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LETTER

Selective recognition of biogenic amine hydrochlorides by heteroditopic dihomooxacalix[4]arenes†

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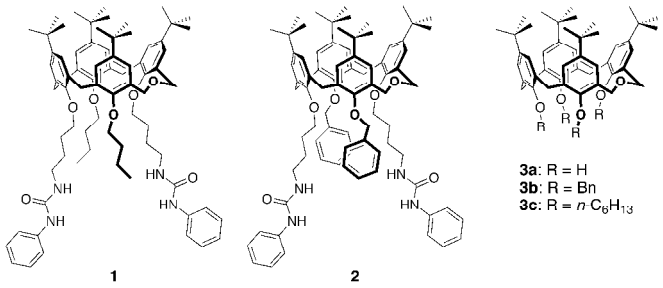
Ion-pair recognition/complexation of monoamine neurotransmitter and trace amine hydrochlorides takes place –with outstanding efficiency and selectivity– within the π-rich cavity and the pocket formed at the lower rim by the two ureido moieties of tailor-made dihomooxacalixarene receptors 1 and 2. The solid-state structure of 1 is also reported.

The so-called 'monoamine neurotransmitters' (e.g. dopamine, histamine, norepinephrine, and serotonin) and 'trace amines' (e.g. 2-phenylethylamine and tyramine) are structurally related species that share an arylethylamine moiety as a common structural feature. The ability to selectively detect such target molecules is of enormous significance in medical and clinical research/analysis as these molecule play a key role in the physiological nervous system's signaling processes, as well as in several psychiatric disorders and neurodegenerative pathologies (e.g., schizophrenia and Parkinson's disease).[1]
In recent years, a number of different artificial receptors, based on calixarenes,[2] homooxacalix[3]arenes,[3] hemicryptophanes[4] and other molecular frameworks[5] have been prepared, but selective recognition nevertheless remains an open challenge. We have a long-standing interest in the fine-tuning of macrocyclic compounds of different type/size as artificial receptors[6] and now, urged by the very recent findings that 18-membered *p-tert*-butyldihomooxacalix[4]arenes **3b,c** can efficiently bind linear alkylammonium substrates, providing a 'superweak' counterion is used,[7] we wish to report our latest results on the ion-binding properties and selectivities of new heteroditopic dihomooxacalix[4]arenes **1** and **2** towards *n*-butylammonium halides and a number of biogenic amine hydrochlorides (see Fig. 3). Based on our earlier findings[7] on **3b,c** –where the mandatory presence of a very loose anion (such as tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate[8]) was required for alkylammonium cation *endo*-cavity complexation to occur– two of the lower rim alkyl/benzyl moieties of these receptors were replaced[9] with ureido pendant groups with the specific aim of obtaining ditopic host molecules.[10]

Derivatives **1** and **2**,[9] owing to their additional ureido anionic recognition sites,[11] were then expected to simultaneously bind the two ionic counterparts of alkylammonium salts and, as a result, minimize the detrimental ion-pairing effect[12] typically encountered in the recognition/binding process of a charged guest by a neutral host.



1 2

To verify this hypothesis, ^{1}H NMR titration experiments were carried out by adding increasing amounts of *n*-butylammonium chloride, bromide and iodide (0.5, 1.0 and 2.0 equiv.) to a 1.0 mM solution of receptors **1** and **2** in $CDCl_3$ to preliminary assess slow *vs* fast mode of complexation on the NMR timescale. Doubling of all the receptor resonances together with a new set of signals compatible with the presence of a guest molecule bound to the host were observed right from the addition of the first salt aliquot. *n*-Butylammonium cation inclusion, inside the homooxacalixarene cavity, is unequivocally substantiated by the appearance of the alkyl-chain resonances in the –1.4 to 0.0 ppm region of the ^{1}H NMR spectrum.[3a,7,13] Owing to the chiral environment –arising from the asymmetric substitution pattern present at the lower rim of the hosts **1** and **2**– the pairs of enantiotopic hydrogen atoms belonging to the α- and β-CH_2 groups of the included guest display chemically non-equivalent signals once the alkylammonium ion is firmly anchored within the dihomooxacalixarene cavity.‡ On the other hand, simultaneous halide binding to the ureido moieties is underlined by the down-field shift observed for all the resonances assigned to the NHs (Fig. 1 and Fig. S4; ESI†). Collectively, these observations are

fully consistent with a slow complexation mode on the NMR timescale. Further addition of salt aliquots caused the disappearance of the free hosts' resonances.

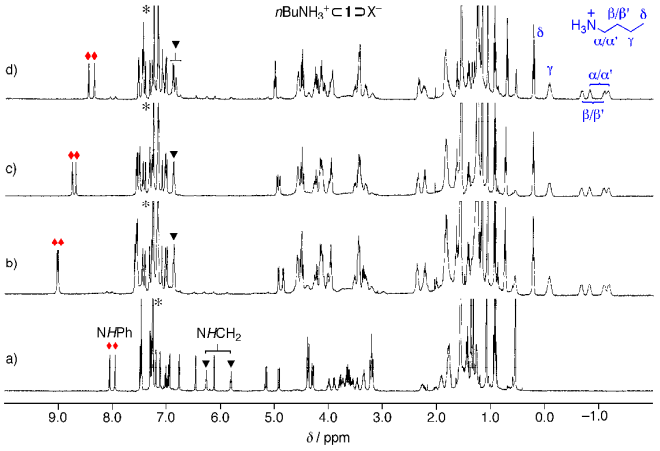


Fig. 1 ^{1}H NMR spectra (500 MHz, $CDCl_3$, 298 K) of: a) [**1**] = 1.0 mM, b) [**1** = [*n*-$BuNH_2$·HCl] = 1.0 mM; c) [**1**] = [*n*-$BuNH_2$·HBr] = 1.0 mM and d) [**1**] = [*n*-$BuNH_2$·HI] = 1.0 mM. The asterisk indicates the resonance of the residual solvent signals.

All host-guest ternary systems under investigation (1.0 mM, 1:1 host/guest salt solutions in $CDCl_3$) displayed very high percentages of complexation (≥ 95%, corresponding to K_{ass} >10^9 M^{-2}), preventing us from reliably calculating the pertinent association constants by ^{1}H NMR analysis. The complexation induced shifts (CISs) of the receptor N*H*Ph and the guest α- to γ-CH_2 resonances (acting as anion and cation binding probes, respectively), observed upon dihomooxacalixarene/*n*-$BuNH_2$·HX binding, indicate that halide ions interact with the ureido binding pocket of **1** and **2** in a similar fashion, while the alkylammonium chain, irrespective of its counterion, is accommodated at the same depth inside the macrocycle cavity. Accordingly, the CIS values of the latter probe-resonances do not vary in the presence of different anions, while those of the N*H*Phs decrease with an anion dependent pattern ($I^- < Br^- < Cl^-$) which may suggest a correlation with the halogen electronegativity scale (Table S4; ESI†).[14]

The solid-state structure§ of receptor **1** (Figs 2, S1, S2 and Tables S1–S3; ESI†) provides the means to explain the marked efficiency in the recognition of *n*-butylammonium halides. Similarly to what has been observed with calix[5]arenes,[15] dihomooxacalix[4]arene **1** possesses a highly preorganized aromatic cavity, ready to accommodate the incoming butylammonium cation. In addition, the proclivity of the ureido moieties to act as anion-binding sites is highlighted by the fact that, even in the absence of guest molecules, they interact with each other, self-assembling into an infinite one-dimensional H-bonded array.

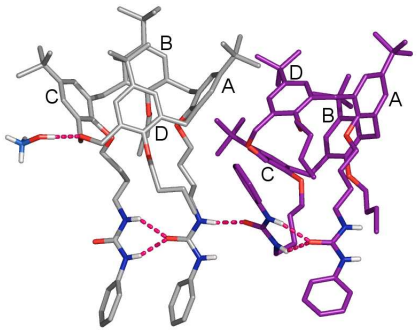


Fig. 2 The solid state structure of dihomooxacalix[4]arene **1**, showing the presence of molecules **I** and **II** (depicted in the figure in grey and violet, respectively with the pertinent ring labeling) in the asymmetric unit. Molecules **I** and **II** are seen to adopt similar *cone*-in conformations with their phenylureido moieties being involved in an infinite array of intra- and intermolecular N–H···O hydrogen bonds.

Having assessed the heteroditopic nature of hosts **1** and **2**, we then turned our attention to monoamine neurotransmitters and trace amines (as the corresponding hydrochlorides) **4**–**10** (Fig. 3).

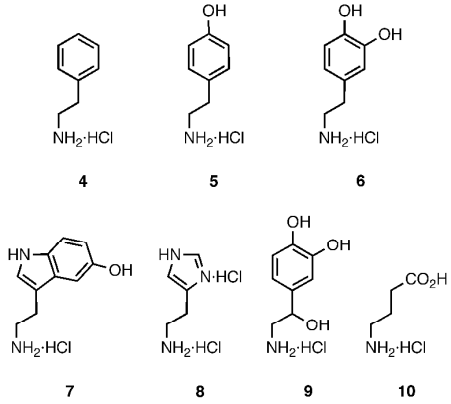


Fig. 3 Structures of the monoamine neurotransmitters and trace monoamines (tested as the corresponding hydrochlorides): 2-phenylethylamine (Pea·HCl, **4**), tyramine (Tyrm·HCl, **5**), dopamine (Dopa·HCl, **6**), serotonin (Sert·HCl, **7**), histamine (Hist·2HCl, **8**), norepinephrine (Nore·HCl, **9**) and □-aminobutyric acid (Gaba·HCl, **10**).

^{1}H NMR selectivity screening experiments were carried out in a $CDCl_3/CD_3OD$ solvent mixture (10:1, v/v) to ensure adequate solubility of both host and guest. Preliminary tests, carried out by adding 1 equiv. of ammonium guests **4**–**7** and **10** to a 1.0 mM solution of the host at 298 K caused a severe broadening of all ^{1}H NMR signals, indicating a strong host-guest interaction, but gave no clues as to the mode and/or the stoichiometry, nor to the extent of binding taking place in solution. For a slow –on the NMR timescale– host-guest complexation/decomplexation regime to be fully established, lowering of the temperature to 233 K was necessary and, as a result, analysis of the complexation process became possible (see Figs 4, S5 and S6 in the case of **1** and Tyrm·HCl; ESI†).

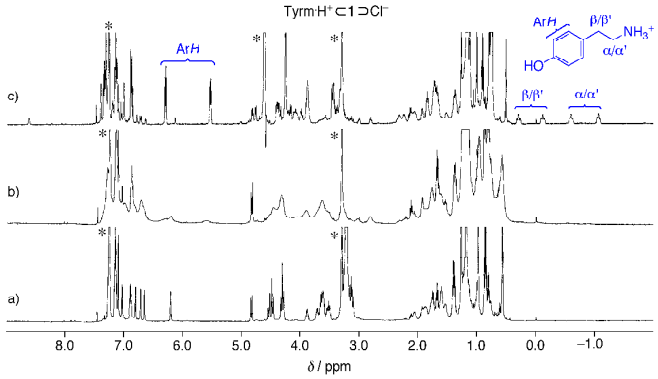


Fig. 4 ^{1}H NMR spectra (500 MHz, $CDCl_3/CD_3OD$ 10:1 v/v) of: a) [**1**] = 1.0 mM at 298 K, b) [**1**] = [Tyrm·HCl] = 1.0 mM at 298 K and c) [**1**] = [Tyrm·HCl] = 1.0 mM at 233 K.

In analogy with the butylammonium halide cases, the α- and β-CH_2s of the guests are recognized and included inside the asymmetric cavity of **1** and **2** and as a result display four distinct resonances in the high field region of their ^{1}H NMR spectrum.[16] The percentages of complex formation and the association constants (K_{ass}), determined by ^{1}H NMR, are summarized in Table 1.

Table 1 Percentages of complex formation and corresponding association constants, K_{ass} ($\times 10^3$ M^{-2}), determined[a] by ^{1}H NMR (500 MHz, in $CDCl_3/CD_3OD$ (10:1, v/v), at 233 K) between dihomooxacalix[4]arenes **1** and **2** and amine hydrochlorides **4**–**10**.

	Pea·H Cl (**4**)	Tyrm·H Cl (**5**)	Dopa·H Cl (**6**)	Sert·H Cl (**7**)	Hist·2H Cl (**8**)	Nore·H Cl (**9**)	Gaba·H Cl (**10**)
1	86% 41±4.5	85% 36±4.3	67% 6.3±0.9	61% 4.1±0.6	n.o.[b]	n.o.[b]	63% 4.5±0.2
2	83% 30±4.4	81 % 23±2.9	63% 4.5±0.6	60% 3.7±0.5	n.o.[b]	n.o.[b]	60% 3.7±0.3

[a]Percentage values derive from an average of three independent measurements. [b] N.o. stands for no complexation observed.

A closer inspection of these data shows that host **1** is marginally more efficient than **2**. Moreover, K_{ass} values indicate a comparable affinity trend between arylalkyl amines and both hosts (Pea·HCl > Tyrm·HCl > Dopa·HCl > Sert·HCl). It is reasonable to speculate that guests **4** and **5** best fit inside the calixarene cavities as a result of their less bulky aryl moiety. According to our data, the lower association constants observed in the case of the aliphatic neurotransmitter Gaba suggest that π-π interactions, very often operating in the binding pockets of biological receptors,[17] play a key role in the recognition/binding process between *p-tert*-butyldihomooxacalix[4]arenes **1** and **2** and phenylethylamine or tyramine. Interestingly, no interaction at all was detected with the β-substituted norepinephrine·HCl or the dicationic histamine·2HCl, either at 298 or at 233 K (see Fig. S7; ESI†). Despite the structural similarity of the neurotransmitters tested (**4**–**9** contain an arylethylammonium moiety), selectivity data –calculated as the ratio of two given K_{ass} values, Table 2– indicate that receptors **1** and **2** show a higher affinity (in the 5–10-fold range) for Pea·HCl and Tyrm·HCl over the other amine hydrochorides.

Table 2 Selectivities of dihomooxacalix[4arenes **1** and **2** for monoamine hydrochlorides **4**–**7** and **10**.

	$S_{Pea/Dopa}$	$S_{Pea/Sert}$	$S_{Pea/Gaba}$	$S_{Tyrm/Dopa}$	$S_{Tyrm/Sert}$	$S_{Tyrm/Gaba}$
1	6.6	10.1	9.2	5.8	8.9	8.1
2	6.6	8.1	8.0	5.0	6.1	6.0

In conclusion, our studies demonstrate that dihomooxacalix[4]arenes **1** and **2** behave as heteroditopic receptors efficiently binding organic ammonium halides in organic media. Their preorganized π-rich cavities mimic the hydrophobic binding pockets of the G protein-coupled receptors, displaying high association constants and a good degree of selectivity towards 2-phenylethylamine, tyramine, dopamine and serotonin neurotransmitters. These features make receptor **1** and **2** promising candidates for the development of sensing devices capable of monitoring the level of biogenic amines in biological fluids.

Experimental

General

Dihomooxacalix[4]arenes **1** and **2** were available from previous studies.[9] Amine hydrochlorides [**4**–**10**] were purchased from Sigma-Aldrich and were used as received.

^{1}H NMR Complexation Experiments

All spectra were recorded at 500 MHz at either 298 or 233 K. Percentages of the host-guest ternary complex formation (required for the calculation of the corresponding association constants, K_{ass}) were determined by direct ^{1}H NMR integration analysis of the 'free' and 'complexed' resonances of the guest and/or the host, present at equilibrium, in a equimolar host-guest solution. A set of three different equimolar sample solutions was examined for each K_{ass} determination. In the case of dihomooxacalix[4]arenes **1** and **2** with n-$BuNH_3^+X^-$ (X^- = Cl^-, Br^- and I^-), where percentages of complexation were found to be ≥ 95%, K_{ass} values were estimated to be $>10^9$ M^{-2}.
All samples were prepared by mixing together aliquots of stock solutions of host (600 mL) and guest (60 mL) to obtain a final equimolar host-guest solution (1.0 mM). The following stock solutions were used: [**1**–**2**] = 1.1 mM in $CDCl_3$ or $CDCl_3/CD_3OD$ (10:1, v/v), [n-$BuNH_3^+X^-$] = 11.0 mM in $CDCl_3$ and [**4**–**10**] = 11.0 mM in $CDCl_3/CD_3OD$ (10:1, v/v). For the assessment of the NH resonance complexation induced shifts a $CDCl_3/CH_3OH$ (10:1, v/v) solution of [**1**] = [Tyrm·HCl] = 1.0 mM was used.

X-ray crystallography

Colourless very small single crystals (typical size 0.05 × 0.08 × 0.1 mm) suitable for X-ray analysis by synchrotron radiation were obtained from slow diffusion of CH_3OH into a $CHCl_3$ solution of dihomooxacalix[4]arene **1** at room temperature. Data collection was carried out at the X-ray diffraction beam-line of the Elettra Synchrotron, Trieste, Italy, employing the rotating-crystal method with the cryo-cooling technique. The crystal dipped in Paratone, as cryo-protectant, was mounted in a loop and flash frozen to 100 K under a stream of nitrogen. Diffraction data were indexed and integrated using MOSFLM[18] and scaled with SCALA.[19,20]
The structure was solved by direct methods using SIR2011.[21] Non-hydrogen atoms were refined by full-matrix least-square methods on F^2 using SHELXL-13[22] with the contribution of H atoms placed at the geometrically calculated positions and refined using the riding model. The crystallographic model is affected by disorder and a detailed description is provided in

the ESI†. Crystallographic data and refinement details are reported in Table S1, see the ESI†.

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Notes and references

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† Electronic supplementary information (ESI) available: additional ^{1}H NMR spectra and crystal data for **1**. CCDC reference number 1009330. See DOI: 10.1039/x0xx00000x

‡ Signal assignment follows from COSY experiments (see Fig. S3).

§ The asymmetric unit of the triclinic cell contains two crystallographically independent receptor molecules (**I** and **II**, as seen in Fig. 2) and a methanol solvent molecule. See the ESI† for a full description.

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