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Structural studies and binding properties of pendant diazacoronands—precursors to macrocyclic compounds of planar chirality

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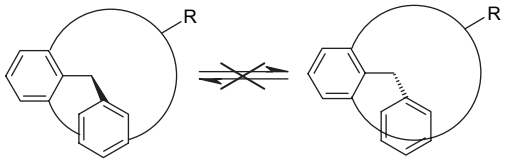
Abstract—Structural studies of pendant diazacoronands having an *N*-benzoyl, *N*-acetyl, *O*-benzyl or *O*-benzoyl side arm were performed by means of X-ray and temperature-dependent ^{1}H NMR experiments. The energies of macroring flipping process were determined for three pendant diazacoronands. The complexation properties of pendant diazacoronands toward the alkali metal cations (Na^+, K^+, and Rb^+) were estimated by ESI-MS experiments.

1. Introduction

The design and synthesis of macrocyclic compounds are closely related to the supramolecular chemistry and host–guest interactions.[1] However, up to now, no special effort has been made to prepare receptors of planar chirality.[2] Among the known macrocyclic compounds of planar chirality, most of them are based on a [2.2]paracyclophane framework having small, rigid macroring structure.[3] For these reasons, they cannot be efficient receptors for supramolecular applications. Hitherto, only several examples of such chiral compounds having a larger macroring have been published.[4] This is probably caused by the difficult preparation sequence requiring non-commercially available substrates. In addition, contrary to the [2.2]paracyclophane derivatives, the chiral compounds having larger macroring are conformationally flexible, thus their structural analysis and determination of energy barrier of deformation are indispensable to the design and synthesis of stable atropoisomers.[5]

Recently, our attention has been focused on the synthesis of diazacoronands of planar chirality, as potential receptors for supramolecular applications.[6] To the existence of such atropoisomers, two independent requirements are indispensable: (1) the presence of a large pendant arm, which is located on only one side of the macroring and cannot easily jump through it; (2) the presence of a non-symmetric moiety in the molecule (Scheme 1).



Scheme 1. The source of planar chirality in the pendant macrocyclic compounds.

The intraannular arm is an essential part of the presented planar–chiral system. Its size strongly affects the stability of such enantiomers and additionally it could modify the binding properties of the macrocyclic compounds. Therefore, the synthesis of efficient and stable macrocyclic receptors of planar chirality requires initial structural studies for simpler, non-chiral pendant diazacoronands. Additionally, knowledge of the influence of the type of intraannular group on the binding properties makes it possible to design appropriate chiral receptors.

In this contribution, we would like to present the conformational analysis of pendant diazacoronands investigated by variable temperature ^{1}H NMR spectroscopy and X-ray analysis. The binding properties of pendant diazacoronands toward alkali metal cations (Na^+, K^+, and Rb^+) were estimated by the electrospray ionization mass spectrometry (ESI-MS) experiments.

Keywords: Binding properties; Diazacoronands; ESI-MS; Supramolecular chemistry.
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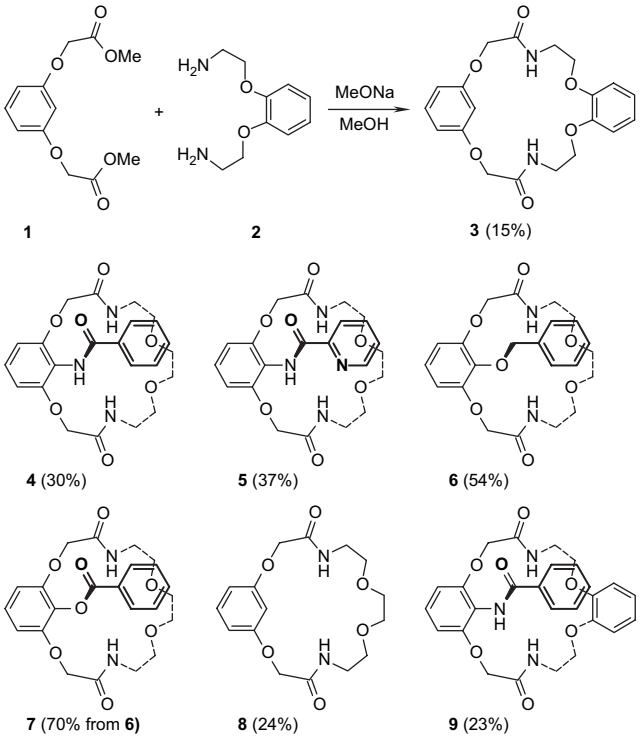
2. Results and discussion

2.1. Synthesis

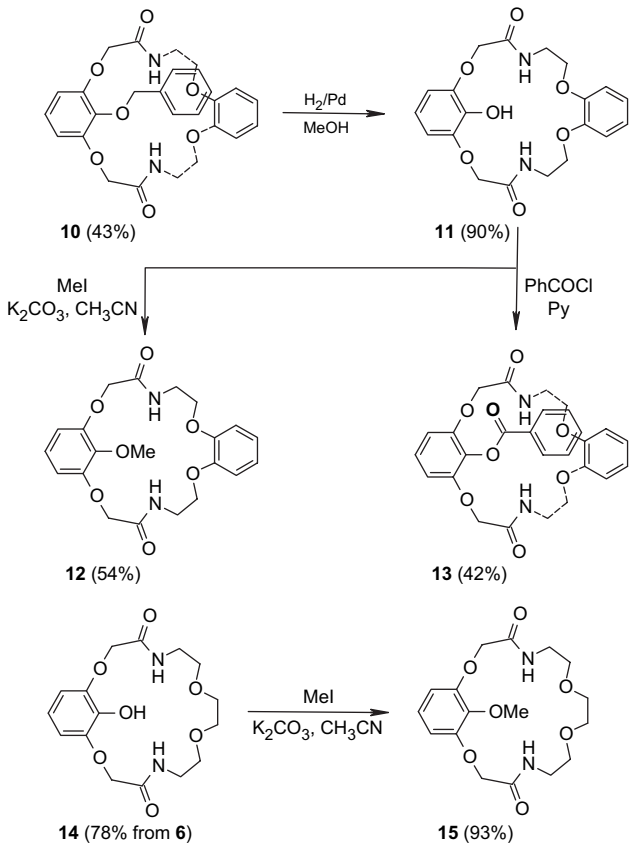
For the preparation of the title compounds, the double-amidation reaction was applied. In this reaction, originally introduced by Tabushi,[7] and developed in our laboratory,[8] dimethyl α,ω-dicarboxylates react with a primary α,ω-diamine in the presence of MeO^- under non-high dilution conditions. For example, diazacoronand **3** was prepared via the reaction of the appropriate diester **1**[9] with diamine **2**[10] in moderate yield (15%). To assess the influence of pendant arm on binding properties, two types of diazacoronands were compared, namely (1) those having a pendant arm, i.e., **4**–**7**,[11] **9**,[6a] **10**,[12] **13**, and (2) their analogs, compounds **3** and **8**,[13] unsubstituted at the intraannular position (Scheme 2).



Scheme 2. Pendant diazacoronands **4**–**7**, **9** and their unsubstituted analogs **3** and **8**.

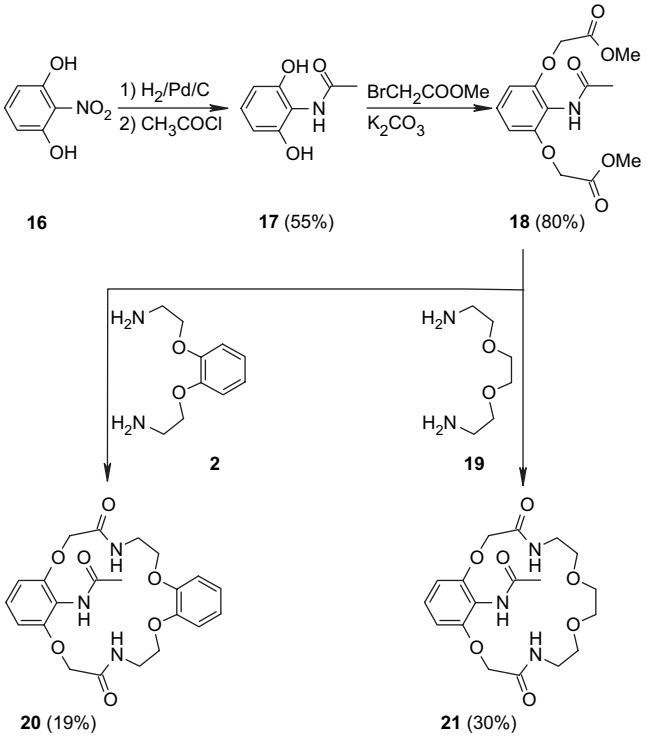
An advantage of compounds **6** and **10** is their chemical versatility resulting from the presence of the *O*-benzyl group. Starting from diazacoronand **10**, the intraannular function was easily removed by hydrogenation to form the hydroxy derivative **11** in good yield (90%). Compound **11** could be modified in various ways, including alkylation and acylation, and it was easily transformed into the *O*-methyl derivative **12** as well as into the *O*-benzoyl compound **13**, in satisfactory yields of 80% and 42%, respectively (Scheme 3). The alkylation of phenol **14**[11] was performed analogously and the reference *O*-methyl compound **15**[14] was isolated in good yield.

The syntheses of the reference compounds having the less sterically demanding *N*-acetyl intraannular group, were performed via the reaction sequence shown in Scheme 4. Starting from 2-nitroresorcinol **16**, after catalytic reduction and acylation of the resulting amino group, we obtained compound **17**, which in turn was elongated by means of



Scheme 3. Modifications of macrocyclic phenols **11** and **14**.

methyl bromoacetate. Diester **18** was then examined in macrocyclization reactions with the diamino-ethers **2**[10] and **19** to afford macrocyclic compounds **20** and **21**, respectively



Scheme 4. The synthesis of *N*-acetyl diazacoronands **20** and **21**.

(Scheme 4). Interestingly, the isolated yields of these compounds are comparable to the yields of *N*-benzoyl derivatives **4** and **9**, although the *N*-acetyl side arm is sterically less demanding. Furthermore, the compounds with no intraannular group (**3** and **8**) were synthesized in even lower yields (15% and 24%, respectively). This proves that the intraannular group plays an important role in the macrocyclization step.

2.2. Structural analysis

2.2.1. Structural analysis of *N*-substituted compounds. Diazacoronands **4**, **5**, and **9** having N-type side arm readily crystallized from methanolic solutions in a vapor diffusive system (*n*-pentane or diethyl ether). X-ray analysis of **4** displayed the presence of two types of hydrogen bonds:

(1) intramolecular between the oxygen atom of the benzamide group and the amide function (Fig. 1A);
(2) intermolecular between the proton of the benzamide group and the oxygen atom from the other molecule (Fig. 1B).

In addition, the macroring adopts a U-shaped arrangement with the intraannular function turned away from the macroring.

The solid-state analysis of compound **5** reveals analogous intra- and intermolecular hydrogen bonds. The pendant arm is turned out of the macroring as well. The characteristic crystal packing, observed also for compound **4**, is a 'molecular zipper'. Two chains of molecules of **5** make sides of the 'zipper', which are linked together by intermolecular π–π interactions of the pyridine moieties (Fig. 2).

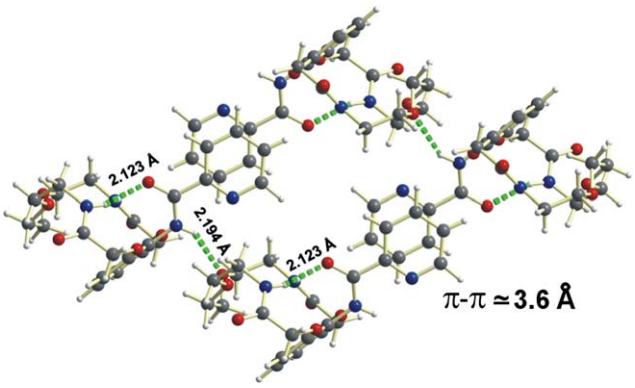


Figure 2. X-ray analysis of **5** reveals a 'molecular zipper'.

Structural analysis of compound **9** reveals a similar shape to the aliphatic analogs **4** and **5**; however, two intramolecular hydrogen bonds are observed (Fig. 3A). Additionally, the benzamide function participates in the intermolecular interactions, forming a network of hydrogen bonds with the methanol molecules (Fig. 3B).

2.2.2. ^{1}H NMR studies of *N*-substituted compounds. The conformational studies of pendant diazacoronands in solution were performed by means of ^{1}H NMR spectroscopy. The temperature-dependent experiment was designed to establish the transition state free energy at the coalescence temperature ($\Delta G_c^{\#}$), which represents the energy barrier of a macroring flipping process. According to the structural studies of compounds **4**, **5**, and **9** in the solid state, the length of the intraannular group is greater than the diameter of the macroring, thus the pendant arm cannot easily jump through it. Therefore, diazacoronands **4**, **5**, and **9** should exhibit a satisfactory structural stability also in solution. In fact, at room

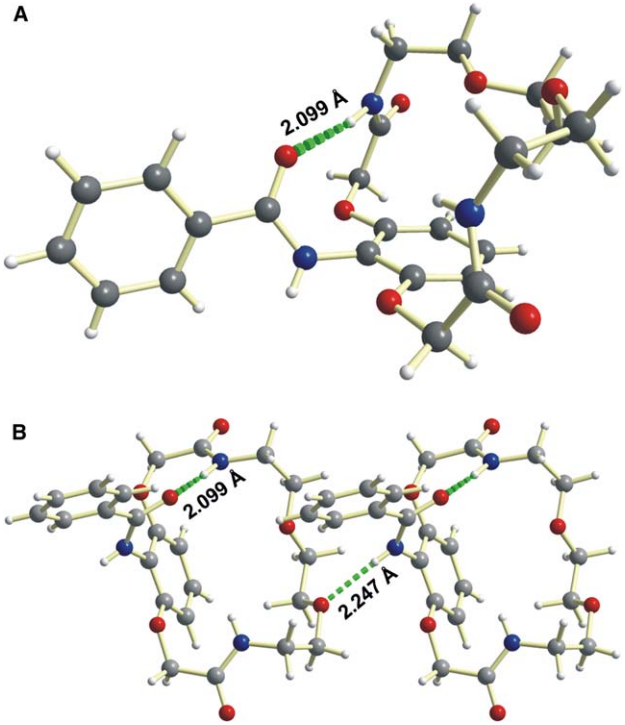


Figure 1. X-ray analysis of compound **4**. (A) Intramolecular hydrogen bond and (B) intermolecular hydrogen bond.

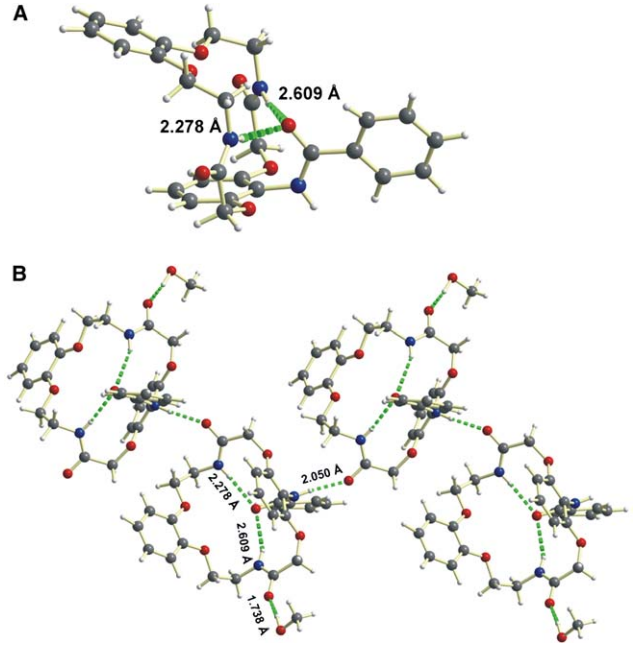


Figure 3. X-ray analysis of compound **9**. (A) Intramolecular hydrogen bonds and (B) a network of hydrogen bonds.

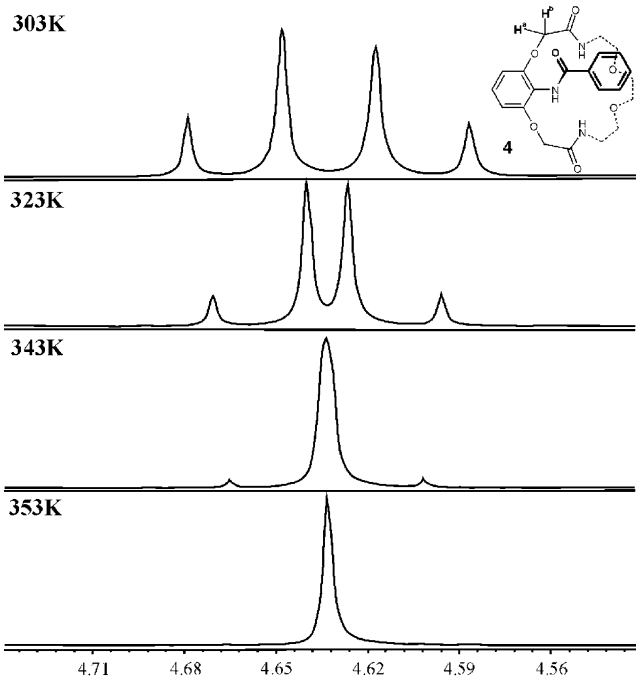


Figure 4. The temperature-dependent ^{1}H NMR spectrum of isolated CH_aH_b protons of compound **4** in DMSO-d_6.

temperature, the protons H^a, H^b of the isolated methylene group appear as an AB quartet and they are diastereotopic. The ^{1}H NMR experiment for compound **4** at various temperatures revealed coalescence of the AB-type signal at 353 K (Fig. 4).

To establish the influence of the pyridine moiety on the structural stability, an analogous experiment was carried out for compound **5** and the conformational stability was determined to be higher than that of compound **4**. The AB-type signal coalesces only at 390 K.

To verify the influence of the size of the intraannular function on the conformational stability, an analogous ^{1}H NMR experiment was carried out for the reference *N*-acetyl compound **21**. Surprisingly, the AB-type signal coalesces at 373 K, even higher than that of the *N*-benzoyl derivative **4**. This suggests that the size of the side arm has a minor influence on the conformational stability of *N*-substituted diazacoronands.

The ^{1}H NMR experiments for compounds **9** and **20** have shown that the widths of the AB-type signals at 373 K are close to these widths at room temperature. Due to limitation of the NMR apparatus, we could not establish $\Delta G_c^{\#}$ for them, but, from the viewpoint of this work, we could assume that if the signal of the methylene group did not coalesce at 373 K, then the pendant diazacoronand possessed conformational stability sufficient for the further purposes. Our assumption was also supported by our earlier results where enantiomers of a non-symmetrical diazacoronand based on the framework of compound **9** retained their enantiomeric purity for at least six months at room temperature and even extended boiling of solutions in acetonitrile (24 h) did not lead to any racemization.[6a]

The free energy of activation for the macroring flipping process ($\Delta G_c^{\#}$) was determined by Eyring[15] equations using the experimentally found coalescence temperature T_c.

$$k_c = \pi/2^{1/2}\left(\Delta\nu^2 + 6J^2\right)^{1/2} \quad (1)$$

$$\Delta G_c^{\#} = 2.303RT_c\left(10.32 + \log T_c - \log k_c\right) \quad (2)$$

where k_c is a rate constant, $\Delta\nu$ is the shift difference at low temperature and J is a coupling constant. According to Eq. 2, the values of $\Delta G_c^{\#}$ were calculated and amounted to 73.0 kJ/mol for **4**, 80.2 kJ/mol for **5**, and 77.1 kJ/mol for **21** (Table 1).

To find the reason for the significantly higher structural stability of diazacoronands with an additional benzene ring (**9** and **20**), NOESY experiment was carried out for compound **9** (Fig. 5). Strong cross peaks were observed between aliphatic and aromatic protons close to the macroring (A and B in Fig. 5). These findings indicate that the macroring system is not planar, and it probably adopts a U-shaped conformation. The absence of any cross peak between the *N*-benzoyl group (dotted line) and the macrocycle protons suggests that the intraannular function is located out of the macrocyclic cavity. This assumption is additionally supported by the fact that chemical shift related to intraannular NH proton is concentration dependent. This implies involvement of amide NH's in the intermolecular hydrogen bonding. The result of the NOESY experiment agrees well with the result of the X-ray analysis for the solid state and gives no explanation of the higher conformational stability of compound **9** over compound **4**.

Considering the similar structural results for diazacoronands **4** and **9**, and because the *N*-benzoyl function is turned away from the macrocyclic cavity, we proposed the following route of the macroring flipping process in compound **4** (Fig. 6).

According to our suggestions, not the intraannular group but the hydrogen atom at *para* position jumps through the macroring plane. Due to high flexibility of the macroring in compound **4**, the *N*-benzoyl side arm can easily rotate and cross the plane defined by macroring. In the case of compound **9**, which bears an additional benzene ring, the macroring is more rigid and such deformation is more energy demanding. This assumption is additionally supported by the fact that the reference diazacoronands **20** and **21** with smaller *N*-acetyl intraannular function possess comparable conformational stability as *N*-benzoyl derivatives **4** and **9**. Surprisingly, according to these findings, the flexibility of the macroring rather than the size of the intraannular group seems to have the major influence on the conformational stability of such diazacoronands. Therefore, the further synthesis of

Table 1. Thermodynamic parameters determined for diazacoronands **4**, **5**, and **21**

	T_c [K]	$\Delta\nu$ [Hz]	J [Hz]	k_c [Hz]	$\Delta G_c^{\#}$ [kJ/mol]
4	353	35.0	16.1	116.7	73.0
5	390	55.0	16.0	150.0	80.2
21	373	39.4	16.1	123.8	77.1

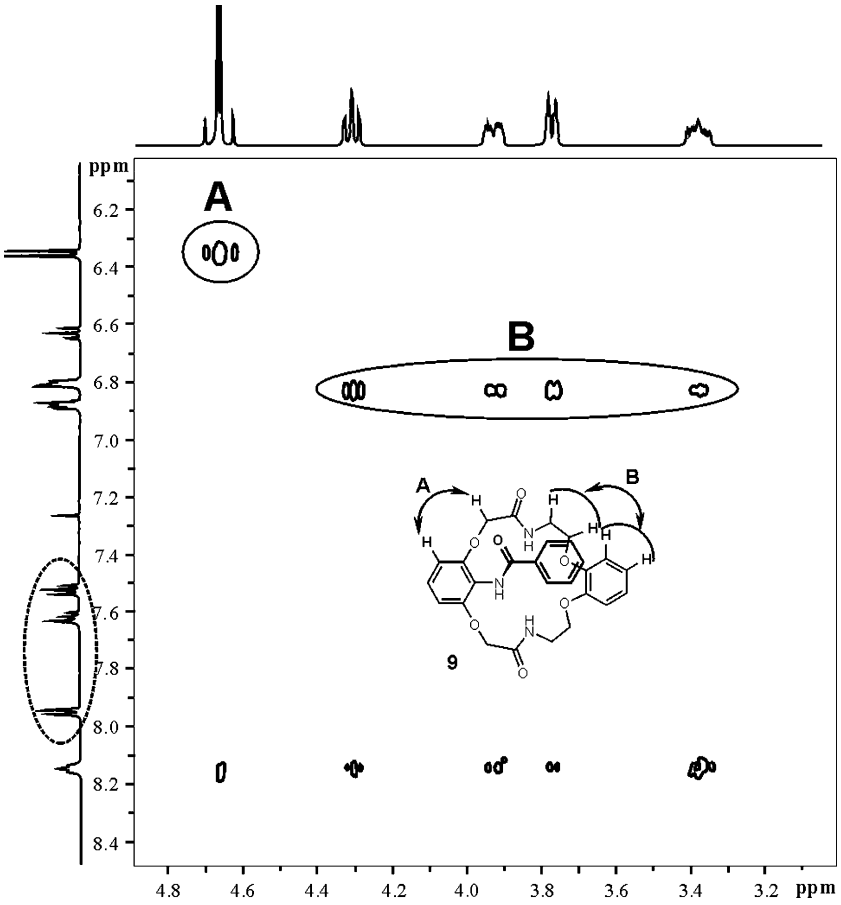


Figure 5. 2D ^{1}H NMR NOESY spectrum of compound **9**; signals from *N*-benzoyl group (dotted line).

a stable, chiral compound with *N*-benzoyl side arm requires the presence of a rigid macroring structure.

2.2.3. Structural analysis of *O*-substituted compounds. Attempts to obtain suitable single crystals of *O*-substituted compounds were unsuccessful, thus the structural studies of these compounds were carried out only in solution. The temperature-dependent ^{1}H NMR experiments carried out for the *O*-substituted compounds **6**, **7**, **10**, and **13** have shown stabilities significantly higher than for the *N*-substituted diazacoronands. The diastereotopic protons of *O*-benzyl derivative **6** do not coalesce at 373 K. Furthermore, the width of the AB-type signals is almost independent of the temperature (Fig. 7).

Comparable ^{1}H NMR results were observed for the derivative **7** as well as for **10** and **13** with an additional benzene ring. ^{1}H NMR spectra for the reference compounds **12** and **15**[14] with an *O*-methyl side arm, the smallest of the possible *O*-substituents, do not reveal a typical AB-type signal. These findings show that the structures of the *O*-substituted derivatives are completely different from the *N*-substituted diazacoronands **4**, **5**, **21**, **9**, and **20**. To support our proposal, a NOESY experiment was carried out for compound **6**, and revealed cross peaks between protons of the benzyl function and the macroring (Fig. 8, A and B). This suggested that the intraannular group was oriented inwards the macroring, which was additionally proved for compound **10**.[12] The

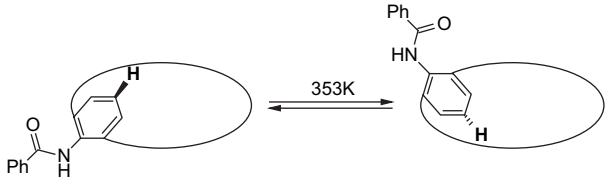


Figure 6. Proposed way of macroring flipping process in compound **4**.

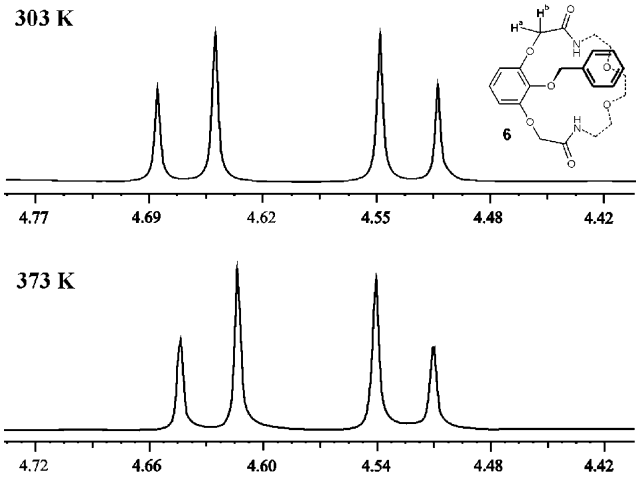


Figure 7. The temperature-dependent ^{1}H NMR spectrum of isolated CH_aH_b protons of compound **6** in DMSO-d_6.

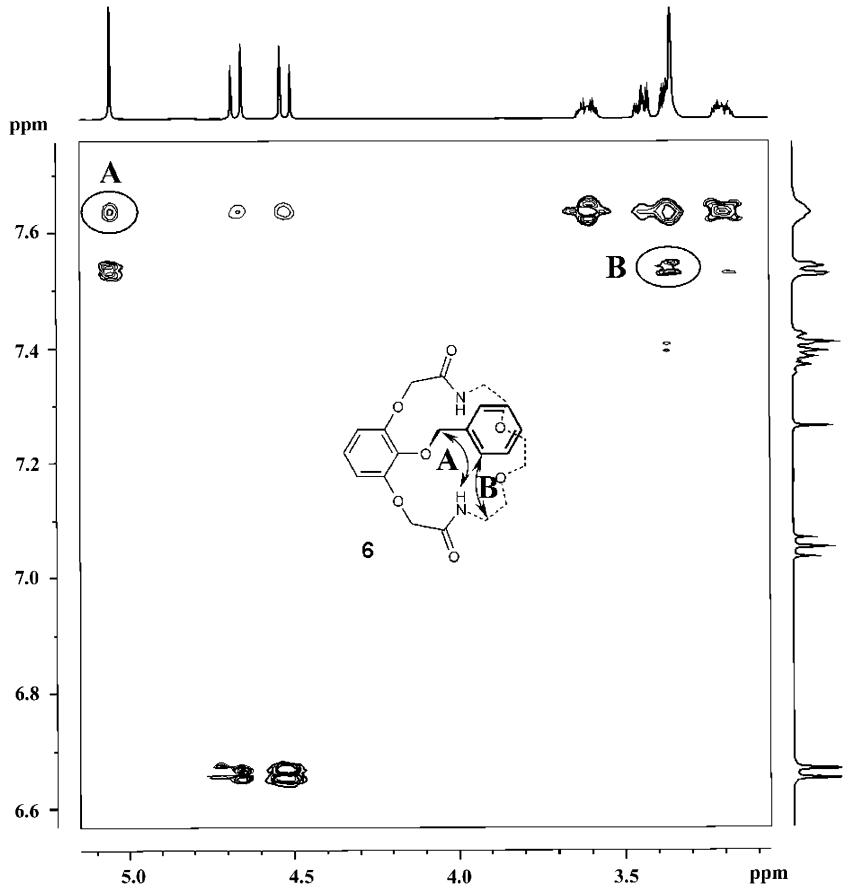


Figure 8. 2D ^{1}H NMR NOESY spectrum of compound **6**.

flipping process is significantly more energy demanding than in the case of the aliphatic *N*-benzoyl derivative **4**. Therefore, in the case of compound **6**, the size and structure of the *O*-benzyl group ensure sufficient conformational stability.

According to the presented results, the type of the intraannular group strongly affects the structural stability of pendant diazacoronands. In the case of compounds **4**, **5**, and **21**, the coalescence temperatures and $\Delta G_c^{\#}$ were measurable. The rest of the presented diazacoronands **6**, **7**, **9**, **10**, **13**, and **20** have significantly higher conformational stability, thus we assume that they are sufficiently stable for our further purposes. The *O*-substituted compounds have higher stability than the *N*-substituted derivatives **4**, **5**, and **21**. Surprisingly, in the case of the latter group of compounds, rigidity of the macroring, and not the size of intraannular function has the main effect on the conformational stability. The *O*-substituted diazacoronands **6** and **7**, although having an aliphatic macroring, reveal a substantial structural stability and the signal from diastereotopic protons do not coalesce at 373 K. Summing up, further synthesis of stable macrocycles of planar chirality requires the presence of additional benzene ring in the case of *N*-substituted derivatives. On the contrary, chiral *O*-substituted diazacoronands can possess an aliphatic macroring.

2.3. Binding properties (ESI-MS)

To estimate the influence of the intraannular group on the binding properties of pendant diazacoronands, ESI-MS was used. Although complexation experiments are typically carried out by means of NMR, potentiometry, extraction or UV–vis techniques, these conventional methods are more time-consuming and require up to 1000 times more analyte than ESI-MS. Up to now, several studies have evaluated the use of ESI-MS for the applications involving non-covalent host–guest interactions,[16] and revealed that this approach is suitable for quick, initial characterization of the considered host.

Our investigations focused on checking competition between two ligands toward one alkali metal cation. It is well known from the ESI-MS technique that the response factor depends on the solvation energy of the given ions. In order to perform a quantitative analysis of the results, one should introduce the corresponding coefficients for correlation of the different ligand response factors. Such a procedure is possible but quite tedious and unnecessary from the viewpoint of this work. For our purposes, it is reasonable to assume that the peak intensity ratios higher than 4:1 are indicative for the stronger complexing properties of one out of the two complexing ligands. To verify how structural changes of diazacoronands affect their binding properties, three ESI-MS experiments were carried out.

(1) *Effect of the intraannular group*: Table 2 shows six pairs consisting of the pendant diazacoronands and the unsubstituted reference compounds **3** and **8**. The peak ratio is the highest in the case of derivatives **4** and **6** (entries 1 and 2). No differences were observed for the pair **7/8**

Table 2. The ratio of signal intensities (ESI-MS spectra) for two ligands and one alkali metal cation

Entry	Ligands		Signal intensities ratio in ESI-MS spectra $[L1+M^+]/[L2+M^+]$		
	L1	L2	Na^+	K^+	Rb^+
1	**4**	**8**	2.5	3.4	5.7
2	**6**	**8**	2.6	4.2	7.6
3	**7**	**8**	1.0	1.3	2.0
4	**9**	**3**	0.7	0.3	0.2
5	**10**	**3**	1.0	0.8	0.71
6	**13**	**3**	0.3	0.1	0.1

The values given in the table are averages of three measurements reproducible within ±10%.

(entry 3). Similar experiments carried out for diazacoronands **9**, **10**, and **13** possessing additional benzene ring revealed surprisingly weaker affinity to alkali metal cations than compound **3** (entries 4–6).

(2) *Effect of the rigidity of the macroring*: In order to thoroughly explore the effect of rigidity of the macroring, four further experiments were carried out. Each diazacoronand with aliphatic macroring was subjected to ESI-MS investigation with an appropriate compound possessing additional benzene ring (Table 3).

In all of the examined pairs, the aliphatic diazacoronands are better receptors for cations than their aromatic analogs. This is probably caused by the higher rigidity of the macroring structure in compounds **3**, **9**, **10**, and **13**, which prevents their geometry from adapting to the guest molecule. In the case of compound **13**, the highest ratio of signal intensities was observed and amounted to 34.2 (entry 10).

(3) *Comparison of the type of intraannular groups*: To determine which pendant arm modifies the binding properties best, direct comparison of two pendant diazacoronands was carried out (Table 4). The best receptors are compounds **4** and **5** with *N*-substituted side arm and only slightly weaker ligand is the derivative **6** possessing the *O*-benzyl function (entries 11 and 12). On the contrary, the weakest receptors are compounds **7** and **12** with *O*-benzoyl side arm (entries 13–15).

As expected, derivative **5** with a pyridine moiety is a slightly more efficient host than its benzene analog **4**. An apparent experiment showing another advantage of diazacoronad **5** over **4** consists in inducing color changes of Cu^{2+} solutions (Fig. 9). Several typical copper salts were used to exclude

Table 3. The ratio of signal intensities (ESI-MS spectra) for two ligands and one alkali metal cation

Entry	Ligands		Signal intensities ratio in ESI-MS spectra $[L1+M^+]/[L2+M^+]$		
	L1	L2	Na^+	K^+	Rb^+
7	**8**	**3**	7.0	6.6	4.7
8	**4**	**9**	15.9	15.2	24.8
9	**6**	**10**	10.1	7.6	8.6
10	**7**	**13**	23.1	31.1	34.2

The values given in the table are averages of three measurements reproducible within ±10%.

Table 4. The ratio of signal intensities (ESI-MS spectra) for two ligands and one alkali metal cation

Entry	Ligands		Signal intensities ratio in ESI-MS spectra $[L1+M^+]/[L2+M^+]$		
	L1	L2	Na^+	K^+	Rb^+
11	**5**	**4**	2.7	3.5	4.3
12	**4**	**6**	2.7	3.0	2.3
13	**4**	**7**	9.1	7.1	6.4
14	**9**	**13**	4.8	4.5	3.9
15	**10**	**13**	8.8	12.5	19.4

The values given in the table are averages of three measurements reproducible within ±10%.

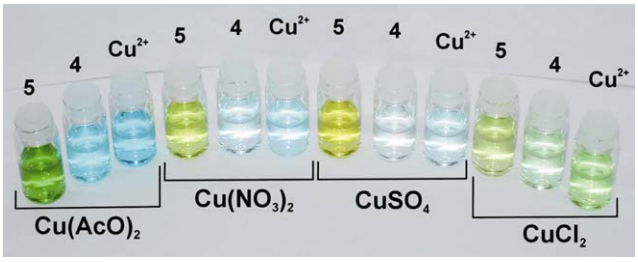


Figure 9. Color changes of Cu^{2+} solution induced by the addition of compounds **4** or **5**. Cu^{2+}=free salt; **4**=**4**+Cu^{2+}; **5**=**5**+Cu^{2+}.

the influence of counterions on color changes. Typically, an appropriate diazacoronand (2 mg in 1 ml of MeOH) was added to an appropriate copper salt solution (ca. 3 mg in 1 ml of MeOH).

Color changes were observed only in the case of compound **5**, although its mixture with $CuCl_2$ gave a slight difference. The derivative **4**, although structurally very similar to **5**, did not give any visible results. This simple experiment demonstrated that a minor change in the structure of diazacoronands can result in different and interesting binding properties.

3. Conclusions

In this paper, we presented the structural studies and initial binding properties of pendant diazacoronands. Here, the intraannular group plays a double role: (1) it ensures a sufficient conformational stability, indispensable in the case of further synthesis of stable atropoisomers and (2) it is an extra binding side, slightly modifying the complexation properties of the macrocyclic receptors. The structural studies performed by means of the X-ray analysis and the variable temperature ^1H NMR experiments show that the *O*-substituted compounds exhibit higher conformational stability than the *N*-substituted analogs. On the contrary, initial binding experiments (ESI-MS) show that the *N*-substituted diazacoronands are slightly better receptors than the *O*-substituted diazacoronands. The main advantage of the presented system is a diversity of intraannular groups, which can be introduced into the diazacoronand framework, and the possibility of almost unlimited modifications. Application of the above-presented synthetic approach to preparation of macrocycles with planar chirality as well as their use in asymmetric synthesis is in progress.

4. Experimental

4.1. General methods

Melting points were determined using a Boëtius M HMK hot-stage apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AM 500 or Varian BB 200 spectrometer. Chemical shifts are reported as δ values relative to TMS peak defined at δ=0.00. The mass spectral analysis was performed by the ESI-TOF technique on a Mariner mass spectrometer from PerSeptive Biosystem. Column chromatography was performed on silica gel (Kieselgel-60, 200–400 mesh).

4.1.1. 2,8,15,21-Tetraoxa-5,18-diazatricyclo[20.3.1.0^{9,14}]hexacosa-1(25),9(14),10,12,22(26),23-hexaene-4,19-dione (3). *Procedure A*: An appropriate diester (39 mmol) was dissolved in dry MeOH (300 ml) and added to diamino-ether **2** or **19** (39 mmol) in dry MeOH (100 ml). Then, a solution of MeONa (5.4 g, 100 mmol) in dry MeOH (100 ml) was added to the mixture. The mixture was left at ambient temperature for a period of 2–7 days (TLC monitored). Subsequently, the solvent was evaporated and the residue was purified by column chromatography (silica gel; AcOEt/MeOH, 9:1 or $CHCl_3$/MeOH, 95:5 in the case of **20** and **21**, respectively) to give the desired product. Yield (15%), crystallization in a vapor diffusive system (MeOH/$CHCl_3$, 2:3/Et_2O) gives white crystals, mp 224.3–225.4 °C. ^{1}H NMR 500 MHz (DMSO): δ=7.93 (br t, 2H, CONH); 7.19 (t, 1H, J=8.2, ArH); 7.02–6.98 (m, 2H, ArH); 6.93–6.88 (m, 2H, ArH); 6.58 (dd, 2H, J^1=8.2, J^2=2.3, ArH); 6.47 (t, 1H, J=2.3, ArH); 4.51 (s, 4H, OCH_2CO); 4.07 (br t, 4H, CH_2O); 3.52 (br q, 4H, CH_2N), ^{13}C NMR 125 MHz (DMSO): δ=167.8 (CONH), 158.7, 148.1, 130.1, 121.3, 114.3, 107.8, 101.1, 67.1, 66.8, 38.2, ESI HRMS (MeOH) m/z calcd for $C_{20}H_{22}N_2O_6Na$ [M+Na]$^+$: 409.1370; found: 409.1394. Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.34; H, 5.45; N, 7.27. Found: C, 62.32; H, 5.63; N, 7.22%.

4.1.2. 26-Hydroxy-2,8,15,21-tetraoxa-5,18-diaza-tricyclo[20.3.1.0^{9,14}]hexacosa-1(25),9(14),10,12,22(26),23-hexaene-4,19-dione (11). A mixture of compound **10** (3 g, 6.1 mmol) and Pd/C (0.5 g, 10%) in MeOH (200 ml) was stirred overnight under an atmosphere of hydrogen (balloon pressure) at rt. The reaction mixture was filtered through Celite and the resulting solution was evaporated. Crystallization from MeOH (120 ml) gave light purple crystals (2.2 g, 90%), mp 168.9–171.4 °C. ^{1}H NMR 500 MHz (DMSO): δ=9.74 (br s, 1H, OH); 8.30 (br t, 2H, CONH); 6.95–6.91 (m, 2H, ArH); 6.88–6.84 (m, 2H, ArH); 6.81–6.78 (m, 2H, ArH); 6.75–6.71 (m, 1H, ArH); 4.58 (s, 4H, OCH_2CO); 4.01 (t, 4H, J=4.9); 3.55 (q, 4H, J=4.9, CH_2N); ^{13}C NMR 125 MHz (DMSO): δ=168.6 (CONH), 148.0, 147.6, 137.8, 121.0, 119.3, 113.5, 111.3, 70.5, 67.1, 38.3, ESI HRMS (MeOH) m/z calcd for $C_{20}H_{22}N_2O_7Na$ [M+Na]$^+$: 425.1319; found: 425.1304. Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.70; H, 5.51; N, 6.96. Found: C, 59.57; H, 5.77; N, 6.91%.

4.1.3. 26-Methoxy-2,8,15,21-tetraoxa-5,18-diaza-tricyclo[20.3.1.0^{9,14}]hexacosa-1(25),9(14),10,12,22(26),23-hexaene-4,19-dione (12). *Procedure B*: To phenol **11** (1 g, 2.5 mmol) dissolved in MeCN (150 ml), 5 equiv of MeI (0.5 ml, 12.5 mmol) and 3 equiv of anhydrous K_2CO_3 (1 g, 7.5 mmol) were added. The reaction mixture was stirred at rt for 12 h. Next, a second portion of MeI (0.5 ml, 12.5 mmol) was added and the reaction was carried out for the subsequent 12 h. After filtration, the solvent was evaporated and the residue was crystallized in a vapor diffusive system (MeOH/$CHCl_3$, 1:1/n-pentane), to give white crystals (0.56 g, 54%), mp 239.8–241.0 °C. ^{1}H NMR 500 MHz (DMSO): δ=7.94 (br t, 2H, CONH); 7.07–6.99 (m, 3H, ArH); 6.91–6.87 (m, 4H, ArH); 4.63 (s, 4H, OCH_2CO); 4.07 (br t, 4H, CH_2O); 3.72 (s, 3H, OMe); 3.60 (br q, 4H, CH_2N). ^{13}C NMR 125 MHz (DMSO): δ=167.9 (CONH), 152.4, 147.8, 140.2, 124.9, 121.0, 112.9, 112.1, 70.8, 67.4, 61.5, 38.2, ESI HRMS (MeOH) m/z calcd for $C_{21}H_{24}N_2O_7Na$ [M+Na]$^+$: 439.1476; found: 439.1480. Anal. Calcd for $C_{21}H_{24}N_2O_7$: C, 60.57; H, 5.76; N, 6.73. Found: C, 60.60; H, 5.93; N, 6.74%.

4.1.4. Benzoic acid 4,19-dioxo-2,8,15,21-tetraoxa-5,18-diaza-tricyclo[20.3.1.0^{9,14}]hexacosa-1(25),9(14),10,12,22(26),23-hexaen-26-yl ester (13). To phenol **11** (1g, 2.5 mmol) dissolved in pyridine (10 ml) and cooled (0 °C), benzoyl chloride (0.34 ml, 3.0 mmol) was added dropwise. The reaction mixture was stirred overnight at rt and subsequently acidified with 1 M aq HCl. After extraction with AcOEt (3×100 ml), the organic layers were combined, dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (silica gel; AcOEt) to give the desired product (42%, 0.53 g). Crystallization in a vapor diffusive system (MeOH/Et_2O) gave white needles, mp 203.4–204.6 °C. ^{1}H NMR 500 MHz ($CDCl_3$): δ=8.22 (br d, 2H, CONH); 7.66 (t, 1H, J=7.5, ArH); 7.48 (t, 2H, J=7.5, ArH); 7.10 (br s, 2H, ArH); 6.91–6.78 (m, 5H, ArH); 6.53 (d, 2H, J=7.5, ArH); 4.69 (d_{AB}, 2H, J=16.5, OCH_2CO); 4.64 (d_{AB}, 2H, J=16.5, OCH_2CO); 4.20–4.14 (m, 2H, CH_2O); 3.90–3.83 (m, 4H, CH_2O+CH_2N); 3.46–3.40 (m, 2H, CH_2N); ^{13}C NMR 125 MHz ($CDCl_3$): δ= 168.2 (CONH), 150.1, 148.0, 134.3, 130.6, 128.8, 128.2, 127.1, 120.8, 111.8, 66.8, 65.8, 39.1, ESI HRMS (MeOH) m/z calcd for $C_{27}H_{26}N_2O_8Na$ [M+Na]$^+$: 529.1581; found: 529.1552. Anal. Calcd for $C_{27}H_{26}N_2O_8$: C, 64.03; H, 5.17; N, 5.53. Found: C, 63.81; H, 5.34; N, 5.42%.

4.1.5. 22-Methoxy-2,8,11,17-tetraoxa-5,14-diaza-bicyclo-[16.3.1]docosa-1(21),18(22),19-triene-4,15-dione (15). *Procedure B*: (93%), mp 108.2–109.9 °C, lit.[14] mp 109–111 °C. ^{1}H NMR 500 MHz (DMSO): δ=7.59 (br t, 2H, CONH); 7.03 (t, 1H, J=8.4, ArH); 6.79 (d, 2H, J=8.4, ArH); 4.58 (s, 4H, OCH_2CO); 3.85 (s, 3H, OMe); 3.47–3.42 (m, 8H, CH_2O); 3.33–3.28 (m, 4H, CH_2N), ^{13}C NMR 125 MHz (DMSO): δ=167.8 (CONH), 151.9, 139.5, 124.3, 110.3, 70.1, 69.6, 68.9, 61.2, 38.7, ESI HRMS (MeOH) m/z calcd for $C_{17}H_{24}N_2O_7Na$ [M+Na]$^+$: 391.1476; found: 391.1471.

4.1.6. *N*-(2,6-Dihydroxyphenyl)acetamide (17). A mixture of compound **16** (10 g, 64 mmol) and Pd/C (1 g, 10%) in MeOH (200 ml) was stirred at rt under an atmosphere of hydrogen (balloon pressure) for 2 days. The catalyst was filtered off on Celite. Then, the solution was cooled to −20 °C and acetyl chloride was added dropwise. The reaction mixture was stirred at −20 °C→rt overnight. After evaporation of the solvent, the residue was crystallized from EtOH to give gray crystals (5.9 g, 55% overall yield), mp 95.5–97.1 °C.

^{1}H NMR 200 MHz ($CDCl_3$): δ=7.53 (br s, 1H, NHCOMe); 6.94 (t, 1H, J=8.3, ArH); 6.49 (d, 2H, J=8.3, ArH); 2.30 (s, 3H, Me), ^{13}C NMR 50 MHz ($CDCl_3$): δ=168.1 (NHCO), 147.8, 129.8, 124.8, 120.9, 25.6, ESI HRMS (MeOH) m/z calcd for $C_8H_9NO_3Na$ $[M+Na]^+$: 190.1556; found: 190.1563. Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.68; H, 5.54; N, 8.26%.

4.1.7. Methyl [2-(acetylamino)-3-(2-methoxy-2-oxoethoxy)phenoxy]acetate (18). To a mixture of **17** (10 g, 149 mmol), and anhydrous K_2CO_3 (40 g, 290 mmol) in anhydrous 2-butanone (300 ml), methyl bromoacetate (26 ml, 290 mmol) was added. The reaction mixture was stirred at 80 °C for 2 days under an argon atmosphere. After cooling the suspension to room temperature, the insoluble inorganic salts were removed by filtration. Then, the solvent was evaporated and the residue was purified by column chromatography (silica gel; AcOEt) to give the desired product (14.9 g, 80%), mp 92.6–93.4 °C. ^{1}H NMR 500 MHz ($CDCl_3$): δ=7.33 (br s, 1H, NHCO); 7.12 (t, 1H, J=8.3, ArH); 6.55 (d, 2H, J=8.3, ArH); 4.67 (s, 4H, OCH_2CO); 3.77 (s, 6H, OMe); 2.18 (br s, 3H, COMe), ^{13}C NMR 125 MHz ($CDCl_3$): δ=169.5 (CO); 168.8 (NHCO); 154.2, 127.5, 117.6, 108.3, 66.9, 52.2, 23.3, ESI HRMS (MeOH) m/z calcd for $C_{14}H_{17}NO_7Na$ $[M+Na]^+$: 334.2839; found: 334.2845. Anal. Calcd for $C_{14}H_{17}NO_7$: C, 54.02; H, 5.50; N, 4.50. Found: C, 54.15; H, 5.44; N, 4.55%.

4.1.8. *N*-(4,19-Dioxo-2,8,15,21-tetraoxa-5,18-diazatricyclo[20.3.1.0^{9,14}]hexacosa-1(25),9(14),10,12,22(26),23-hexaen-26-yl)-acetamide (20). *Procedure A*: (19%) Crystallization in a vapor diffusive system (MeOH/*n*-pentane) gives white needles, mp 221.3–221.9 °C. ^{1}H NMR 500 MHz (DMSO): δ=9.44 (s, 1H, NHCO); 7.54 (br t, 2H, CONH); 6.95 (t, 1H, J=8.5, ArH); 6.82 (s, 4H, ArH); 6.57 (d, 2H, J=8.5, ArH); 4.74 (d_{AB}, 2H, J=16.3, OCH_2CO); 4.66 (d_{AB}, 2H, J=16.3, OCH_2CO); 3.87–3.80 (m, 2H, CH_2O); 3.75–3.63 (m, 4H, CH_2O+CH_2N); 3.13–3.05 (m, 2H, CH_2N); 2.09 (s, 3H, COMe), ^{13}C NMR 125 MHz (DMSO): δ=169.9 (NHCO), 168.1 (CONH), 153.2, 148.3, 127.7, 121.0, 114.9, 113.9, 105.0, 67.0, 66.4, 38.5, 22.6, ESI HRMS (MeOH) m/z calcd for $C_{22}H_{25}N_3O_7Na$ $[M+Na]^+$: 466.1585; found: 466.1562. Anal. Calcd for $C_{22}H_{25}N_3O_7$: C, 59.59; H, 5.64; N, 9.48. Found: C, 59.68; H, 5.73; N, 9.43%.

4.1.9. *N*-(4,15-Dioxo-2,8,11,17-tetraoxa-5,14-diaza-bicyclo[16.3.1]docosa-1(21),18(22),19-trien-22-yl)-acetamide (21). *Procedure A*: (30%) Crystallization in a vapor diffusive system (MeOH/*n*-pentane), gives white needles, mp 174.3–174.6 °C. ^{1}H NMR 500 MHz (DMSO): δ=9.39 (s, 1H, NHCO); 7.72 (br q, 2H, CONH); 7.15 (t, 1H, J=8.5, ArH); 6.58 (d, 2H, J=8.5, ArH); 4.67 (d_{AB}, 2H, J=16.1, OCH_2CO); 4.58 (d_{AB}, 2H, J=16.1, OCH_2CO); 3.56–3.48 (m, 2H, CH_2O); 3.41–3.35 (m, 2H, CH_2O); 3.25–3.19 (m, 2H, CH_2O); 3.11–3.04 (m, 2H, CH_2O); 2.96–2.81 (m, 4H, CH_2N); 2.10 (s, 3H, COMe), ^{13}C NMR 125 MHz (DMSO): δ=169.0 (NHCO), 167.8 (CONH), 153.1, 127.3, 114.7, 104.9, 69.8, 68.6, 66.7, 39.3, 22.8, ESI HRMS (MeOH) m/z calcd for $C_{18}H_{25}N_3O_7Na$ $[M+Na]^+$: 418.1585; found: 418.1605. Anal. Calcd for $C_{18}H_{25}N_3O_7$: C, 54.68; H, 6.33; N, 10.63. Found: C, 54.69; H, 6.40; N, 10.74%.

4.2. ESI-MS comparison measurements

All electrospray ionization mass spectra were recorded on a Micromass instrument equipped with an ESI source. The needle potential for the methanol solution was set to 4.0 kV for all experiments. Each spectrum taken was an average of 25–30 scans.

All solutions were prepared in methanol. The solutions containing chloride salt and two hosts had the concentration ratios of 1:1:1, and the host concentrations were 1×10^{-4} M for each host.

4.3. The X-ray structure investigations

The intensity data were collected on a Kuma KM4CCD diffractometer with a graphite-monochromated Mo Kα radiation (λ=0.71073 Å). The crystal was positioned at 65 mm from the KM4CCD camera, 600 frames were measured at 1° intervals with a counting time of 15 s. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. The structure was solved by the direct method and refined by full-matrix least squares on F^2 using SHELXL 97. The H atoms were located in geometrically calculated positions and were allowed to ride on their parent atom. CCDC data sets No. 264711, 264712, and 264713 for **4**, **9**, and **5**, respectively, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

*Crystal data for **4***: Crystals obtained in a vapor diffusive system MeOH/$CHCl_3$, 1:1/*n*-pentane; $C_{23}H_{29}N_3O_8$, M_r=475.5, monoclinic, $P2(1)/n$, a=8.4650(17), b=20.425(4), c=13.845(3) Å, α=90°, β=96.36(3)°, γ=90°, V=2379.1(8) Å^3, Z=4, D_c=1.338 g/cm^3, F_{000}=1008, T=293(2) K, μ=0.101 mm^{-1}, 4176 reflections collected, 2921 unique. Final GOF=1.129, $R1$=0.0577, $wR2$=0.1892 (all data).

*Crystal data for **5***: Crystals obtained in a vapor diffusive system MeOH/Et_2O; $C_{22}H_{28}N_4O_8$, M_r=476.5, monoclinic, $P2(1)/n$, a=8.3978(17), b=20.422(4), c=13.885(3) Å, α=90°, β=96.41(3)°, γ=90°, V=2366.1(8) Å^3, Z=4, D_c=1.337 g/cm^3, F_{000}=1008, T=150(2) K, μ=0.103 mm^{-1}, 17,400 reflections collected, 4157 unique. Final GOF=0.890, $R1$=0.0424, $wR2$=0.0832 (all data).

*Crystal data for **9***: Crystals obtained in a vapor diffusive system MeOH/$CHCl_3$, 1:1/*n*-pentane; $C_{28}H_{31}N_3O_8$, M_r=537.5, monoclinic, $P2(1)/c$, a=11.4801(7), b=14.5891(8), c=16.5399(3) Å, α=90°, β=95.23(4)°, γ=90°, V=2758.6(3) Å^3, Z=4, D_c=1.294 g/cm^3, F_{000}=1136, T=293(2) K, μ=0.096 mm^{-1}, 38,138 reflections collected, 4318 unique. Final GOF=1.138, $R1$=0.0530, $wR2$=0.1675 (all data).

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