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Bis(diamido)-Bridged Basket Resorcin[4]arenes as Enantioselective Receptors for Amino Acids and Amines

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On the research avenue opened by the rigidified double-spanned resorcin[4]arene **1**, we have synthesized both enantiomers of the two chiral basket resorcin[4]arenes **3** and **4**, each containing two 1,2-diaminocyclohexane and 1,2-diphenylethylenediamine bridges, respectively. In the new compounds, the aromatic rims assume the expected *flattened cone* arrangement, whereas two different conformations, tentatively designated as "open wings" and "folded wings", were attributed to the bridge substituents according to molecular modeling studies. In MS^n (ESI) experiments, the proton-bonded diastereomeric $[\mathbf{4}\cdot H\cdot A]^+$ complexes with amino acidic guests (A) exhibited a pronounced selectivity towards the enantiomers of tyrosine methyl ester (tyr^{OMe}) and amphetamine (amph), whereas the chirality of tryptophan (trp) was ineffective. Moreover, a kinetic study on the base-induced displacement of the guest revealed that the L-tyr^{OMe} (and L-amph) enantiomer is faster displaced from the heterochiral $[\mathbf{4}\cdot H\cdot L\text{-}tyr^{OMe}]^+$ (or $[ent\text{-}\mathbf{4}\cdot H\cdot L\text{-amph}]^+$) complex than from the homochiral $[ent\text{-}\mathbf{4}\cdot H\cdot L\text{-}tyr^{OMe}]^+$ (or $[\mathbf{4}\cdot H\cdot L\text{-amph}]^+$) one.

Introduction

The knowledge of the geometrical positioning and of the manner of interaction of a biomolecule in a receptor cavity is the key for understanding the origin of the amazing selectivity and efficiency of enzyme catalysis.[1a,1b] Biomolecules are often chiral and many biochemical processes show preference for one enantiomer over the other. Chiral recognition, one of the most sophisticated functions of enzymes, motivated chemists to design hosts to be used for enantioselective reactions.[1c,1d] Among various molecular platforms that can be proposed for the construction of such receptors, macrocycles of multiple aromatic units have widely been used. Calixarenes,[2] cavitands[3] such as resorcinarenes,[4] and cyclophanes[5] have largely been studied over the last two decades.

Several chiral calixarenes have been synthesized,[6,7] but just a few of them have shown good chiral recognition properties. Recently, chiral calix[4]arenes bearing optically pure aminol groups[8a] and a 1,2-diphenyl-1,2-oxyamino residue[8b] at the lower rim showed exceptional chiral recognition properties for carboxylic acids. Lower rim bis(urea) calix[4]arene-based receptors have just been described with remarkable enantioselective binding ability for *N*-acetylphenylalaninate and *N*-acetylalaninate anions.[8c]

We have shown that ethereal BF_3 catalyzes the tetramerization of (*E*)-2,4-dimethoxycinnamic acid derivatives to the corresponding resorcin[4]arene octamethyl ethers,[9] which are macrocycles with a cavity-shaped flexible architecture. With the aim to build rigidified hosts and to compare their recognition ability with that of the parent more-flexible macrocycle, we prepared preorganized double-spanned resorcin[4]arenes, such as **1** (Figure 1), by the insertion of two polymethylene bridges,[10] resembling a basket. Following this research, here we report the synthesis of chiral basket resorcin[4]arenes **3** and **4** (Figure 1) starting from the common ethyl tetraester resorcin[4]arene precursor **2**, already described.[9a] Molecular modeling (MM) conformational studies of the new compounds and preliminary molecular recognition studies by electrospray ionization mass spectrometry [MS (ESI)] in the gas phase of compound **4** were also performed.

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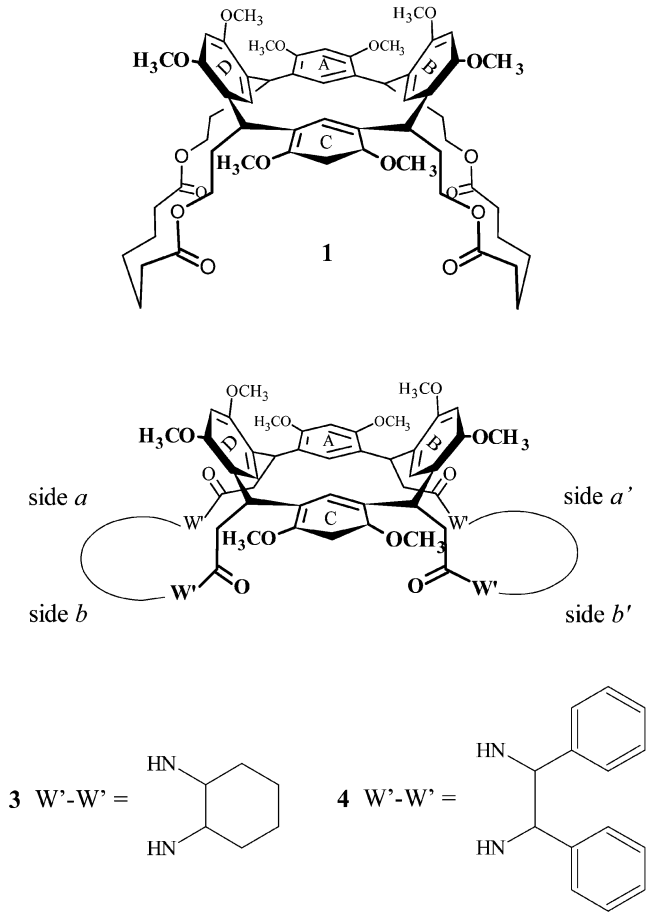
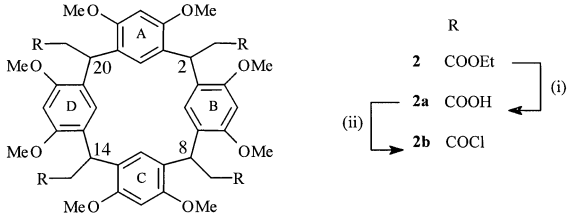


Figure 1. Chemical structures of a basket resorcin[4]arene with two polymethylene bridges (**1**)[10] and of chiral basket resorcin[4]arenes **3** and **4**.

Results and Discussion

Synthesis and NMR Spectroscopic Analysis

Resorcin[4]arene octamethyl ether tetraester **2** (*cone* conformation), obtained as described previously,[9a] was hydrolyzed by treatment with NaOH (2 N in ethanol solution), and the corresponding tetraacid **2a** was quantitatively converted into the tetrachloride derivative **2b** by reaction with thionyl chloride (Scheme 1). Treatment of highly diluted dry THF solutions of **2b** with diisopropylethylamine (DIPEA) and then with (1*R*,2*R*)-(–)-1,2-diaminocyclohexane (DACH) under an atmosphere of nitrogen afforded compound **3** (Scheme 2, 35% yield relative to **2b**). The same synthetic procedure with (1*S*,2*S*)-(+)-1,2-diaminocyclohexane gave *ent*-**3** (36% yield, with opposite $[a]_D$ and coincident NMR/MS spectroscopic data).



Scheme 1. Reagents and conditions: (i) 2 N NaOH, EtOH, reflux, 4 h, glacial AcOH; (ii) thionyl chloride, dry benzene, reflux, 4 h.

To check the general applicability of the synthetic procedure, tetrachloride derivative **2b** was treated with (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (DPEDA) under

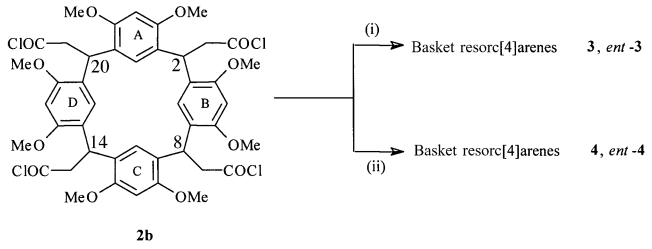
Table 1. ^{13}C and ^{1}H NMR data for chiral basket resorcin[4]arenes **3** and **4**.

Position/Type	Chiral basket resorcin[4]arenes **3**[a]		Chiral basket resorcin[4]arenes **4**[b]	
	$\delta\{^{13}C\}$ [ppm]	$\delta\{^{1}H\}$ [ppm], mult. (*J* [Hz])	$\delta\{^{13}C\}$ [ppm]	$\delta\{^{1}H\}$ [ppm], mult. (*J* [Hz])
C=O	174.65; 172.53	–	174.72; 171.65	–
4,16; 6,18	156.58; 157.48	–	157.34; 156.62	–
10,22; 12,24	156.24; 155.05		155.98; 154.88	
25,27	126.77	5.96, s	126.42	6.00, s
26,28	126.38	6.92, s	126.24	7.07, s
1,13; 3,15;	125.43; 124.53	–	125.15; 124.30	–
5,17; 9,21	121.72; 121.59		121.40×2	
11,23	97.85	6.13, s	97.81	6.22, s
7,19	94.82	6.49, s	94.51	6.46, s
CH–N (*b*)	57.23	2.99, tdd (11, 6.5, 4)	60.27	4.90, dd (11, 7.5)
CH–N (*a*)	51.48	3.86, m (Σ 34.5)	58.09	5.43, dd (11, 8)
OCH_3	56.21×2	3.94, s; 3.90, s	55.93×2	3.86, s; 3.85, s
	55.93; 55.55	3.52, s; 3.24, s	55.80; 55.34	3.57, s; 3.29, s
H–C–H (*b*)	41.85	3.27, dd (14, 5)	41.69	3.24, dd (14, 5.5)
		2.22, dd (14, 12.5)		2.39, dd (14.5, 12.5)
H–C–H (*a*)	40.30	2.94, dd (17, 4)	40.09	3.00, dd (17, 4)
		2.69, dd (17, 13.5)		2.83, dd (17, 13)
8,20 (*b*)	33.69×2	5.03, dd (12.5, 5)	33.49	5.09, dd (12.5, 5)
2,14 (*a*)	–	4.60, dd (13.5, 4)	33.27	4.66, dd (13, 4)
N–H (*a*)	–	6.82, d (6, 5)	–	7.62, d (7, 5)
N–H (*b*)	–	5.49, d (8, 5)	–	5.97, d (8, 2)

[a] Other signals for **3**: $C_4(H_8)$: δ = 32.71, 31.73, 25.38, 24.34 (CH_2) ppm; $(C_4)H_8$: δ = 1.58 (m, 4 H), 1.24 (m, 4 H) ppm. [b] Other signals for **4**: δ = $C_6(H_5)$: 140.05, 137.40 (C-1′); 128.79×2, 128.08×4, 127.57×2 (C-2′, C-3′, C-5′, C-6′); 128.20, 127.11 (C-4′); $(C_6)H_5$: 7.20–7.01 (m, 5 H) ppm.

Table 2. DIF NOE experiments on chiral basket resorcin[4]arenes **3** and **4**.

	Chiral basket resorcin[4]arenes **3**		Chiral basket resorcin[4]arenes **4**	
	Irradiated proton	Enhancement	Irradiated proton	Enhancement
NH (*a*)	6.82	3.86 CHN (*b*); 2.22 CH_2 (*b*)	7.62	7.07 H_i (26,28); 5.43 CHN (*a*) > 4.90 CHN (*b*)
CH (*a*)	4.60	5.49 NH (*b*); 2.94 H_A-CH (*a*)	4.66	5.97 NH (*b*)
NH (*b*)	5.49	3.86 CHN (*b*); 4.60 CH (*a*); 6.92 H_i (26,28)	–	–
H_B-CH (*a*)	2.69	2.94 H_A-CH (*a*); 6.92 H_i > 5.96 H_i; 4.60 CH (*a*)	2.39	7.62 NH (*a*); 7.07 H_i (26,28); 3.24 H_A-CH (*a*)
H_B-CH (*b*)	2.22	3.27 H_A-CH (*b*); 6.92 H_i > 6.82 NH (*b*)	–	–
H_A-CH (*b*)	3.27	2.22 H_A-CH (*b*); 5.03 CH (*b*)	–	–
CHN (*a*)	–	–	5.43	7.07 H_i (26,28); 7.62 NH (*a*); 4.90 CHN (*b*)
CH (*b*)	–	–	5.09	3.57 OMe > 3.85 OMe
H_e (11,23)	–	–	6.22	3.57 OMe; 3.29 OMe



2b

Scheme 2. Reagents and conditions: (i) DIPEA, dry THF, 1,2-DACH, reflux, 3 h; (ii) DIPEA, dry THF, 1,2-DPEDA, reflux, 3 h.

the same experimental conditions to give chiral basket resorcinarene **4** (Scheme 2, 31% yield relative to **2b**).

Analogously, *ent*-**4** (29% yield) with opposite $[\alpha]_D$ and identical NMR/MS spectroscopic data to that of **4** was prepared from **2b** and (1*S*,2*S*)-(–)-1,2-diphenylethylenediamine.

At a first sight, the ^1H and ^{13}C NMR spectra of **3** and **4** (see Table 1) exhibit a close similarity to those of **1**.[10] These compounds are characterized by a *flattened cone* distribution of the aromatic rings and bridged side chains (from C2 to C8 and C14 to C20) surrounding the two vis a vis aromatic rings (*B* and *D*). Because of the presence of the two chiral centers and the restricted rotation of the methylene protons, the *a* and *b* sides of the bridge are not symmetrical with respect to the *B*/*D* aromatic rings. The chemical shifts of the H_i and H_e protons are not influenced by this disposition: for instance, H-25 and H-27 are superimposable after a 180° rotation of the molecule around a C_2 axis, that is to say, C-25 and C-27 are like enantiomeric carbon atoms. This is not valid for the methoxy groups and the pairs of equivalent OMe protons on C4/C16, C6/18, C10/C22, and C12/C24, which give four (6 H) signals.

DIF NOE experiments (Table 2) revealed that the NH (*a*) proton of the methylene unit lies to the *b* side, which suggests that the low-field value of the signal is caused by H-bonding with the C=O (*b*) carbonyl group (notice also the ^{13}C NMR different resonances of the carbonyl groups). Conversely, irradiation of the signal for the NH (*b*) proton revealed the proximity of the H_i (26,28) and CH (*a*) protons and confirmed a distorted arrangement of the double chain wings. The NH signals appear slightly high-field in the ^1H NMR spectrum of **4**, probably because of a different influence of the flattened aromatic (*A*/*C*) rings.

Molecular Modeling

Computational studies, performed by means of the MacroModel/Maestro software package[11] equipped with Amber* force field[12] confirmed the experimental findings and allowed evaluation of both the shape and rigidity of the two basket resorcin[4]arenes **3** and **4**. Three types of molecular simulations were carried out during the calculations: interactive structure building with partial point-charge calculations, geometry optimization, and conformational searching.

A refined 3D structure, obtained from previous studies,[9a] was utilized as an input geometry for the resorcin[4]-arene *nucleus*, whereas the two pairs of joint chains (wings) of each compound were manually built in Maestro by the BUILD tool. To deal with the structural complexity of **3** and **4** (both possessing 14 rotatable bonds), statistical methods of conformational search and molecular dynamics (MD) simulations at 300 K were employed. Access to the conformations of both compounds populated in chloroform solution was gained by using two Monte Carlo statistical analysis methodologies: the MCMM (Monte Carlo multiple minimum search)[13] and the MCMM/LMCS (a mixed-mode procedure, combining MCMM with the low mode conformational search),[14] together with the constant temperature stochastic dynamics (SD).[15] The combination of the two Monte Carlo protocols with the SD simulations was aimed at ensuring a complete and reasonably homogeneous sampling of the whole potential-energy hypersurface of the systems by taking into account dynamic and entropic effects. Indeed, the time evolution of the molecular motions of **3** and **4** was expected to provide a dynamic picture of the two compounds. Moreover, as energy minimizations in molecular mechanics give steric energies corresponding to enthalpies at 0 K, constant-temperature SD simulations are more appropriate to obtain average enthalpies at 300 K for large and flexible systems.

Structure and Conformations of Basket Resorcin[4]arene 3

The Monte Carlo conformational search revealed a quite narrow spectrum for **3**; six minima (low-energy conformers) within 20.0 kJ mol^{-1} above the global minimum were found. The conformations populated at 300 K, according to a

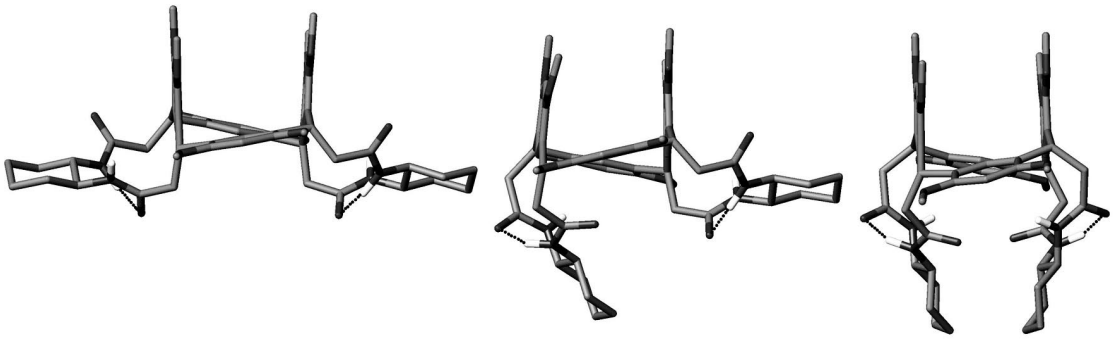


Figure 2. Lowest energy conformers of basket resorcin[4]arene **3** from MCMM and MCMM/LCMS calculations. Left to right **3a**, **3b**, and **3c** (in order of increasing energy).

Boltzmann distribution, were filtered to afford three families of conformers. The lowest-energy member of each family (hereafter named respectively **3a**, **3b**, and **3c**) is depicted in Figure 2 from left to right in order of increasing energy. All the geometries show a slight distortion of the resorcin[4]arene *nucleus*, which is probably due to the chirality and to the resulting asymmetric orientation of the joint chains. In all cases, both cyclohexane rings adopt the energetically favored *chair* geometry, whereas one hydrogen bond is formed within each wing between the carbonyl group of one side chain and the NH functionality of the other one (vide supra). In **3a** (steric energy = –273.4 kJ mol^{-1}), the four aromatic rings lie in a *flattened cone* conformation as in nonchiral baskets such as **1**;[10] both the joint chains are extended outwards in an arrangement tentatively designated as "open wings". In contrast, in **3c** (steric energy = –256.1 kJ mol^{-1}) both the substituents point downwards in a "folded wings" conformation. Finally, in the mixed conformation of **3b** (steric energy = –264.7 kJ mol^{-1}) one wing is outwards and the other downwards ("mixed wings").

SD simulations performed at 300 K and starting from the three minima **3a**, **3b**, and **3c** allowed the identification of the most populated conformation of **3** in solution by comparison of their average enthalpies. Geometries **3a**, **3b**, and **3c** showed enthalpy values roughly equal to 168, 177, and 184 kJ mol^{-1}, respectively. As a result, the lowest enthalpy SD geometry and the Monte Carlo global minimum matched perfectly, and the **3a** conformation can be considered as the most likely 3D structure of **3** in chloroform.

Structure and Conformations of Basket Resorcin[4]arene 4

The conformational search of **4** revealed a conformational spectrum broader than **3**, and 34 low-energy conformers within 20.0 kJ mol^{-1} above the global minimum were found, which highlighted a larger flexibility of this molecule. Again, three families of conformers were collected after filtration. The lowest-energy member of each family (hereafter named **4a**, **4b**, and **4c**) is depicted in Figure 3 from left to right in order of increasing energy. The three geometries of **4** showed similar features to those of **3**, such as the slight distortion of the resorcin[4]arene *nucleus* and the H-bonding interactions, whereas the phenyl pendants assume a roughly parallel equatorial orientation two by two. Analogous to geometries **3a**–**c**, **4a** (steric energy = –240.5 kJ mol^{-1}), **4b** (steric energy = –233.1 kJ mol^{-1}), and **4c** (steric energy = –232.6 kJ mol^{-1}) were designated as "open wings", "mixed wings", and "folded wings" conformations, respectively. In conclusion, the Monte Carlo search at 0 K depicted a conformational scenario for **4** that is comparable to **3**. SD simulations for both **4b** and **4c** gave steadily constant enthalpy values roughly equal to 271 kJ mol^{-1} at 300 K and did not show interconversion during the runs. In contrast, in the case of **4a**, the initial enthalpy value of ca. 268 kJ mol^{-1} decreased by a few

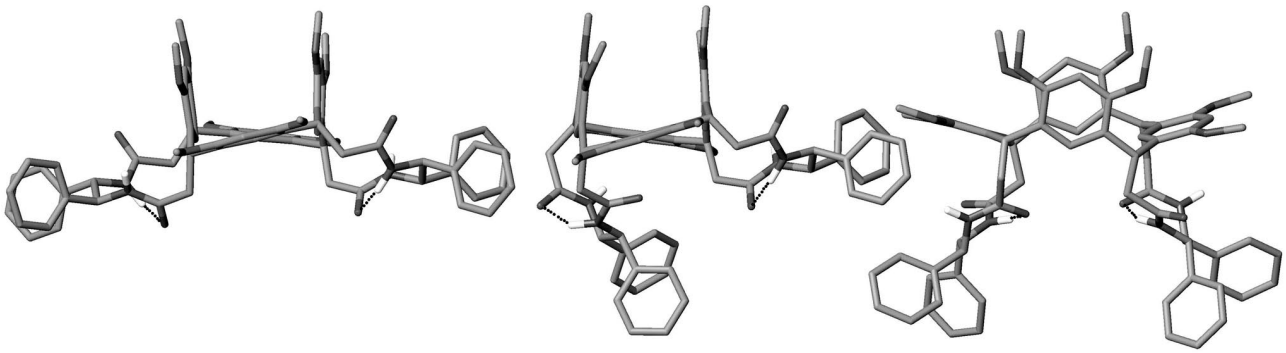


Figure 3. Lowest energy conformers of basket resorcin[4]arene **4** from MCMM and MCMM/LCMS calculations. Left to right **4a**, **4b**, and **4c** (in order of increasing energy).

kJ mol^{-1} during the simulation. Notably, the enthalpy change was accompanied by the irreversible conversion of **4a** into a conformation of the **4c** family through a change in the orientation of the *flattened cone* that brought the aromatic *A*/*C* rings face to face. The distance between two dummy atoms, each one corresponding to the center of the bond connecting the two phenyl-substituted carbon atoms of each wing, was estimated during the SD run to testify the occurrence of such an event. Figure 4 gives signs of the irreversible conversion of **4a** into **4c** after about 1200 ps (300 frames), which culminates into the matching between the lowest enthalpy SD geometry in solution of **4** and the Monte Carlo minimum **4c**. The low steric energy difference between the Monte Carlo minima **4a** and **4c** (less than 3.0 kcal mol^{-1} at 0 K), and the irreversible conversion of the former input structure into the latter during the SD run at 300 K supports the **4c** geometry as the most likely 3D structure of **4** in chloroform.

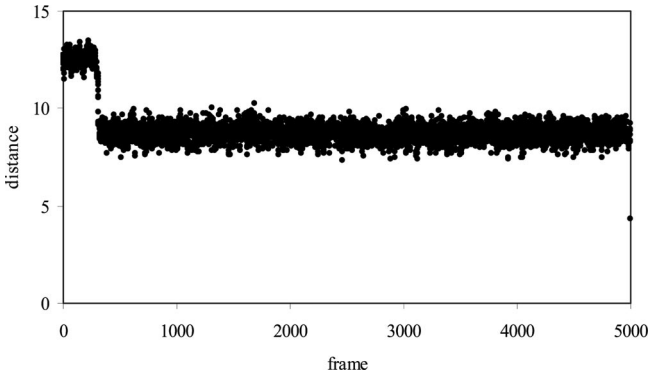


Figure 4. Distance between two dummy atoms corresponding to the center of the bond connecting the two phenyl-substituted carbon atoms of each wing estimated during the SD run for **4a**.

Mass Spectrometry

Some insights into the molecular recognition of basket resorcin[4]arene **4** towards representative chiral molecules were gathered in the gas phase by MS (ESI) experiments.[16] For this purpose, the proton-bonded diastereomeric [**4**·H·A]$^+$ complexes [A = tyrosine methyl ester (tyr^{OMe}), tryptophan (trp), or amphetamine (amph); see Figure 5] were generated in the source of an ion-trap mass spectrometer, and their collision-induced decomposition (CID) spectra were investigated. A common feature of the CID fragmentation spectra is the exclusive observation of the [**4**·H]$^+$ fragment at any collision energy employed (10–25 eV, lab frame), which indicates that the gas-phase basicity of host **4** largely exceeds that of all the A guests used.

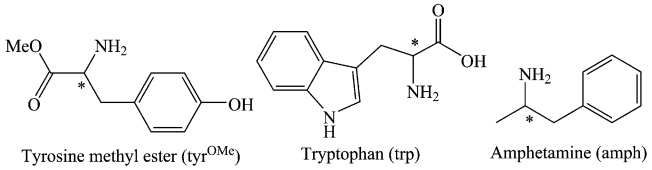


Figure 5. Chemical structures of chiral guests A.

In the 15-eV CID spectra of the proton-bonded diastereomeric [**4**·H·trp]$^+$ complexes (*m*/*z* = 1389), no significant effects of the configuration of the amino acidic guest was observed (Figure S1, Supporting Information). In contrast, resorcin[4]arene **4** exhibited an appreciable selectivity towards the enantiomers of tyr^{OMe} (Figure S2, Supporting Information) and amph (Figure S3, Supporting Information). In particular, the 15-eV CID spectra of the diastereomeric [**4**·H·tyr^{OMe}]$^+$ adducts (*m*/*z* = 1380) were characterized by a [**4**·H]$^+$/[**4**·H·trp]$^+$ abundance ratio that strongly decreased from the heterochiral [**4**·H·L-tyr^{OMe}]$^+$ complex (2.26) to the homochiral [**4**·H·D-tyr^{OMe}]$^+$ one (0.72). In contrast, the 15-eV CID spectra of the diastereomeric [**4**·H·amph]$^+$ complexes (*m*/*z* = 1320) exhibited a [**4**·H]$^+$/[**4**·H·amph]$^+$ ratio that slightly increased on going from the heterochiral [**4**·H·D-amph]$^+$ (0.36) to the homochiral [**4**·H·L-amph]$^+$ adduct (0.75). These findings lend support to the view that the homochiral [**4**·H·D-tyr^{OMe}]$^+$ complex is significantly more stable than its heterochiral counterpart. The reverse is true for the [**4**·H·amph]$^+$ diastereomers, whereas the [**4**·H·trp]$^+$ ones are essentially degenerate.

To verify whether the relative stabilities of the diastereomeric [**4**·H·tyr^{OMe}]$^+$ and [**4**·H·amph]$^+$ complexes are mirrored by their kinetic enantioselectivity, we carried out a detailed kinetic study on their base-induced displacement reaction [Equation (1)], which took place in the cell of an electrospray ionization fourier-transform ion cyclotron resonance mass spectrometer [FTICR (ESI)] filled with the enantiomers of 2-aminobutane (B) kept at a constant partial pressure (P_B).

$$[M{\cdot}H{\cdot}A]^+ + B \rightarrow A + [M{\cdot}H{\cdot}B]^+ \quad (1)$$

Figures 6 and 7 summarize the relevant kinetic plots, where *I* is the intensity of the [M·H·A]$^+$ complex (M = **4** or *ent*-**4**; A = L-tyr^{OMe} and L-amph, respectively) at the delay time *t* and I_0 is the sum of the intensities of the [M·H·A]$^+$ and [M·H·B]$^+$ adducts. The pseudo-first-order rate constants *k*′ of Equation (1) were obtained from the slopes of the kinetic curves of Figures 6 and 7. The values of the corresponding second-order rate constants, $k = k'/[B]$, are listed in Table 3 together with the relevant reaction efficiencies (eff) calculated from the ratio between *k* and the collision rate constant (k_{coll}).[17] The enantioselectivity is defined by $\rho = k_{homo}/k_{hetero}$, when referred to the configuration of the M/A pair, or by $\xi = k_R/k_S$, when referred to the configuration of the amine B. The $\rho < 1$ values indicate that the amine B displaces the guest L-tyr^{OMe} (or L-amph) faster from the heterochiral [**4**·H·L-tyr^{OMe}]$^+$ (or [*ent*-**4**·H·L-amph]$^+$) complex than from the homochiral [*ent*-**4**·H·L-tyr^{OMe}]$^+$ (or [**4**·H·L-amph]$^+$) one. The reverse is true for values $\rho > 1$. A $\xi < 1$ value indicates that the displacement of the A guest is faster with the (*S*)-amine (B_S) than with the (*R*)-amine (B_R). The reverse is true with $\xi > 1$.

The results of Table 3, in particular the ρ and ξ terms diverging from unity, indicate that the kinetics of the gas-phase displacement is found to depend on the nature and the configuration of the guest A and the configuration of

Table 3. Exchange rate constants ($k \times 10^{-10}$ cm^3 molecule^{-1} s^{-1}).

Host	Guest	(*R*)-(–)-2-butylamine			(*S*)-(+)-2-butylamine			
		k	eff	$\rho = k_{homo}/k_{hetero}$	k	eff	$\rho = k_{homo}/k_{hetero}$	$\xi = k_R/k_S$
4	L-tyr^{OMe}	1.20 ± 0.01	0.10	0.93 ± 0.03	1.35 ± 0.03	0.11	0.78 ± 0.04	0.89 ± 0.03
ent-**4**	L-tyr^{OMe}	1.12 ± 0.02	0.09		1.06 ± 0.02	0.09		1.06 ± 0.04
4	L-amph	1.34 ± 0.05	0.11	1.26 ± 0.09	1.07 ± 0.03	0.09	0.91 ± 0.06	1.25 ± 0.09
ent-**4**	L-amph	1.06 ± 0.02	0.09		1.17 ± 0.04	0.10		0.91 ± 0.05

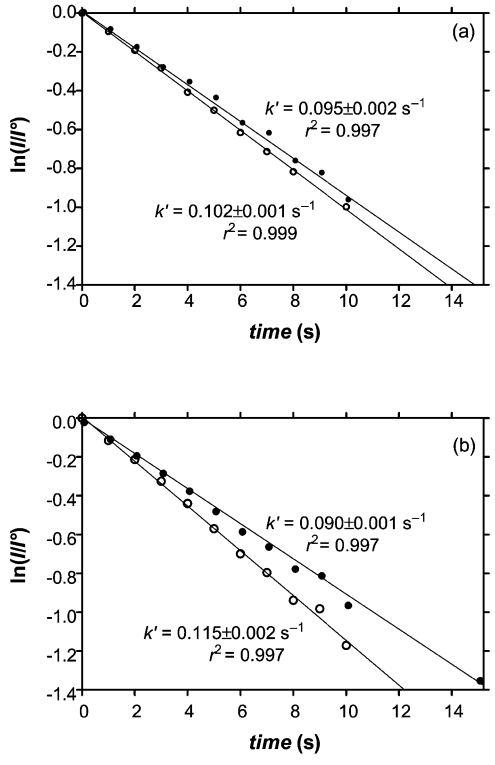


Figure 6. (a) Kinetic plots for the gas-phase reaction between (*R*)-(–)-2-butylamine ($P_B = 4.6 \times 10^{-8}$ mbar) and [**4**·H·L-tyr^{OMe}]$^+$ (open circles) or [*ent*-**4**·H·L-tyr^{OMe}]$^+$ (full circles); (b) kinetic plot for the gas-phase reaction between (*S*)-(+)-2-butylamine ($P_B = 4.6 \times 10^{-8}$ mbar) and [**4**·H·L-tyr^{OMe}]$^+$ (open circles) or [*ent*-**4**·H·L-tyr^{OMe}]$^+$ (full circles).

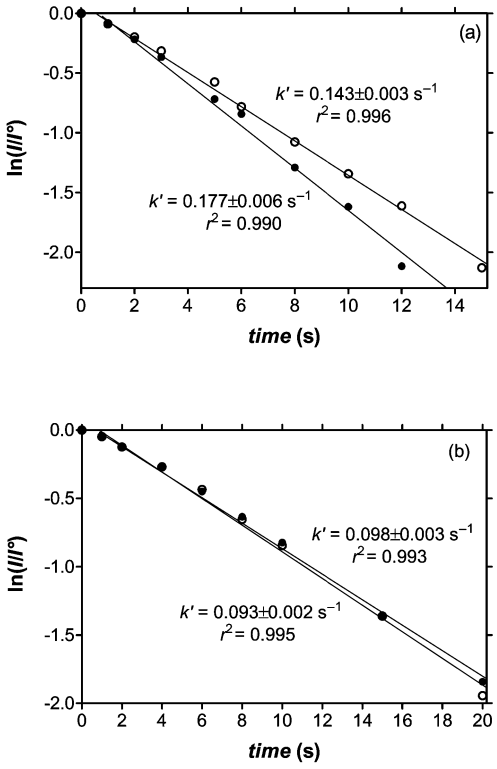


Figure 7. (a) Kinetic plots for the gas-phase reaction between (*R*)-(–)-2-butylamine ($P_B = 7.2 \times 10^{-8}$ mbar) and [*ent*-**4**·H·L-amph]$^+$ (open circles) or [**4**·H·L-amph]$^+$ (full circles); (b) kinetic plot for the gas-phase reaction between (*S*)-(+)-2-butylamine ($P_B = 4.7 \times 10^{-8}$ mbar) and [*ent*-**4**·H·L-amph]$^+$ (open circles) or [**4**·H·L-amph]$^+$ (full circles).

the B amine. Thus, the diastereomeric [**4**·H·tyr^{OMe}]$^+$ complexes invariably exhibit $\rho < 1$ values, which is in qualitative agreement with the stability trend of the diastereomeric [**4**·H·tyr^{OMe}]$^+$ complexes (homo > hetero). In contrast, the diastereomeric [**4**·H·amph]$^+$ complexes do not follow an univocal trend, as they display $\rho > 1$ factors in the reaction with B_R and $\rho < 1$ factors in that with B_S. This opposite enantioselectivity is reflected in the corresponding ξ terms, which exhibit a $\xi < 1$ value with the heterochiral complex and a $\xi > 1$ value with the homochiral one. This picture confirms the view that the enantioselectivity of Equation (1) with [**4**·H·amph]$^+$ is essentially kinetic. It is governed by the effects of the resorcin[4]arene frame upon the transition structures involved in the displacement reaction, whereas the relative stability of the diastereomeric [**4**·H·amph]$^+$ complexes plays only a minor role.

Conclusions

If the previously synthesized basket resorcin[4]arene **1** is taken as a model, the resorcin[4]arene precursor **2b** was rigidified by the introduction of two bridges built by reaction of the acid chloride functionalities of two adjacent substituents with *trans*-1,2-diaminocyclohexane or 1,2-diphenylethylendiamine. The *ent* forms of the synthetic resorcinarenes with satisfactory $[\alpha]_D$ values were also prepared. The investigation by MM on the possible conformation produced a series of low-energy conformers, where the aromatic rings are arranged in a *flattened cone* form, as suggested by the distribution pattern of the signals in the NMR spectra. H-bonding between the carbonyl group and the opposite NH drives the two bridges to different asymmetric frameworks, which were designated as "open", "mixed", and "folded wings". Notably, the two different "open" and

"folded wings" orientations were attributed by calculations to **3** and **4**, respectively. Examination of the CID spectra of the proton-bonded diastereomeric $[M{\cdot}H{\cdot}A]^+$ complexes between **4** and a number of chiral guests A led to the conclusion that the host had a pronounced selectivity towards the enantiomers of some guests (tyr^{OMe}, amph), but was unaffected by the chirality of others (trp). The homochiral complex $[\mathbf{4}{\cdot}H{\cdot}\text{D-tyr}^{OMe}]^+$ was more stable than its heterochiral counterpart, but the opposite was true for the $[\mathbf{4}{\cdot}H{\cdot}\text{amph}]^+$ complexes. In spite of their similar thermodynamic stabilities, a detailed kinetic study of the their base-induced replacement reactions revealed that the $[M{\cdot}H{\cdot}A]^+$ complexes undergo an enantioselective loss of the guest governed by the effects of the chiral conformation of the resorcinarene architecture

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectra were recorded at 400 and 75 MHz, respectively (TMS = 0 ppm as internal standard in $CDCl_3$ solutions). Mass spectra (MS) were obtained with a Thermo Finnegan LCQ Deca XP-Plus ion-trap mass spectrometer equipped with an electrospray ionization (ESI) source. Conditions as follows: source voltage = +5.0 kV, sheath gas = 25 AU (Arbitrary Units), auxiliary gas = 10 AU, capillary voltage = +40.0 V, capillary temperature = 200 °C, tube lens offset = +15 V. The FTICR experiments were performed with an APEX III (7 T Magnet) FTICR mass spectrometer equipped with an Apollo ESI source (Bruker Daltonik GmbH, Bremen). Optical rotations were measured with a Jasco P-1030 polarimeter.

Resorcin[4]arene Tetraacid 2a: Compound **2** (1.6 g, 1.7 mmol), synthesized as described previously,[9a] was dissolved in EtOH (10 mL), and 2 N NaOH (1.2 g, 30 mmol) was added (5 mL). The reaction mixture was stirred for 4 h at reflux. EtOH was removed in vacuo, and the aqueous solution was acidified with glacial acetic acid. The precipitate was filtered, rinsed several times with water, and dried to give **2a** in a quantitative yield. ^1H NMR (400 MHz, $CDCl_3$, 298 K): δ = 9.57 (br. s, 1 H, COOH), 6.52 (s, 4 H, H_i), 6.30 (s, 4 H, H_e), 4.95 (t, J = 7.0 Hz, 4 H, CH), 3.63 (s, 24 H, OMe), 2.78 (d, J = 7.0 Hz, 8 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 175.86 (COOH), 156.03 (C-O), 125.88 (CH_i), 123.99 (C-C), 96.28 (CH_e), 55.89 (OMe), 36.25 (CH_2), 33.01 (CH) ppm.

Resorcin[4]arene Tetrachloride (2b): $SOCl_2$ (2.4 mL, 33 mmol) was added under an atmosphere of nitrogen to a solution of **2a** (0.15 g, 0.18 mmol) in dry benzene (15 mL). The reaction mixture was heated at reflux whilst stirring for 4 h and allowed to stand at room temperature overnight. Final evaporation in vacuo under an atmosphere of nitrogen gave **2b** as a solid in a quantitative yield.

Basket Bis(diamidocyclohexane) Resorcin[4]arene 3: Diisopropylethylamine (DIPEA; 0.062 mL, 0.36 mmol) was added to a solution of **2b** (0.054 g, 0.06 mmol) in dry THF (5 mL), and the mixture was stirred at room temperature for about 20 min. A solution of (1*R*,2*R*)-(–)-1,2-diaminocyclohexane (0.020 g, 0.18 mmol) in dry THF (5 mL) was then added dropwise over 1.5 h. The mixture was stirred and heated at reflux for 3 h. Standard workup and purification (silica gel; $CHCl_3$/MeOH, 97:3) afforded **3** (0.021 g, 35%) as a vitreous solid. $[\alpha]_D^{20}$ = –2.45 (c = 0.20, $CHCl_3$). ^1H and ^{13}C NMR signals as in Table 1. MS (ESI+): m/z = 1012.2 $[M + Na]^+$. $C_{56}H_{68}N_4O_{12}$ (989.17): calcd. C 68.00, H 6.93, N 5.66; found C 68.20, H 6.95, N 5.68.

***ent*-3:** Treatment of **2b** with (1*S*,2*S*)-(+)-1,2-diaminocyclohexane under the same conditions as those used for the preparation of **3** afforded *ent*-**3** (0.021 g, 36%) as a vitreous solid. $[\alpha]_D^{20}$ = +2.54 (c = 0.15, $CHCl_3$). ^1H and ^{13}C NMR signals and MS (ESI) data are coincident with those reported for **3**.

Basket Bis(diamidodiphenylethylene) Resorcin[4]arene (4): DIPEA (0.062 mL, 0.36 mmol) was added to a solution of **2b** (0.054 g, 0.06 mmol) in dry THF (5 mL), and the mixture was stirred at room temperature for about 20 min. A solution of (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (0.038 g, 0.18 mmol) in dry THF (5 mL) was then added dropwise over 1.5 h. The mixture was stirred and heated at reflux for 3 h. Standard workup and purification (silica gel; $CHCl_3$/MeOH, 99.5:0.5) gave compound **4** (0.022 g, 31%) as a vitreous solid. $[\alpha]_D^{20}$ = –59.9 (c = 0.22, $CHCl_3$). ^1H and ^{13}C NMR signals as in Table 1. MS (ESI+): m/z = 1208.4 $[M + Na]^+$. $C_{72}H_{72}N_4O_{12}$ (1185.38): calcd. C 72.95, H 6.12, N 4.73; found C 72.73, H 6.10, N 4.71.

***ent*-4:** Treatment of **2b** with (1*S*,2*S*)-(–)-1,2-diphenylethylenediamine under the same conditions as those used for the preparation of **4** afforded *ent*-**4** (0.021 g, 29%) as a vitreous solid. $[\alpha]_D^{20}$ = +59.9 (c = 0.12, $CHCl_3$). ^1H and ^{13}C NMR signals and MS (ESI) data are coincident with those reported for **4**.

Mass Spectrometric Experiments: The D- and L enantiomers of guests A [A = tryptophan (trp), tyrosine (tyr), and amphetamine (amph)] were purchased from Aldrich Co. and used without further purification. The same source provided (*R*)-(–)-2-butylamine (B_R) and (*S*)-(+)-2-butylamine (B_S), which were purified in a vacuum manifold with several freeze–thaw cycles. A simple and safe procedure was used to prepare the pure enantiomers of tyr^{OMe}: acetyl chloride (5 mL) was added dropwise to cooled dry methanol (50 mL; T = 0 °C) containing L- or D-tyrosine (1.7 mmol). The mixture was heated at reflux for about 2 h and then evaporated to dryness.

The proton-bound diastereomeric complexes $[M{\cdot}H{\cdot}A]^+$ were generated by electron-spraying hydroalcoholic solutions of **4** (1×10^{-5} M; H_2O/CH_3OH, 1:3) containing a fivefold excess of the single enantiomers of guests A. Abundant signals corresponding to the natural isotopomers of the proton-bound complex $[M{\cdot}H{\cdot}A]^+$ were monitored and isolated from the accompanying ions. The single complexes were then individually subjected to collision-induced dissociation (CID) by using He (10^{-5} Torr) as target gas.

For the FTICR experiments, stock solutions (1×10^{-5} M; H_2O/CH_3OH, 1:3) of either **4** or *ent*-**4** containing a fivefold excess of L-tyr^{OMe} or L-amph were electrosprayed through a heated capillary (T = 130 °C) into the external source of the FTICR mass spectrometer, and the resulting positive ions were transported into the analyzer cell. Abundant signals corresponding to the natural isotopomers of the proton-bound complex $[M{\cdot}H{\cdot}A]^+$ were monitored and isolated by broad-band ejection of the accompanying ions. When a background pressure of $4.6–7.3 \times 10^{-8}$ mbar of the chiral amine B was introduced into the FTICR cell, the exchange reaction [Equation (1)] exclusively took place. The appearance of the exchanged product $[M{\cdot}H{\cdot}B]^+$ was monitored as a function of time. All the exchange reactions represented by Equation (1) obey pseudo-first-order kinetics (corr. coeff. $r^2 > 0.990$). This indicates that the $[M{\cdot}H{\cdot}A]^+$ complexes were thermalized in their reactions with B. The corresponding second-order rate constants k were calculated from the ratio between the slope of the first-order plots and the B pressure. Their values, compared with the relevant collision rate constants (k_{coll}), estimated according to Su's trajectory calculation method,[17] provides directly the efficiency of the reaction (eff = k/k_{coll}).

Supporting Information (see footnote on the first page of this article): CID spectra of the proton-bonded diastereomeric $[4\cdot H\cdot A]^+$ complexes [A = tyrosine methyl ester (tyr^{OMe}), tryptophan (trp), or amphetamine (amph)].

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