Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 1717

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COMMUNICATION

Unprecedented gas-phase chiroselective logic gates†

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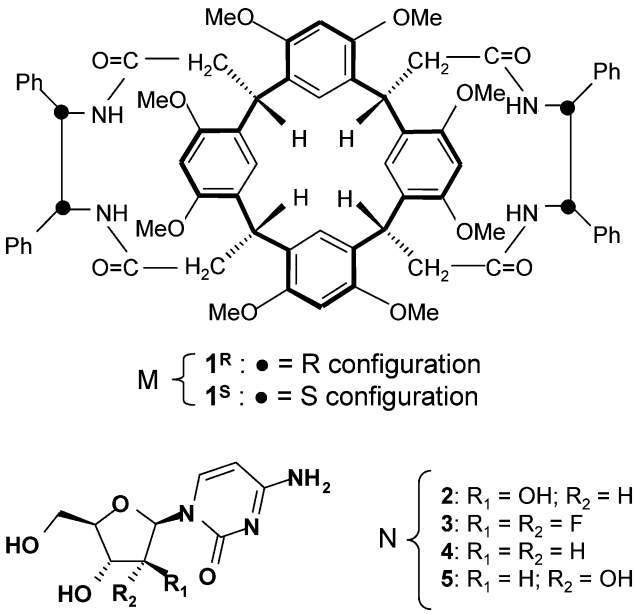
Received 3rd September 2010, Accepted 5th January 2011
DOI: 10.1039/c0ob00664e

The gas-phase encounters between 2-aminobutane and proton-bound chiral resorcin[4]arene/nucleoside complexes behave in the gas phase as supramolecular "chiroselective logic gates" by releasing the nucleoside depending on the resorcin[4]arene and the 2-aminobutane configurations.

Nucleosides are buildings blocks of RNA and DNA biomacromolecules, which may also act as neuromodulators or as chemotherapeutic agents.[1–3] Nucleoside analogues are widely used for the treatment of human cancers. The study of the molecular recognition of nucleobases and their derivatives by synthetic hosts is aimed at a better understanding of the noncovalent interactions that play a role in relevant biological processes and may also contribute to the design of artificial receptors for therapeutic purposes.

We recently found that the bis(diamido)-bridged basket resorcin[4]arene enantiomers $\mathbf{1^R}$ and $\mathbf{1^S}$ (Scheme 1)[4] are capable of incorporating selectively chiral amino acids,[5] amines,[5] and amphetamine[6] in the gaseous phase, *i.e.* under conditions excluding solvation and ion pairing interference.[7] Therefore, we believe it is worth investigating the interactions between either $\mathbf{1^R}$ or $\mathbf{1^S}$ and some pyrimidine nucleosides (N), *i.e.* 2′-deoxycytidine **4**,[8] cytidine, **5**,[9] cytarabine **2**,[10] which is an epimer of cytidine, and gemcitabine **3**,[11] which is the *gem*-difluoro derivative of 2′-deoxycytidine. Aim of the investigation is to gain some information on the sensitive molecular regions and functional groups which allow their selective interaction with protonated $\mathbf{1^R}$ and $\mathbf{1^S}$. In this communication, it is reported that one of the systems investigated behaves as a supramolecular device which, depending on its chirality, is capable to keep the nucleoside firmly bound to it or to release it slowly.

Proton-bound diastereomeric $[M{\cdot}H{\cdot}N]^+$ complexes (M stands for either $\mathbf{1^R}$ or $\mathbf{1^S}$; N stands for one among the nucleosides **2–5** of Scheme 1) have been generated in the cell of a Fourier-Transform Ion Cyclotron Resonance (FT-ICR) mass spectrometer



Scheme 1 Formulae of the cone resorcin[4]arene macrocycles $\mathbf{1^R}$ and $\mathbf{1^S}$ and of the selected pyrimidine nucleosides N (**2–5**). The stereogenic centers of $\mathbf{1^R}$ and $\mathbf{1^S}$ are denoted by the black dots.

by nano-electrospray ionization (nano-ESI) of M/N methanolic mixtures. After collisional quenching with argon, the complexes were isolated by broad-band ejection of the accompanying ions and eventually allowed to react with a chiral amine B (either (*R*)-(–)- ($\mathbf{B^R}$) or (*S*)-(+)-2-aminobutane ($\mathbf{B^S}$)), present in the FT-ICR cell at defined concentrations.

Two products are exclusively formed: the addition $[M{\cdot}H{\cdot}N{\cdot}B]^+$ (B stands for either $\mathbf{B^R}$ or $\mathbf{B^S}$) and the guest exchange $[M{\cdot}H{\cdot}B]^+$ derivative. The time-dependent decay of the $[M{\cdot}H{\cdot}N]^+$ reactant was monitored by measuring its intensity (I) at any reaction time t relative to that at $t = 0$ (I^0), calculated as the sum of I and of the intensities of the addition (I_{add}) and guest exchange (I_{exc}) products. The dependence of $\ln[I/(I+I_{add}+I_{exc})]$ *vs* t is not linear, as expected for simple parallel or consecutive reaction patterns, but invariably exhibits a curvature towards an asymptotic limit, different for each system (Figure S1 of the ESI†). This behavior is consistent with the $[M{\cdot}H{\cdot}N]^+/[M{\cdot}H{\cdot}N{\cdot}B]^+$ ratio converging towards a constant value at long reaction times (Fig. 1).

Such a behaviour strongly supports the presence of a pseudo-equilibrium step in their reaction sequence. Since the neutral

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† Electronic supplementary information (ESI) available: Experimental Section. Kinetic results. Reaction mechanism. Kinetic equations. Table of results. See DOI: 10.1039/c0ob00664e

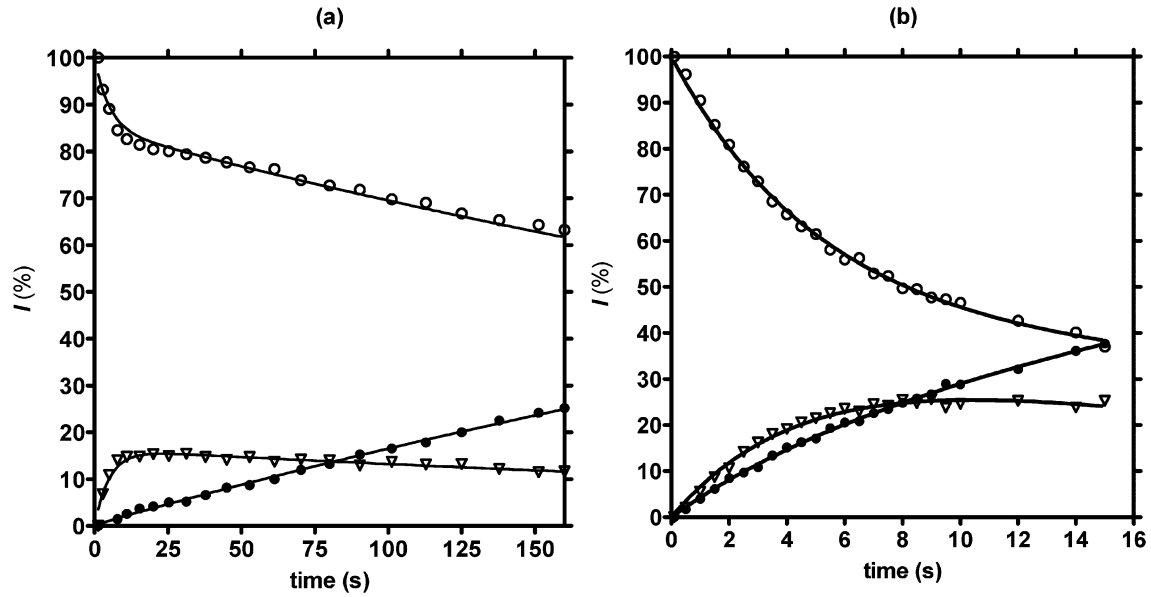

Fig. 1 Time-dependent relative abundances of $[M{\cdot}H{\cdot}N]^+$ (open circles), $[M{\cdot}H{\cdot}N{\cdot}B]^+$ (triangles), and $[M{\cdot}H{\cdot}B]^+$ (full circles) for the reactions between $\mathbf{B^S}$ and $[M{\cdot}H{\cdot}\mathbf{5}]^+$ (M = $\mathbf{1^R}$ (a); $\mathbf{1^S}$ (b)). The continuous lines represent the relative abundance of reactants and products calculated from the exact rate expressions for sequence (1) (see ESI†).

nucleoside N is completely absent in the FT-ICR reaction cell, the pseudo-equilibrium step must necessarily concern the reversible addition of B to $[M{\cdot}H{\cdot}N]^+$ to yield $[M{\cdot}H{\cdot}N{\cdot}B]^+$. It is concluded that all $[M{\cdot}H{\cdot}N]^+$ complexes follow the reaction sequence

$$[M\cdot H\cdot N]^+ + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [M\cdot H\cdot N\cdot B]^+ \xrightarrow{k_2} [M\cdot H\cdot B]^+ + N \quad (1)$$

Best fit of the experimental results with the exact rate expressions for each step of the reaction sequence (1) (see Figures S2–S15 and the kinetic equations in the ESI†) allows extraction of the kinetic constants k_1, k_{-1}, and k_2 (Table S1, ESI†). The second-order k_1 constants have been compared with the relevant collision rate constants (k_{coll}), calculated using the trajectory calculation method.[12] From this comparison, it results that less than 3.5% of the collisions between $[M{\cdot}H{\cdot}N]^+$ and B leads to the formation of the $[M{\cdot}H{\cdot}N{\cdot}B]^+$ addition complex (eqn (1).

Previous experimental studies[5,6] pointed out that the N guest in $[M{\cdot}H{\cdot}N]^+$ is proton bonded to one of the amidocarbonyls of the resorcin[4]arene host and that its loss requires a prototropic transfer from N to B. The appreciable effect of the configuration of both the host and the amine B strongly support the view that the nucleoside N resides inside the cavity of the host among its chiral pendants and that the amine B must enter the same cavity to displace the guest. Thus, the relatively inefficient addition of B to $[M{\cdot}H{\cdot}N]^+$ to yield $[M{\cdot}H{\cdot}N{\cdot}B]^+$ can be accounted for by the establishment of preliminary electrostatic interactions between the host pendants and B outside the host cavity. This view is supported by the $10^{11}k_1/k_{-1}$ ratios of Table 1 which increase in the guest order: **4** < **2** ≈ **5** < **3**, namely by increasing the electron withdrawing character of the substituents at the C2′ centre of the nucleoside (H,H < H,OH < F,F). Since the basicity of the nucleoside is expected to decrease in the order: **4** > **2** ≈ **5** > **3**, it follows that the fraction of positive charge on the host pendants and, therefore, the strength of the electrostatic interactions between them and B increase in the inverse guest order, as actually found.

Table 1 Rate Constant Ratios (eqn (1))

	$10^{11}k_1/k_{-1}$ (cm^3 molecule^{-1})		k_{-1}/k_2	
Complexes	B = $\mathbf{B^R}$	B = $\mathbf{B^S}$	B = $\mathbf{B^R}$	B = $\mathbf{B^S}$
$[\mathbf{1^R}{\cdot}H{\cdot}\mathbf{2}]^+$	2.4	0.5	4.6	21.5
$[\mathbf{1^S}{\cdot}H{\cdot}\mathbf{2}]^+$	1.1	0.9	7.6	12.7
$[\mathbf{1^R}{\cdot}H{\cdot}\mathbf{3}]^+$	18.4	23.4	6.2	5.3
$[\mathbf{1^S}{\cdot}H{\cdot}\mathbf{3}]^+$	4.3	7.6	22.2	4.1
$[\mathbf{1^R}{\cdot}H{\cdot}\mathbf{4}]^+$	$< 2\times10^{-3}$	$< 2\times10^{-3}$	$> 5\times10^3$	$> 5\times10^3$
$[\mathbf{1^S}{\cdot}H{\cdot}\mathbf{4}]^+$	0.5	0.5	25.1	24.4
$[\mathbf{1^R}{\cdot}H{\cdot}\mathbf{5}]^+$	1.8	2.4	43.1	70.1
$[\mathbf{1^S}{\cdot}H{\cdot}\mathbf{5}]^+$	6.4	9.8	1.3	2.1

Once formed, the $[M{\cdot}H{\cdot}N{\cdot}B]^+$ addition complex can either back dissociate to $[M{\cdot}H{\cdot}N]^+$ and B (k_{-1}) or rearrange to allow interaction between B and the protonated amidocarbonyls of the resorcin[4]arene host holding the leaving nucleoside N (k_2). Even though the first pathway invariably prevails over the latter one ($k_{-1}/k_2 > 1$; Table 1), the relative efficiency of the two competing steps still depends on the nature and the spatial orientation of the substituents at the C2′ centre of the nucleoside.

Indeed, with N = **5** as the guest, the k_{-1}/k_2 ratio from $[\mathbf{1^R}{\cdot}H{\cdot}\mathbf{5}]^+$ exceeds that from $[\mathbf{1^S}{\cdot}H{\cdot}\mathbf{5}]^+$ by *ca.* 40 times. By simply inverting the C2′ configuration (N = **2**), the k_{-1}/k_2 ratio does not depend much on the host configuration, but rather on the B configuration by increasing in passing from $\mathbf{B^R}$ to $\mathbf{B^S}$. With N = **3** as guest, the k_{-1}/k_2 ratio depends on both the host and the B configuration, thus indicating that the presence of two electron-withdrawing fluorine atoms in the 2′ position appreciably affects the activation free energies of the two competing pathways.

However, the more outstanding effect of the host configuration is observed for the complexes with N = **4**, as guest. Indeed, when the host is $\mathbf{1^R}$, no reaction products were observed even after 300 s reaction time and at a [B] = 7.4×10^9 molecule cm^{-3}, whereas, under the same conditions, the reaction involving $\mathbf{1^S}$ as host proceeded

Table 2 Supramolecular chiroselective "*logic gates*"

	Host	$\mathbf{1^R}$	$\mathbf{1^R}$	$\mathbf{1^S}$	$\mathbf{1^S}$
Input	Amine	$\mathbf{B^R}$	$\mathbf{B^S}$	$\mathbf{B^R}$	$\mathbf{B^S}$
	Guest, N				
Output	**2**	*low*	*high*	*low*	*high*
	3	*low*	*low*	*high*	*low*
	4	*high*	*high*	*low*	*low*
	5	*high*	*high*	*low*	*low*

to over 20%. Since the normal dynamic range of the FT-ICR is *ca.* 10^3:1, it can be concluded that the pseudo-equilibrium step involving $[\mathbf{1^R}\cdot H\cdot\mathbf{4}]^+$ (eqn (1)) is *ca.* 200 times more shifted towards the reactants ($k_1/k_{-1} < 2 \times 10^{-14}$ cm^3 molecule^{-1} and $k_{-1}/k_2 > 5 \times 10^3$) than that involving $[\mathbf{1^S}\cdot H\cdot\mathbf{4}]^+$ ($k_1/k_{-1} = 5 \times 10^{-12}$ cm^3 molecule^{-1} and $k_{-1}/k_2 \sim 25$). This means that the $[\mathbf{1^R}\cdot H\cdot\mathbf{4}]^+$ complex is inert towards B, whereas the same amine B can efficiently add to the $[\mathbf{1^S}\cdot H\cdot\mathbf{4}]^+$ diastereoisomer and displace the nucleoside from it.

Thus, the diastereomeric complexes of Table 1 behave as supramolecular devices which, depending upon the configuration of both the macrocycle and the amine B, can or cannot release the nucleoside. In particular, the $[\mathbf{1^R}\cdot H\cdot\mathbf{4}]^+$ and $[\mathbf{1^S}\cdot H\cdot\mathbf{4}]^+$ systems can be regarded as the first example of gas-phase supramolecular "*logic gate*" that, in the presence of a suitable reactant (B), can selectively release one enantiomer of a chiral guest and keeping bound the other enantiomer (Fig. 2 and Table 2). This view can be somewhat extended to the other complexes investigated, although in this case the adverb "selectively" must be replaced by "preferentially".

In conclusion, the present gas-phase results provide a first example of selective release of biomolecules from chiral supramolecular systems (bio-"*logic gates*"). Assessment of the factors governing the process may be a starting point for understanding controlled drug delivery from chiral molecular carriers.

Acknowledgements

Work supported by the Ministero dell'Istruzione dell'Università e della Ricerca (MIUR-PRIN-2007H9S8SW) and the Consiglio Nazionale delle Ricerche (CNR). Research grant from Fondazione Roma (Italy) to B.B. is gratefully acknowledged.

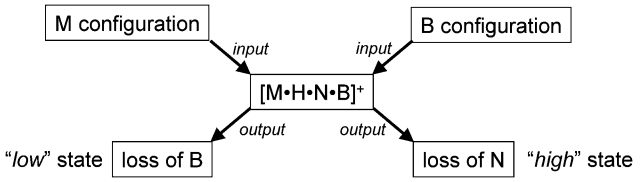

Fig. 2 "*Logic gate*" is a term borrowed from electronics where it represents an elementary building block of a digital circuit. Most logic gates have two inputs and one output. At any given moment, every terminal is in one of the two binary conditions *low* (0) or *high* (1), represented by different voltage levels. Extending the concept to the present systems, the two inputs are the configuration of the macrocycle M and of the amine B and the output is either the loss of B (relatively large k_{-1}/k_2; *high* state) or the loss of nucleoside N (relatively small k_{-1}/k_2; *low* state) from the $[M\cdot H\cdot N\cdot B]^+$ "*logic gates*"(Table 1).

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9 *Cytidine*: 4-amino-1-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-furan-2-yl)-1H-pyrimidin-2-one.
10 *Cytarabine*: 4-amino-1-[(2R,3S,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)-tetrahydro-furan-2-yl]-1H-pyrimidin-2-one.
11 *Gemcitabine*: 4-amino-1-((2R,4R,5R)-3,3-difluoro-4-hydroxy -5-hydroxymethyl-tetrahydro-furan-2-yl)-1H-pyrimidin-2-one.
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