PYR**), *N*-(*p*-nitrophenyl)-sarcosine sodium salt (**SRC**), 3-methyl-1-[2-(*p*-nitrophenyl- amino)-ethyl)-imidazolium *p*-toluen-sulfonate (**IMD**), *N1,N1,N1,N3,N3*-pentamethyl-*N3*-{3-[(*p*-nitro-phenyl)-amino]-propyl}-propane-1,3-diaminium iodide (**PDA**) and commercial dyes Toluidine blue (**TLB**) and Methylorange (**MOR**). Noticeably, these guests have different charge statuses under neutral pH; moreover, *p*-nitroaniline derivatives have been used as guests of

Table 1. Portentiometric titration data (Diprotic-like model) for CyCaNSs (in the presence of NaCl at I = 0.1 mol L-1, 25 °C).

	LogK_1 (M⁻¹)[a]	Logβ_2[a]	Log$\beta_{1/2}$[a]	σ[b]	Ionizable groups (μmol/g)[c]	Ionizable groups (μmol/g)[c] from NMR
A1	7.83	14.21	7.11	0.025	0.49	1.66
A2	7.91	14.25	7.13	0.027	0.60	2.02
A3	7.69	14.08	7.04	0.025	0.42	1.46
A4	6.63			0.020	0.40	1.66
	8.86	16.77	8.39[d]		0.68[d]	1.71[d]
A5	8.95	16.49	8.25	0.028	0.69	2.71
	4.47[e]				0.75[e]	1.64[e]
B1	8.07	14.76	7.38	0.019	0.19	1.41
B2	7.73	14.24	7.12	0.031	0.63	1.70
B3	7.40	13.81	6.91	0.028	0.53	1.68
B4	6.05			0.019	0.17	1.45
	8.74	16.52	8.26[d]		0.53[d]	1.89[d]
B5	9.24	17.17	8.58	0.032	0.77	2.57
	4.77[e]				0.57[e]	1.27[e]
C1	8.23	14.85	7.43	0.037	0.58	1.95
C2	8.02	14.13	7.07	0.049	0.65	2.26
C3	8.28	14.77	7.38	0.034	0.51	1.84
C4	6.67			0.027	0.80	1.96
	9.28	17.56	8.78[d]		0.84[d]	1.81[d]
C5	8.92	16.38	8.19	0.035	0.81	3.45
	4.29[e]				0.79[e]	2.13[e]

[a] All data are given within a ± 0.01 indetermination. [b] Std. dev on the fit. [c] relevant to triazole groups, unless differently indicated. [d] -NH₂ groups. [e] -COOH groups.

choice in order to assess the microscopic interactions occurring for host-guest binding phenomena in solution.[15] We studied the affinity of these molecules towards some selected materials only, namely: *i*) **A2**, **B2** and **C2**, i.e. the "pristine" materials bearing the largest amount of triazole linker groups (according to NMR); *ii*) **A4** and **B4**, i.e. the post-modified ones decorated with the largest amount of amine groups; *iii*) **A5**, **B5** and **C5**, i.e. the post modified decorated with carboxylic groups. The materials were tested under different pH conditions (aqueous buffer at pH 1.0, 4.4, 6.7, 10.7); relevant data are collected in Tables 2-4, and compared with those for **PNA** and **BCG** reported elsewhere.[6]

The first set of experiments allowed us to confirm that the presence of the triazole linkers, as the only possible ionizable groups, is sufficient to provide the materials with pH-dependent adsorption abilities, at least in the case of ionic guests. In particular, for anionic **SRC** a significant decrease in the affinity towards the materials is found on increasing the pH (as well as observed for **BCG**). This behavior can be easily explained considering that under acidic conditions very favorable Coulomb

interactions occur between the anionic guest and the average positive charge density on the material framework, due to protonation of the triazole groups. Of course, under neutral or alkaline conditions this interaction is lost, and adsorption is disfavored by the hydrophilic character of the guest. On the contrary, cations **IMD**, **PDA** and **TLB** show a reversed effect of the pH, i.e. a large decrease in adsorption efficiency is found on passing from alkaline to strongly acidic conditions. Differently, only minor differences in adsorption abilities are observed for neutral guests **PNA** and **PYR**. The behavior of **MOR** is interesting, because data for this guest pass through a maximum at intermediate pH values. This may be justified considering that **MOR** passes from a zwitterionic to an ionic form on increasing the pH, and that its large and easily polarizable molecule allows the occurrence of effective van der Waals and π-π interactions, able to counterbalance Coulomb effects. The outcome of the presence of an average positive charge on the nanosponge scaffold is confirmed by the second set of experiments performed with materials decorated with amine groups, i.e. **A4** and **B4**. Once again, the adsorption of anions **SRC** and **BCG** largely decreases under alkaline conditions, whereas the opposite occurs with cation **TLB**. Noticeably, in this case a fair but significant decrease of the affinity for the materials on increasing the pH value can be observed even with neutral guests **PNA** and **PYR**. The third set of experiments enabled us to further explore the effect of the average charge density on the material. In fact, materials **A5**,

Table 2. Percent adsorption data for materials A2, B2 and C2.[a]

guest	pH	A2	B2	C2
PYR	1.0	94	95	91
	4.4	85	88	88
	6.7	80	86	85
	10.7	84	81	91
SRC	1.0	85	90	85
	4.4	81	87	41
	6.7	14	93	23
	10.7	10	26	18
IMD	1.0	22	13	37
	4.4	78	71	80
	6.7	69	67	86
	10.7	87	84	92
PDA	1.0	21	9	31
	4.4	69	70	79
	6.7	78	65	84
	10.7	85	78	89
MOR	1.0	54	55	65
	4.4	85	64	89
	6.7	80	60	93
	10.7	72	52	88

[a] All data are given with a ±3% indetermination.

Table 3. Percent adsorption data for materials A4 and B4.[a]

guest	pH	A4	B4
PNA	4.4	100	93
	6.7	89	87
	10.7	78	71
PYR	4.4	89	94
	6.7	84	77
	10.7	62	69
SRC	4.4	61	93
	6.7	74	37
	10.7	4	12
BCG	4.4	100	100
	6.7	100	100
	10.7	21	15
TLB	4.4	49	38
	6.7	92	70
	10.7	73	85

[a] All data are given with a ±3% indetermination.

Table 4. Percent adsorption data for materials **A5**, **B5** and **C5**.[a]

guest	pH	A5	B5	C5
PNA	1.0	83	86	71
	4.4	13	22	14
	6.7	3	3	5
	10.7	0	0	0
PYR	1.0	76	82	67
	4.4	67	78	60
	6.7	85	80	69
	10.7	82	71	69
SRC	1.0	83	86	71
	4.4	13	22	14
	6.7	3	3	5
	10.7	0	0	0
BCG	1.0	92	93	94
	4.4	96	69	90
	6.7	45	33	44
	10.7	14	10	11
IMD	1.0	0	28	29
	4.4	70	85	88
	6.7	90	88	90
	10.7	93	94	93
TLB	1.0	48	72	85
	4.4	100	98	98
	6.7	94	98	99
	10.7	91	90	90
PDA	1.0	13	31	36
	4.4	80	87	88
	6.7	92	87	89
	10.7	94	95	93
MOR	1.0	32	43	24
	4.4	63	52	57
	6.7	55	46	66
	10.7	31	22	37

[a] All data are given with a ±3% indetermination.

B5 and **C5** decorated with carboxyl groups pass from a positively charged status under acidic conditions to a negatively charged one under alkaline conditions, due to the concomitant different ionization status of the carboxyl groups and the triazole linkers. Data trends reported in Table 4 confirm the behavior of both anionic (**SRC**, **BCG**) and cationic (**IMD**, **TLB**, **PDA**) guests. Moreover, a strong pH effect is shown also by neutral **PNA**, the inclusion of which results quite large at pH 1.0, but is strongly disfavored already at pH 4.4, i.e. when carboxyl groups are at least partly in their anionic deprotonated form. By contrast, lesser pH effects occur for **PYR**, probably because of the concomitant occurrence of favorable interactions with the aliphatic moiety. Again, data for **MOR** pass through a maximum on changing the pH. Overall, these data confirm the observations discussed in our previous works,[3-4,7-8,16] i.e. Coulomb interactions appear the main driving force of the binding equilibrium. It is noteworthy that, owing to the different effects of pH changing for the differently charged guest, a comparison between the behavior of the different materials is not straightforward. However, data suggest that the different substitution pattern of the monomer host units (i.e. possible methylation of the secondary hydroxyl groups of the cyclodextrin or de-alkylation of the calixarene units), though affecting the hydrophobic character of the materials, has only a modest outcome on the sequestration abilities observed.

In order to gain a deeper understanding of the adsorption process at the microscopic level, we studied the adsorption isotherms at 25 °C for neutral guest **PYR** with the various materials. Experiments were generally performed at pH 4.4; however, post-modified materials **A4**, **B4** and **C4** were studied also at pH 10.7, whereas material **A5** was examined also at pH 1.0, 6.7 and 10.7. In general, increasing amounts of the materials were equilibrated with a fixed volume of a 0.05 mM solution of the guest. Adsorption data could be generally rationalized by means of the Freundlich model, according to the relationship:

$$Log(q_i) = Log(K_F) + (1/n_F) \cdot Log(C_i) \qquad (1)$$

where q_i and C_i are the amount of guest adsorbed per weight unit of material and the equilibrium concentration of the guest in the generic i-th sample, respectively. Alternatively, data could also be analyzed according to the empiric reationship:

$$(C_i/C_0) = 1/(1 + K_{app} \cdot m_i^n) \qquad (2)$$

where C_i and m_i are the equilibrium concentration and the amount of material of the generic i-th sample, C_0 is the initial concentration, K_{app} is the apparent adsorption constant, m_i is the amount of material and n is an empiric parameter, somehow analogous to the n_F coefficient present in Freundlich equation. Relevant results are reported in Table 5. Although apparent constants K_F and K_{app} for the various materials are not immediately comparable, due to the concomitant differences in the values of the relevant parameters n_F and n respectively, some interesting trends can be easily envisaged. First, as long as the composition of the materials is concerned, binding abilities generally decrease on decreasing the amount of the cyclodextrin co-monomer.[7] The introduction of amine groups decreases binding abilities, likely due to the more hydrophilic character assumed by the material; in fact, materials **A4**-**C4**

Table 5. Fitting parameters for the adsorption isotherms.

material	pH	Freundlich equation		empiric equation		material	pH	Freundlich equation		empiric equation	
		Log K_F	n_F	K_{app}	n			Log K_F	n_F	K_{app}	n
A1	4.4	-4.2 ± 0.1	1.53 ± 0.03	1.56 ± 0.06	1.26 ± 0.05	**B1**	4.4	-4.5 ± 0.1	1.69 ± 0.06	1.55 ± 0.07	1.20 ± 0.06
A2	4.4	-3.6 ± 0.3	1.36 ± 0.09	2.23 ± 0.06	1.30 ± 0.06	**B2**	4.4	-3.0 ± 0.1	1.10 ± 0.06	1.32 ± 0.03	1.07 ± 0.03
A3	4.4	-2.4 ± 0.3	0.87 ± 0.06	0.39 ± 0.01	0.96 ± 0.03	**B3**	4.4	-0.11 ± 0.04	0.58 ± 0.05	0.18 ± 0.07	0.83 ± 0.03
A4	4.4	-2.8 ± 0.3	1.02 ± 0.07	0.82 ± 0.06	1.08 ± 0.04	**B4**	4.4	-3.7 ± 0.2	1.23 ± 0.09	0.77 ± 0.02	1.10 ± 0.04
	10.7	-3.1 ± 0.3	1.11 ± 0.05	0.93 ± 0.06	1.15 ± 0.03		10.7	-3.9 ± 0.2	1.33 ± 0.08	0.97 ± 0.02	1.15 ± 0.03
A5	1.0	-4.3 ± 0.1	1.50 ± 0.07	0.70 ± 0.03	1.24 ± 0.05	**B5**	4.4	-3.8 ± 0.2	0.81 ± 0.03	0.75 ± 0.01	1.14 ± 0.02
	4.4	-2.6 ± 0.1	0.97 ± 0.03	0.91 ± 0.01	0.99 ± 0.02	**C1**	4.4	-4.9 ± 0.1	2.06 ± 0.06	2.02 ± 0.05	1.59 ± 0.05
	6.7	-3.7 ± 0.1	1.21 ± 0.02	0.51 ± 0.01	1.09 ± 0.02	**C2**	4.4	-3.8 ± 0.2	1.32 ± 0.06	1.27 ± 0.06	1.06 ± 0.06
	10.7	-3.0 ± 0.2	1.00 ± 0.04	0.47 ± 0.01	1.02 ± 0.02	**C3**	4.4	-3.3 ± 0.2	1.06 ± 0.05	0.45 ± 0.01	1.02 ± 0.02
						C4	4.4	-3.4 ± 0.1	1.06 ± 0.03	0.39 ± 0.01	1.02 ± 0.01
							10.7	-3.7 ± 0.1	1.22 ± 0.03	0.67 ± 0.01	1.10 ± 0.02
						C5	4.4	-3.8 ± 0.1	1.15 ± 0.04	0.32 ± 0.01	1.11 ± 0.02

work better under alkaline (pH 10.7) than acidic (pH 4.4) conditions. On the other hand, the effect of the introduction of the carboxyl groups deserves a more articulated discussion. Indeed, material **A5** apparently works better than the analogous non-post-modified **A3** at pH 4.4; by contrast, the opposite can be found on comparing **B5** and **C5** with **B3** and **C3** respectively. Material **A5** was also studied at different pH values. Data indicate that binding properties seem passing through a maximum at pH 4.4, close to the LogK_a value of carboxyl groups. On passing to analyze the values of coefficients n_F and *n*, similar trends as for *K* values can be found. Noticeably, the very fact that most of these values are slightly but significantly different from unit, implies that adsorption cannot be laid back to a simple 1:1 supramolecular inclusion mechanism with the host units present in the materials. This, in turn, can be tentatively explained assuming that occasionally two host units might be so close in space to form a sort of 1:2 complex with a single guest unit, and that the nanochannels present in the structure of the materials might contribute to the adsorption abilities of the material up to a certain extent. It is worth recalling here that, on the grounds of porosimetric determinations (BET) reported elsewhere,[7] a significant fraction of the channels is comparable in size with the host units; therefore nanochannels can positively interact with the guest molecules, contributing to the overall adsorption abilities. Finally, the question arises whether the possible existence (suggested by titration experiments) of hydrophobic microregions hardly accessible to aqueous solution, might somehow affect the binding abilities of the material. Therefore, we prepared a composite by saturating material **A3** with **PYR**. After elution with methanol we found out that the composite contained an 8.5 % in weight of guest. On the grounds of analytical data reported elsewhere,[7] we can easily

calculate that the composite contained ca. 409 μmoles/g of guest, 225 μmoles/g of cyclodextrin units and 775 μmoles/g of calixarene units. This result is interesting, because it implies that the saturation of host units (ca. 41 %) is significantly larger than the fraction of ionizable groups actually subjected to the titration procedure (ca. 29%). Therefore, this indicates the hydrophobic guest actually undergoes an effective mass transfer from the aqueous medium and the more hydrophilic microregions of the material towards the hydrophobic microregions.

Conclusions

In the present work we investigated the acid-base characteristics and the pH-dependent adsorption abilities of a set of diversely structured CyCaNS nanosponges. The whole of the results indicates a complex behavior, affected by the presence in the materials of hydrophobic microregions, hardly interacting with the aqueous medium, and by the fact that the triazolyl linkers present in the material are much more basic than expected on the grounds of the behavior of the free molecule in solution. The possible existence of hydrophobic microregions does not seem to hinder the adsorption abilities of the materials, due to the occurrence of effective mass transfer processes. This idea is consistent with the fact that the adsorption isotherms of the materials can be adequately described by the Freundlich equation. Coulomb interactions apparently assume a paramount role in affecting binding properties. The latter point is in perfect agreement with previous reports.[3-4,6-7,16] It is worth recalling here that this observation is consistent with the idea that the host subunits embedded in the polymeric network are relatively stiff, due to hyper-cross-linking. Hence, the usual "induced-fit

effect"[17] occurring in the formation of host-guest complexes in solution cannot properly operate. As a consequence, the adsorption process is much more strictly controlled by long-range interactions (such as electrostatic ones) rather than being finely tuned by the possible simultaneous occurrence of short-range van der Waals or hydrogen bonding interactions.

For the sake of completeness, as a final remark, it should be mentioned that a question remains open regarding the reason why triazolyl linker groups undergo an increase of ca. six orders of magnitude in their basic strength, consequent to their insertion in the hyper-cross-linked structure of the CyCaNS. Such a large variation closely resembles the one occurring in proton sponges,[18] which is justified by the formation of a very favorable hydrogen bond interaction between a protonated basic site and a proximal acceptor group. In our case, it seems quite reasonable to assume that any triazolyl linker has plenty of hydrogen bond acceptors stably present in its sourroundings, for instance the -OH groups of the cyclodextrin sub-units or even other triazolyl rings. Therefore, we might tentatively explain the aforementioned increase in basic strength as the consequence of particularly stable "intramolecular" (or better "intra-network") hydrogen bonding occurring upon protonation.

Supporting Information Summary

Supporting Information reports: *i*) the complete Experimental Section (Materials, Instrumentation, Potentiometric titrations, Sequestration tests, Adsorption isotherms, Preparation of the **A3-PYR** composite); *ii*) **Table S1.** Portentiometric titration data (modified Henderson-Hasselbach and Högfeldt equations).

Keywords: Adsorption • Calixarene • Cyclodextrin • Nanosponges • Potentiometric titration

[1] a) N. Falcone, H. B. Kraatz, *Chemistry-a European Journal* **2018**, *24*, 14316-14328; b) X. Fu, L. Hosta-Rigau, R. Chandrawati, J. W. Cui, *Chem* **2018**, *4*, 2084-2107; c) A. Rahikkala, S. A. P. Pereira, P. Figueiredo, M. L. C. Passos, A. Araujo, M. Saraiva, H. A. Santos, *Advanced Biosystems* **2018**, *2*; d) P. Samaddar, Y. S. Son, D. C. W. Tsang, K. H. Kim, S. Kumar, *Coord. Chem. Rev.* **2018**, *368*, 93-114; e) A. Shah, M. S. Malik, G. S. Khan, E. Nosheen, F. J. Iftikhar, F. A. Khan, S. S. Shukla, M. S. Akhter, H. B. Kraatz, T. M. Aminabhavi, *Chem. Eng. J.* **2018**, *353*, 559-583; f) Y. Zhao, Y. G. Guo, L. Tang, *Nano Research* **2018**, *11*, 5355-5371.

[2] a) R. Cavalli, F. Trotta, W. Tumiatti, *J. Incl. Phenom. Macrocycl. Chem.* **2006**, *56*, 209-213; b) D. Lembo, M. Donalisio, A. Civra, M. Argenziano, R. Cavalli, *Expert Opin. Drug Del.* **2018**, *15*, 93-114; c) D. Li, M. Ma, *Clean Products and Processes* **2000**, *2*, 112-116; d) A. P. Sherje, B. R. Dravyakar, D. Kadam, M. Jadhav, *Carbohydr. Polym.* **2017**, *173*, 37-49; e) F. Trotta, in *Cyclodextrins in Pharmaceutics, Cosmetics, and Biomedicine*, John Wiley & Sons, Inc., **2011**, pp. 323-342.

[3] M. Russo, M. L. Saladino, D. Chillura Martino, P. Lo Meo, R. Noto, *RSC Adv.* **2016**, *6*, 49941-49953.

[4] A. Di Vincenzo, A. P. Piccionello, A. Spinella, D. C. Martino, M. Russo, P. Lo Meo, *Beilstein J. Org. Chem.* **2019**, *15*, 633-641.

[5] M. Russo, A. Spinella, A. Di Vincenzo, G. Lazzara, M. R. Correro, P. Shahgaldian, P. Lo Meo, E. Caponetti, *ChemistrySelect* **2019**, *4*, 873-879.

[6] V. Cinà, M. Russo, G. Lazzara, D. Chillura Martino, P. Lo Meo, *Carbohydr. Polym.* **2017**, *157*, 1393-1403.

[7] P. Lo Meo, G. Lazzara, L. Liotta, S. Riela, R. Noto, *Polym. Chem.* **2014**, *5*, 4499-4510.

[8] M. Massaro, V. Cina, M. Labbozzetta, G. Lazzara, P. Lo Meo, P. Poma, S. Riela, R. Noto, *RSC Adv.* **2016**, *6*, 50858-50866.

[9] a) A. Katchalsky, P. Spitnik, *Journal of Polymer Science* **1947**, *2*, 432-446; b) A. Katchalsky, *Journal of Polymer Science* **1954**, *12*, 159-184.

[10] E. M. Högfeldt, T.; Marinsky, J. A. and Muhammed, M., *Acta Chem. Scand.* **1989**, *43*, 496-499.

[11] E. A. Guggenheim, *Application of Statistical Mechanics*, Clarendon Press, Oxford, **1966**.

[12] F. Crea, C. De Stefano, A. Gianguzza, A. Pettignano, D. Piazzese, S. Sammartano, *Journal of Chemical & Engineering Data* **2009**, *54*, 589-605.

[13] a) A. Giacalone, A. Gianguzza, A. Pettignano, S. Sammartano, *Appl. Organomet. Chem.* **2006**, *20*, 706-717; b) C. De Stefano, A. Gianguzza, A. Pettignano, D. Piazzese, S. Sammartano, *J. Radioanal. Nucl. Chem.* **2011**, *289*, 689-697; c) C. Bretti, S. Cataldo, A. Gianguzza, G. Lando, G. Lazzara, A. Pettignano, S. Sammartano, *J. Phys. Chem. C* **2016**, *120*, 7849-7859; d) F. Crea, A. Gianguzza, A. Pettignano, S. Sammartano, *Journal of Chemical & Engineering Data* **2010**, *55*, 3044-3050.

[14] J. L. M. Abboud, C. Foces-Foces, R. Notario, R. E. Trifonov, A. P. Volovodenko, V. A. Ostrovskii, I. Alkorta, J. Elguero, *Eur. J. Org. Chem.* **2001**, 3013-3024.

[15] a) F. D'Anna, P. Lo Meo, S. Riela, M. Gruttadauria, R. Noto, *Tetrahedron* **2001**, *57*, 6823-6827; b) P. Lo Meo, F. D'Anna, S. Riela, M. Gruttadauria, R. Noto, *Tetrahedron* **2002**, *58*, 6039-6045; c) P. Lo Meo, F. D'Anna, S. Riela, M. Gruttadauria, R. Noto, *Org. Biomol. Chem.* **2003**, *1*, 1584-1590; d) P. Lo Meo, F. D'Anna, M. Gruttadauria, S. Riela, R. Noto, *Tetrahedron* **2004**, *60*, 9099-9111; e) P. Lo Meo, F. D'Anna, S. Riela, M. Gruttadauria, R. Noto, *Tetrahedron Lett.* **2006**, *47*, 9099-9102; f) P. Lo Meo, F. D'Anna, S. Riela, M. Gruttadauria, R. Noto, *Tetrahedron* **2007**, *63*, 9163-9171; g) P. Lo Meo, F. D'Anna, M. Gruttadauria, S. Riela, R. Noto, *Tetrahedron* **2009**, *65*, 10413-10417; h) P. Lo Meo, F. D'Anna, S. Riela, M. Gruttadauria, R. Noto, *Tetrahedron* **2009**, *65*, 2037-2042; i) M. Russo, D. La Corte, A. Pisciotta, S. Riela, R. Alduina, P. Lo Meo, *Beilstein J. Org. Chem.* **2017**, *13*, 2751-2763; j) M. Russo, P. Lo Meo, *Beilstein J. Org. Chem.* **2017**, *13*, 2698-2709.

[16] A. Spinella, M. Russo, A. Di Vincenzo, D. C. Martino, P. Lo Meo, *Beilstein J. Org. Chem.* **2018**, *14*, 1498-1507.

[17] M. V. Rekharsky, H. Yamamura, M. Kawai, Y. Inoue, *J. Org. Chem.* **2003**, *68*, 5228-5235.

[18] A. L. Llamassaiz, C. Focesfoces, J. Elguero, *J. Mol. Struct.* **1994**, *328*, 297-323.
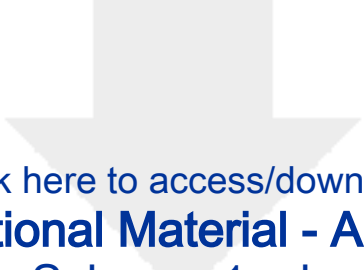
Entry for the Table of Contents
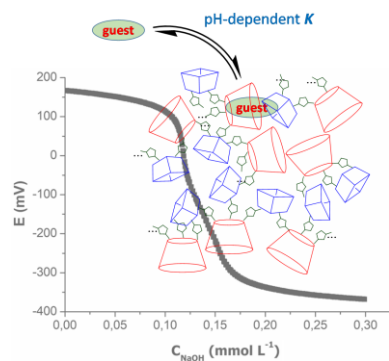
The pH-responsivity of a set of variously structured and modified cyclodextrin-calixarene nanosponges was investigated. A smart approach integrating different methodologies from analytical and supramolecular chemistry aided to achieve a thorough understanding of the microscopic features of these materials.
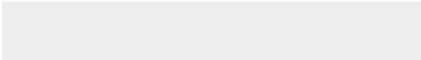
Click here to access/download

Supporting Information

Suporting Information .docx

Click here to access/download

Additional Material - Author

Scheme 1.cdx