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PAPER

Synthesis of novel enantiomerically pure tetra-carbohydrazide cyclophane macrocycles†

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A total of twelve novel enantiomerically pure tetra-carbohydrazide cyclophane macrocycles have been synthesised in quantitative yields by reacting chiral (4*R*,5*R*)- and (4*S*,5*S*)-1,3-dioxolane-4,5-dicarbohydrazides with aromatic bis-aldehydes in a [2 + 2]-cyclocondensation reaction. The compounds show a dynamic behaviour in solution, which has been rationalized in terms of an unprecedented conformational interconversion between two conformers one stabilised by intramolecular hydrogen bonding and π–π stacking interactions.

Introduction

In recent years supramolecular chemistry has emerged as one of the most actively pursued fields of the chemical sciences. Its implications now reach from the basis of molecular recognition in natural systems such as protein substrate interactions to exciting new applications in chemical technology and material sciences.[1–9] Molecular recognition of metal cations using non-natural receptors has reached a high level of maturity and sophistication and as a consequence is successfully applied on an industrial scale.[10–12] Molecular recognition of anions using non-natural receptors is making rapid progress,[13] whereas molecular recognition of small to medium sized organic molecules is somehow lingering behind mainly due to the complexity of the scientific challenge.[9,10] However, a diverse number of potentially useful applications of molecular recognition of small organic molecules using synthetic receptors have been suggested and are actively pursued. Among the most promising applications of molecular recognition are the binding and remediation of environmental toxins from soil, water and food and the binding and removal of undesired trace by-products from the bulk manufacturing of fine chemicals, which all require good water solubility of the supramolecular host.[14] Moreover, chiral recognition and resolution of enantiomers, the development of sensors and biosensors and finally the design, development and synthesis of nano-gadgets and molecular machines form exciting challenges for supramolecular chemistry for the next decade.[8,9] The majority of supramolecular systems employ synthetic macrocyclic compounds as host molecules.

Certain classes of macrocyclic molecules have dominated the field including calix[*n*]arenes, cyclodextrins, crown-ethers and cucurbiturils. These macrocycles were characterised by synthetic methods making them easily available in large quantities, functional groups allowing simple transformations to access more sophisticated structures with elaborate binding motifs, good water solubility for cyclodextrins and cucurbiturils and their ability to bind a large variety of important guest molecules.

In the search for an ideal class of macrocycle, we have reported on numerous occasions on the synthesis of trianglimine macrocycles, obtained through a [3 + 3]-cyclocondensation reaction.[1,2,15–20] These macrocycles fulfil, from a synthetic point of view, all the requirements for an ideal macrocycle. Since the compounds are available in a simple synthetic procedure in almost quantitative yields from versatile building blocks, purification is simple, the structure of building blocks can be largely varied to allow a modular assembly of compounds with tunable sizes and ample functionalities and finally they are enantiomerically pure and are accessible in both enantiomeric forms.

Despite all of these synthetic advantages, we have failed in the last decade to obtain trianglimine derivatives showing good solubility in polar solvents and additionally reported binding constants have on no occasion exceeded the mM range. For this reason we decided to redesign the synthetic approach we successfully employed in trianglimine chemistry to obtain novel macrocycles with improved properties. Maintaining the attractive concept of conformationally biased macrocyclisations in [*n* + *n*]-cyclocondensation reactions, we searched for suitable novel chiral building blocks that allow incorporation of ample functionality into the macrocycle combined with improved solubility properties. Work by Sanders and co-workers have demonstrated on numerous occasions that the combination of hydrazides with reactive carbonyl compounds allow an efficient construction of

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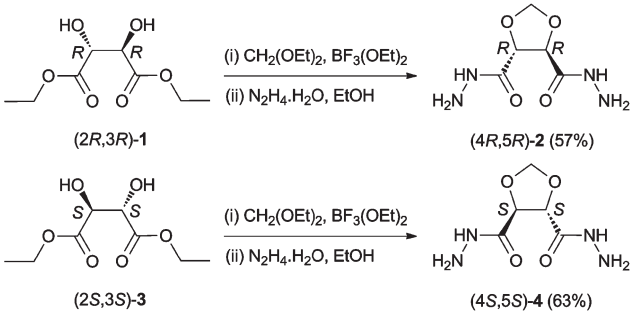
multifunctional macrocyclic structures.[21,22] Adapting this approach to the synthesis of novel macrocycles by [$n+n$]-cyclocondensation, meant that we investigated the reaction between a selection of chiral dihydrazides with aromatic dicarbonyl compounds. In this contribution we report on the successful synthesis of novel chiral tetra-carbohydrazide cyclophane macrocycles based on dihydrazides obtained from tartaric acid and a selection of aromatic dialdehydes.

Results and discussion

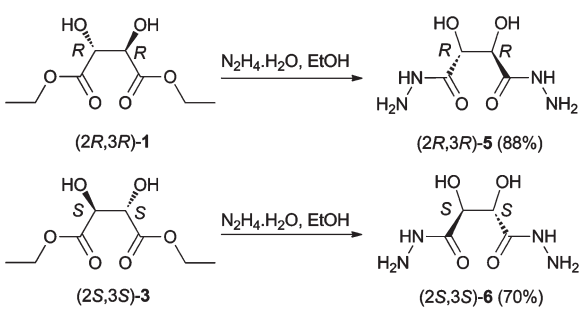
For the modular assembly of chiral macrocycles we decided to investigate dihydrazides based on tartaric acid, offering the advantage that both enantiomeric forms of a macrocycle will be accessible. Our approach towards the synthesis of dihydrazide building blocks involves protection of the *vicinal* hydroxyl groups of commercially available (+)-diethyl L-tartrate (**1**) and (−)-diethyl D-tartrate (**2**) with diethoxymethane in the presence of the Lewis acid catalyst $BF_3(OEt)_2$.[23]

In situ condensation of the protected diesters with hydrazine monohydrate in absolute ethanol afforded the corresponding (4*R*,5*R*)-1,3-dioxolane-4,5-dicarbohydrazide (**2**) and (4*S*,5*S*)-1,3-dioxolane-4,5-dicarbohydrazide (**4**), which serve as the building blocks for the novel macrocycles (Scheme 1).

Similarly, chiral dihydroxy (2*R*,3*R*)-hydrazide (**5**) and (2*S*,3*S*)-hydrazide (**6**) were synthesised by reacting (+)-diethyl L-tartrate (**1**) and (−)-diethyl D-tartrate (**3**) with hydrazine mono-hydrate in absolute ethanol (Scheme 2).[24] Structures of hydrazides (**2**), (**4**), (**5**) and (**6**), were fully characterised using various spectroscopic techniques. ^{1}H NMR spectrum for (*i.e.*, dicarbohydrazide **2**) showed broad signals at δ 9.42, 5.04, 4.41 and 4.32 ppm corresponding to (N*H*), (C*H*), (CH_2) and (NH_2), respectively.



Scheme 1 Synthetic route to chiral hydrazides (**2**) and (**4**).



Scheme 2 Synthetic route to chiral hydrazides (**5**) and (**6**).

^{13}C NMR spectrum showed three signals at δ 168.0, 96.8 and 77.2 ppm corresponding to (C═O), (CH_2) and (CH), respectively.

FT-IR (Fourier transform infrared spectroscopy) spectrum showed strong absorption band at ν 1667 cm^{-1} corresponding to the stretching vibration of the ν C═O. It showed also weak absorption bands at ν 3191 and 3320 cm^{-1} corresponding to the hydrazide NH moieties. ESI-TOF (electrospray ionization time-of-flight) mass spectrum showed the expected pseudo molecular ion peak at 403.1277 Da as the sodium adduct of two molecules of the hydrazide (2M + Na$^+$).

It is worth noting that the novel dicarbohydrazides adopt conformations in which the carbonyl groups assume *anti*-orientation to each other.[25] These conformations are stabilised by strong n → π* interaction and intramolecular hydrogen bonding as suggested by computational calculations (Fig. 1). Consequently, the dicarbohydrazides become good candidates for macrocyclisation based on conformational bias, rather than polymerisation.

Next we turned out attention to the macrocyclisation reaction of the obtained dihydrazides **2**, **4**, **5** and **6** with a selection of aromatic dialdehydes. The [2 + 2]-cyclocondensation reaction was optimised in terms of stoichiometries and concentration of the reactants. The common strategies for the synthesis of macrocycles involve either using external template to assist the macrocyclisation process or applying high dilution conditions to avoid polymerisation.[26–29] We conducted the [2 + 2]-cyclocondensation reaction in CH_2Cl_2 at 0.1 and 0.01 M. After 24 h we noticed that, the macrocyclic product neither form by stirring at room temperature nor by refluxing. However, some intermediates were detected by ESI-TOF mass spectrometry which existed in equilibration over the course of the reaction (see ESI†). Following our strategy, the [2 + 2]-cyclocondensation reaction took place efficiently in MeOH at relatively high concentration of the reactants (0.05 M or less) under reflux for 7 h in the presence of few drops of AcOH as a catalyst. The [3 + 3]- and [4 + 4]-cyclocondensation products were observed along with the [2 + 2]-macrocycle under high dilution conditions (1 M), however the [2 + 2]-macrocycle was the predominant product. We also found that, the [2 + 2]-macrocycle forms selectively in analytically pure form in case where a slightly excess of the dicarbohydrazide was used (*i.e.*, 1.2 to 1 M).

(4*R*,5*R*)-1,3-Dioxolane-4,5-dicarbohydrazide (**2**) reacted with isophthaldehyde, terephthaldehyde, 4,4′-diformylbiphenyl, 4-(4-formylphenoxy)-benzaldehyde and 4,4′-diformyltriphenylamine

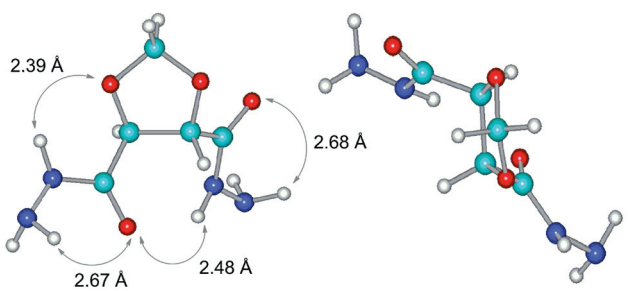
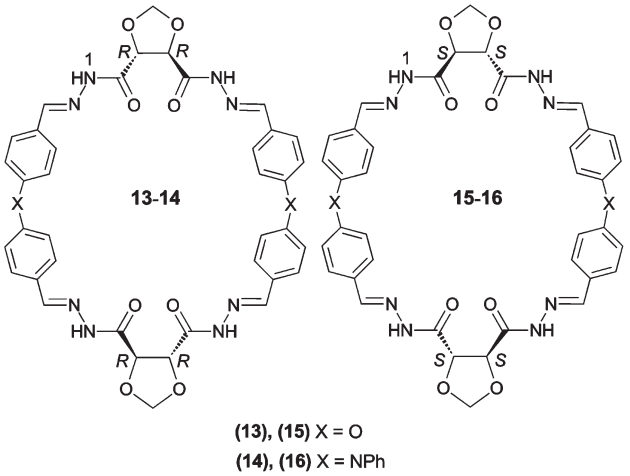


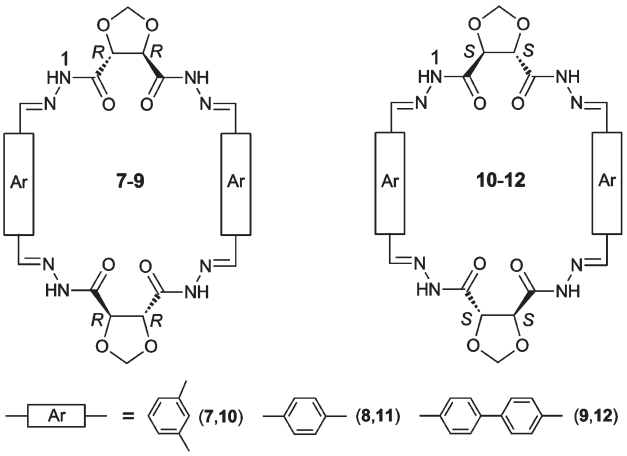
Fig. 1 Bird's-eye view for the computed structure of chiral dihydrazides (**2**) and (**4**). Structures were energy minimised using AM1 method and a Polak–Ribiere conjugate gradient with rms < 0.01 kcal. mol^{-1}.

to afford the corresponding [2 + 2]-cyclocondensation products (**7–9**), (**13**) and (**14**) in quantitative yields which were sufficiently pure as judged by ^{1}H NMR and ESI-TOF mass spectra (Schemes 3 and 4). Similarly, macrocycles (**10–12**), (**15**) and (**16**) were synthesised according to the above mentioned procedure from (4*S*,5*S*)-1,3-dioxolane-4,5-dicarbohydrazide (**4**) (Schemes 3 and 4).

Structures of the novel macrocycles were fully assigned on the basis of ^{1}H NMR, ^{13}C NMR, 2D-NMR, VT-(variable temperature) NMR, CD-spectroscopy, ESI- or APCI-TOF (atmospheric pressure chemical ionisation) and FT-IR. APCI-TOF mass spectrum for macrocycle (**10**) showed the expected molecular ion peak (M + Na^{+}) at 599.1599 Da (Fig. 2, see ESI† for ESI-mass spectra and fragmentation mechanisms). High resolution TOF-mass spectrometry data are given in Table 1. FT-IR spectrum for macrocycle (**10**) showed the presence of a strong absorption band at ν 1680 cm^{-1} corresponding to the stretching vibration of the ν C═O and ν C═N. ^{1}H NMR spectra for the novel macrocycles at ambient temperature in both DMSO-d_6 and DMF-d_7 showed broad signals suggesting conformational flexibility in



Scheme 4 [2 + 2]-Cyclocondensation products (**13–16**).



Scheme 3 [2 + 2]-Cyclocondensation products (**7–12**).

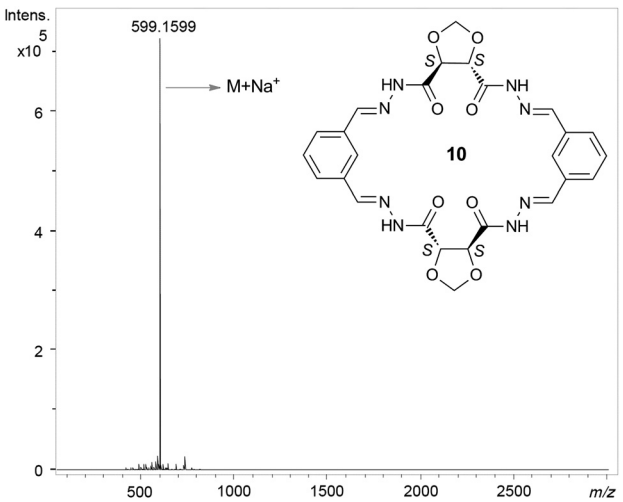


Fig. 2 APCI-TOF mass spectrum for macrocycle (**10**), from DMSO.

Table 1 High resolution TOF-mass data for the novel chiral macrocycles and isolated yields

Compound	Molecular formula		*m/z*	Meas. *m/z*	Error (ppm)	Yield (%)
2	$C_{10}H_{20}N_8NaO_8$	2M + Na^{+}	403.1296	403.1277	4.7	57
4	$C_{10}H_{20}N_8NaO_8$	2M + Na^{+}	403.1296	403.1276	5.1	63
5	$C_8H_{20}N_8NaO_8$	2M + Na^{+}	379.1296	379.1285	3.1	88
6	$C_8H_{20}N_8NaO_8$	2M + Na^{+}	379.1296	379.1281	4	70
7	$C_{26}H_{24}N_8NaO_8$	M + Na^{+}	599.1609	599.1596	2.3	99
8	$C_{26}H_{25}N_8O_8$	M + H^{+}	577.1790	577.1782	1.4	99
9	$C_{38}H_{33}N_8O_8$	M + H^{+}	729.2475	729.2508	4.5	98
10	$C_{26}H_{24}N_8NaO_8$	M + Na^{+}	599.1609	599.1599	1.7	99
11	$C_{26}H_{25}N_8O_8$	M + H^{+}	577.1429	577.1450	3.6	99
12	$C_{38}H_{31}N_8O_8$	M − H^{+}	[b]	727[b]	[a,b]	97
13	$C_{38}H_{33}N_8O_{10}$	M + H^{+}	761.2314	761.2292	2.9	99
14	$C_{50}H_{42}N_{10}NaO_8$	M + Na^{+}	933.3079	933.3048	3.4	99
15	$C_{38}H_{32}N_8NaO_{10}$	M + Na^{+}	783.2134	783.2113	2.6	98
16	$C_{50}H_{43}N_{10}O_8$	M + H^{+}	911.3260	911.3292	−3.5	99
17	$C_{24}H_{25}N_8O_8$	M + H^{+}	553.1844	553.1816	5	99
18	$C_{24}H_{25}N_8O_8$	M + H^{+}	553.1941	553.1954	−2.3	99

[a] Error value could not be estimated due to poor solubility and hence low peak intensity. [b] APCI-MS^2.

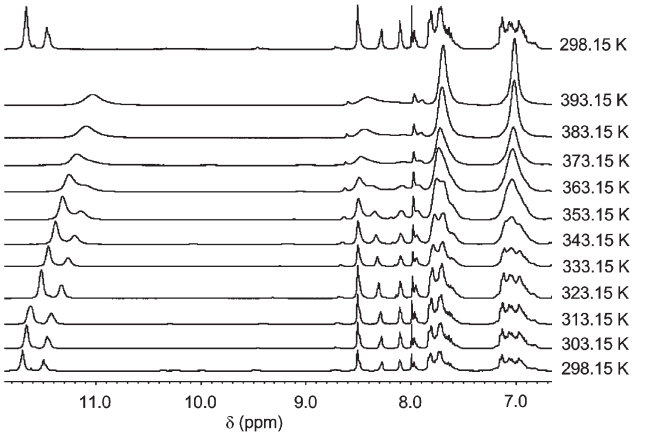


Fig. 3 Variable temperature ^{1}H NMR spectra for compound (**13**), 400 MHz, DMF-d_7.

solution. ^{1}H NMR spectrum for macrocycle (**13**) in DMSO-d_6 showed a broad signal at δ 11.66 ppm with an integration of four (4 × N*H*). It showed also four broad singlets at δ 8.34, 8.06, 7.93 and a signal at 7.71 ppm overlapping with the aromatic protons corresponding to four non-equivalent azomethine protons (see Fig. 3). In DMF-d_7 the signal corresponding to the (N*H*) protons splits into two broad signals appearing at δ 11.70 and 11.54 ppm, each signal integrated with two (4 × N*H*). In addition, four broad signals appeared at δ 8.51, 8.28, 8.12 and 7.97 ppm corresponding to four non-symmetrical azomethine protons.

In order to characterise the behaviour of the novel macrocycles in solution, we performed VT-NMR studies for macrocycles (**13**) and (**14**). VT-NMR was performed from 303 to 393 K in DMF-d_7. The two broad signals appearing at δ 11.70 and 11.54 ppm corresponding to the four (N*H*) protons coalesced at 383 K to a broad singlet appearing at δ 11.10 ppm (Fig. 3). Cooling the NMR to 298 K yields the same spectrum as first recorded illustrating the reversibility of the process.

We suggest that two distinct conformational isomers could result from intramolecular hydrogen bonding interactions (–NH···O═C), whose interconversion involved fast exchange during the ^{1}H NMR time scale and resulted in reducing the solubility of the macrocycles in common organic solvents and water.

VT-NMR spectra for macrocycle (**14**) is available with the ESI.† The change in chemical shifts in response to changing temperature can be graphically represented by plotting the values of chemical shift (δ in ppm) *versus* temperature (°C) as shown in Fig. 4.

It can be inferred that a intramolecular hydrogen bond breaks upon heating, resulting in upfield shift of the associated (N*H*) protons. Our hypothesis of conformational isomers was further supported by 2D-NMR experiments. The 2D-ROESY spectrum for macrocycle (**14**) showed through space interactions between two (N*H*) protons with two azomethine protons (*H*C═N) and two methine protons (C*H*) (Fig. 5 and 6).

The other (N*H*) protons interacted through space with two azomethine protons (*H*C═N), while no interactions were observed with methine protons.

In order to further understand the nature of the intramolecular hydrogen bonding, we performed several molecular modelling

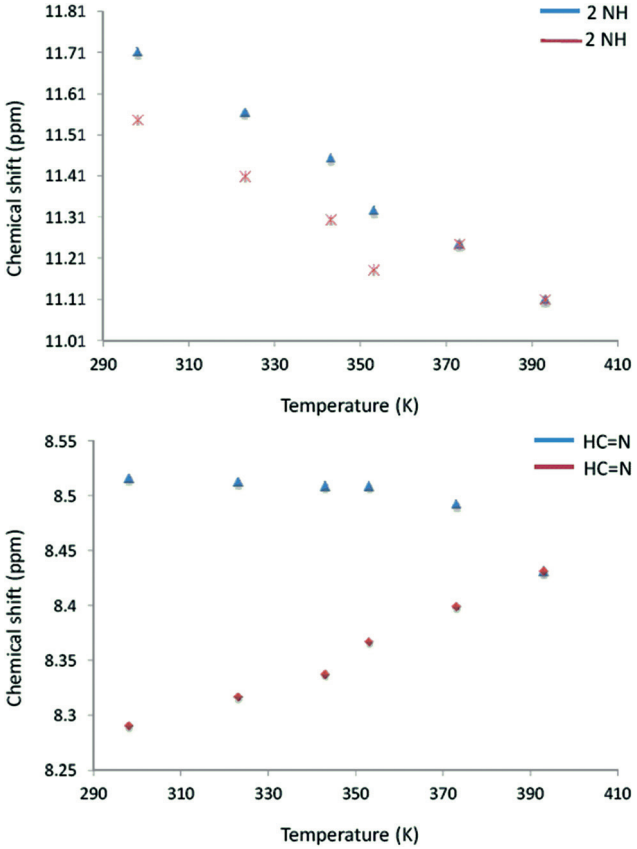


Fig. 4 Graphical representation for the change of chemical shift in response to increasing temperature.

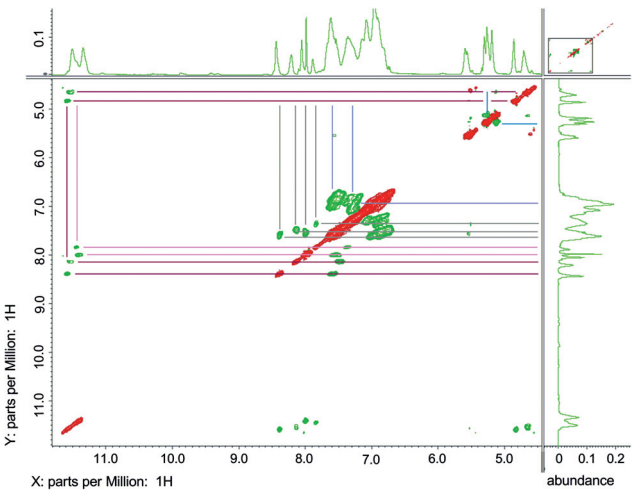


Fig. 5 2D-ROESY spectrum for macrocycle (**14**), 400 MHz, DMF-d_7.

based studies. Data from 2D-ROESY experiments were used for subsequent structure modelling calculations. Structures of the novel macrocycles (*i.e.*, macrocycle **14**) were optimised using HyperChem software (Release 8).

The molecular structures were optimised at the AMBER (assisted model building with energy refinement) and PM3 (parameterised model number 3) levels using the Polak–Ribiere algorithm until the root mean square (RMS) gradient was

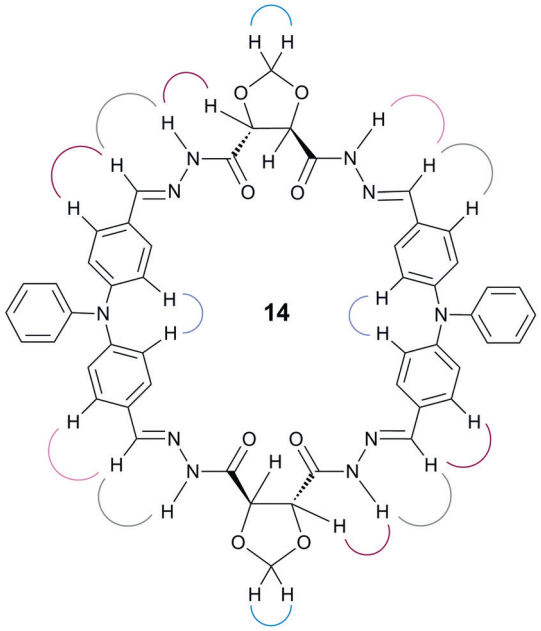


Fig. 6 2D-ROESY interactions for macrocycle (**14**).

0.01 kcal. mol^{-1} or less. The results of molecular modelling are in good agreement with the structures suggested by 2D-ROESY experiment and confirm the presence of intramolecular hydrogen bonding interactions (Fig. 7).

In solution, macrocycle (**14**) can assume a minimum energy conformation (**14b**) which comprises intramolecular hydrogen bonding and π–π stacking interactions. Upon heating (**14b**) rapid interconversion to the more symmetric conformation (**14a**) occurs measurable on the NMR time scale.

Next, we turned our attention to assessing the reactivity of the unprotected dicarbohydrazides towards the [2 + 2]-cyclocondensation reaction. (2*R*,3*R*)-hydrazide (**5**) and (2*S*,3*S*)-hydrazide (**6**) reacted with terephthaldehyde in methanol (<0.05 M) in the presence of few drops of catalytic AcOH to form highly C_2-symmetrical [2 + 2]-cyclocondensation products (**17**) and (**18**) as judged by the ^{1}H and ^{13}C NMR spectra (Fig. 8).

This indicated the presence of only one conformer in solution. ^{1}H NMR spectrum for macrocycle (**17**) showed a broad signal at δ 11.27 ppm (4 × N*H*). It also showed broad signals at δ 8.44 ppm corresponding to four azomethine protons (4 × *H*C═N). APCI-TOF mass data for macrocycles (**17**) and (**18**) are shown in Table 1. 2D-ROESY spectrum showed through space interactions between (N*H*), (*H*C═N) and (O*H*) protons (see ESI†). In an attempt to investigate and to explain the behaviour of the non-protected macrocycles in solution, we performed molecular modelling studies at the MM+ (molecular mechanics) level based on data from 2D-ROESY experiments. Molecular modelling showed that macrocycle (**17**) adopts a conformation in which all azomethine protons (*H*C═N) are *anti*-oriented. The free hydroxyl groups can form concerted intramolecular hydrogen bonding with the carbonyl groups to yield symmetrical and stable conformers (Fig. 9).

Distances (Å) between some selected atoms based on molecular modelling calculations for macrocycles (**13**) and (**14**) are shown in Table 2.

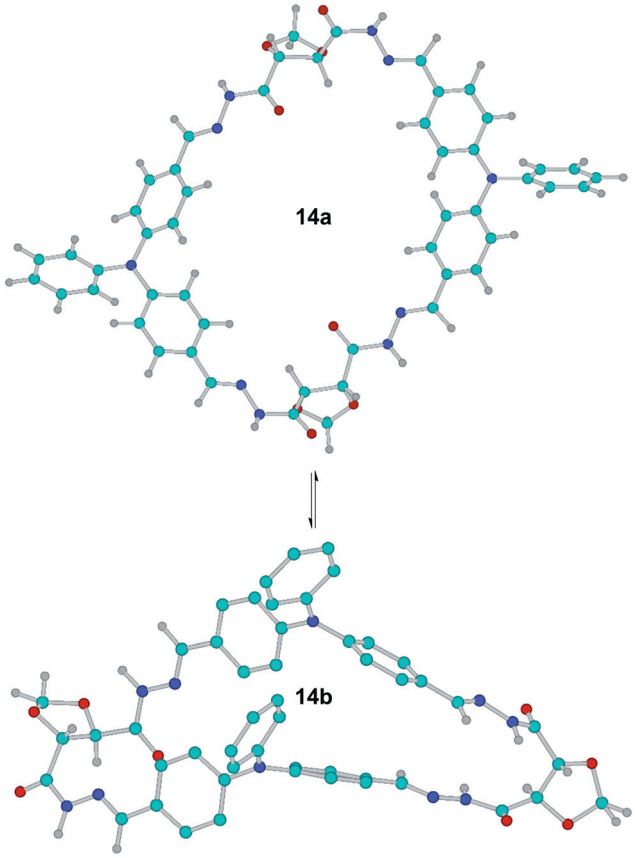


Fig. 7 Computed structures for macrocycle (**14**) at the PM3 and AMBER levels. A Polak–Ribiere conjugate gradient with rms < 0.01 kcal.mol^{-1} was used. Some hydrogen atoms were omitted for clarity.

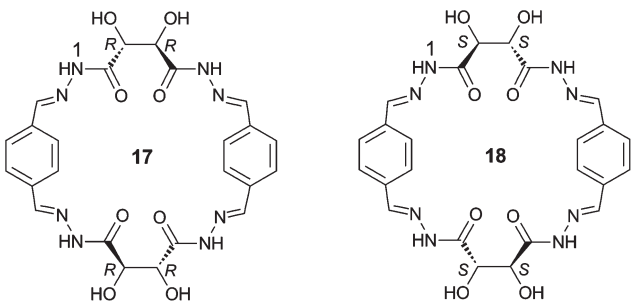


Fig. 8 [2 + 2]-cyclocondensation products (**17**) and (**18**).

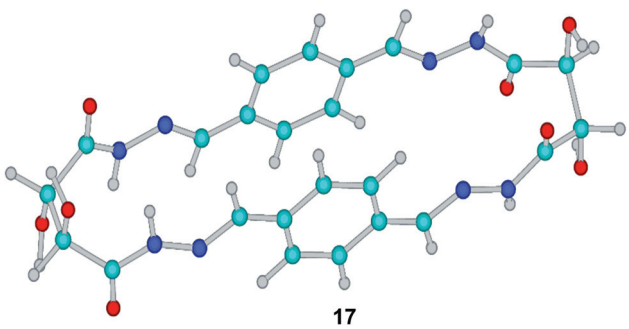


Fig. 9 Computed structure for macrocycle (**17**).

Table 2 Distances (Å) between some selected atoms for macrocycles (**13**) and (**14**)

Atoms	Macrocycle (**13**) (Å)	Macrocycle (**14a**) (Å)	Macrocycle (**14b**) (Å)
C2–C21	11.83	11.12	16.64
C3–C22	14.02	13.51	17.14
C4–C23	13.56	13.45	15.77
C5–C24	15.56	15.43	13.45
N6–N25	15.90	16.04	12.21
N7–N26	14.02	14.29	10.18
C8–C27	14.99	15.43	9.31
C9–C28	13.79	14.40	7.33
C12–C31	13.25	14.18	6.60
X13–X32	14.09	14.94	5.28
C14–C33	12.51	13.27	6.29
C17–C36	11.49	11.70	9.84
C18–C37	12.06	12.00	12.00
N19–N38	11.59	10.55	13.15
N20–N1	12.42	11.92	15.27

The chirality of the novel macrocycles and their precursors was confirmed by CD-spectroscopy as shown in Fig. 10. *All-R* macrocycle (**14**) shows for example a positive Cotton effect with a zero intercept at around 370 nm, whereas its enantiomeric counterpart *all-S* (**16**) shows a negative Cotton effect. Similar to trianglimines the observed Cotton effect is a consequence of the interaction of the two aromatic chromophores within the macrocycle.

Conclusion

In summary, we have synthesised a novel class of chiral non-racemic tetra-carbohydrazide macrocycles starting from commercially available diethyl tartrates. After conversion of the chiral building block to a dihydrazide, reaction with aromatic dialdehydes yielded the novel macrocycles. The macrocyclisation reaction takes place at relatively high concentration of the reactants in MeOH (<0.05 M) to afford, presumably under conformational bias, selectivity the [2 + 2]-cyclocondensation products. Macrocycles are available in both enantiomeric forms. VT-NMR along with 2D-NMR experiments confirmed the presence of a dynamic behaviour in solution, which has been rationalized in terms of an unprecedented conformational interconversion between two conformers one stabilised by intramolecular hydrogen bonding and π–π stacking interactions. Further work aimed at assessing molecular recognition of the novel macrocycles in DMF and enhancing solubility in other organic solvents is under investigation and will be published in due course.

Experimental

All the reagents used for the reactions were purchased from Sigma-Aldrich, Applichem or Flucka (Germany) and were used as obtained. Whenever possible the reactions were monitored by thin layer chromatography (TLC). TLC was performed on Macherey–Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}). Column chromatography was carried out on silica gel 60 (0.040–0.063 mm) under flash conditions. Melting points were determined in open capillaries using a Buechl

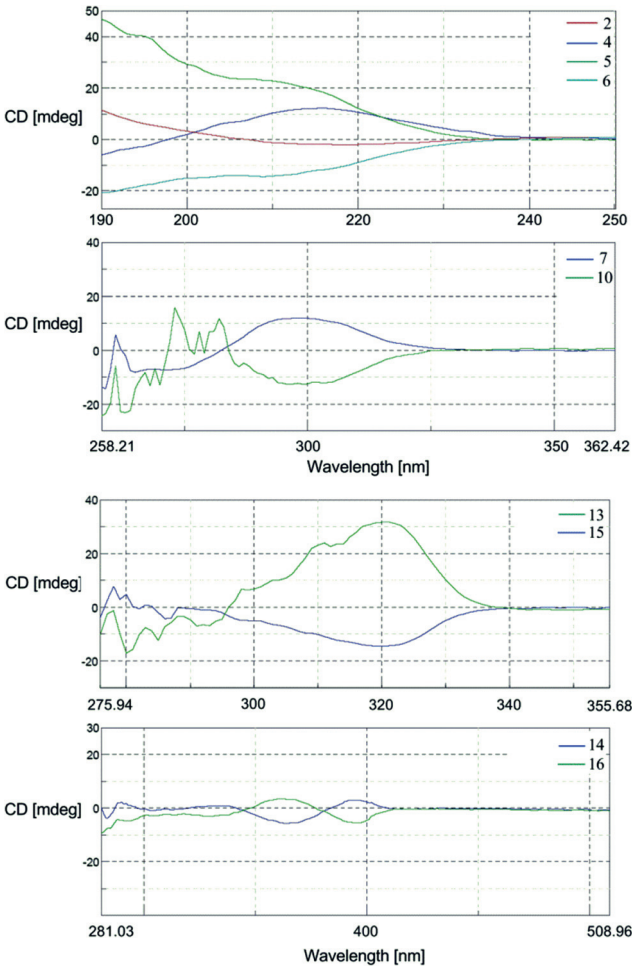


Fig. 10 CD-spectra for chiral hydrazides (**2,4–6**) in water and [2 + 2]-cyclocondensation products (**7**,**10** and **13–16**) in DMSO.

B-545 melting point apparatus and are not corrected. Infrared spectra were determined using a Vector-33 Bruker FT-IR spectrometer.

The samples were measured directly as solids or oils; ν_{max} values were expressed in cm^{-1} and were given for the main absorption bands. ^1H NMR and ^{13}C NMR spectra were acquired on a JEOL ECX-400 spectrometer operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR in DMSO-d_6, D_2O, $CDCl_3$ or DMF-d_7 using a 5 mm probe. The chemical shifts (δ) are reported in parts per million and were referenced to the residual solvent peak. The following abbreviations are used: s, singlet; m, multiplet; br, broad signal. Mass spectra were recorded using HCTultra and ESI- or APCI-TOF Bruker Daltonics mass spectrometers and samples were dissolved in DMSO, DMF and acetonitrile or water using the positive and negative electrospray ionisation modes. Calibration was carried out using a 0.1 M solution of sodium formate in the enhanced quadratic mode prior to each experimental run. The results of measurements were processed using Compass 1.3 data analysis software for a Bruker Daltonics time-of-flight mass spectrometer (micrOTOF). Molecular modelling calculations were carried out with Hyperchem software (Release 8.0) at the AM1, PM3, AMBER and MM+ levels *in vacuo* and no influence of solvents was taken into

account in these calculations.[30,31] 4,4′-Biphenyl dicarboxaldehyde was synthesised according to the literature.[32] Circular Dichroism measurements were carried out using Jasco-J-810 Spectropolarimeter in H_2O and DMSO. We could not measure the ^{13}C-spectrum for macrocycles (**9**) due to its poor solubility in DMSO-d_6. All products were suitable for use without further purification.

(4*R*,5*R*)-1,3-dioxolane-4,5-dicarbohydrazide (2)

To a stirred solution of (+)-diethyl L-tartrate (17.8 mL, 71.70 mmol) in isopropyl acetate (100 mL) were added diethoxymethane (12.1 mL, 96.86 mmol) and boron trifluoride diethyl etherate (23.8 mL, 192.84 mmol), and the mixture was refluxed for 7 h. The reaction mixture was carefully quenched with saturated aqueous sodium bicarbonate and the layers were separated. The water phase was extracted with isopropyl acetate (2 × 100 mL) and the combined organic layers were dried with sodium sulfate, filtered and evaporated under reduced pressure. The crude mixture (21.9 g) was dissolved without further purification in ethanol (100 mL) and hydrazine monohydrate (6.8 mL, 213.44 mmol) was added. The reaction mixture was refluxed for 7 h. The precipitate was filtered off, washed with ethanol and diethyl ether to give the title compound (**2**) as a white solid (11.58 g, 57%); mp 210–211 °C; IR ν_{max}/cm^{-1} 3320, 3191 (NH), 1667 (C═O); ^1H NMR (400 MHz, DMSO-d_6) δ_H 9.42 (2H, brs, N*H*), 5.04 (2H, brs, C*H*), 4.41 (2H, brs, CH_2), 4.32 (4H, brs, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 168.0, 96.8, 77.2; MS (ESI-MS, H_2O, HCTultra) *m*/*z* (Calcd 190.1; exp. 212.8, M + Na^+, 100%), (Calcd 190.1; exp. 402.9, 2M + Na^+, 74%), (HRMS, ESI-TOF, H_2O) *m*/*z* (Calcd 403.1296; meas. 403.1277, 2M + Na^+).

(4*S*,5*S*)-1,3-dioxolane-4,5-dicarbohydrazide (4)

To a stirred solution of (−)-diethyl D-tartrate (17.8 mL, 71.70 mmol) in isopropyl acetate (100 mL) were added diethoxymethane (12.1 mL, 96.86 mmol) and boron trifluoride diethyl etherate (23.8 mL, 192.84 mmol), and the mixture was refluxed for 7 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate and the layers were separated. The water phase was extracted with isopropyl acetate (2 × 100 mL), and the combined organic layers were dried with sodium sulfate, filtered and evaporated under reduced pressure. The crude mixture (22.63 g) was dissolved without further purification in ethanol (100 mL) and hydrazine monohydrate (6.5 mL, 207.6 mmol) was added to the reaction mixture. The reaction mixture was refluxed for 7 h. The precipitate was filtered off, washed with ethanol and diethyl ether to give the title compound (**4**) as a white solid (13.11 g, 63%); mp 209–210 °C; IR ν_{max}/cm^{-1} 3320, 3193 (NH), 1667 (C═O); ^1H NMR (400 MHz, DMSO-d_6) δ_H 9.41 (2H, brs, N*H*), 5.04 (2H, brs, C*H*), 4.41 (2H, brs, CH_2), 4.31 (4H, brs, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 168.0, 96.8, 77.2; MS (ESI-MS, H_2O, HCTultra) *m*/*z* (Calcd 190.1; exp. 212.8, M + Na^+, 100%), (Calcd 190.1; exp. 402.9, 2M + Na^+, 67%), (HRMS, ESI-TOF, H_2O) *m*/*z* (Calcd 403.1296; meas. 403.1276, 2M + Na^+).

(2*R*,3*R*)-2,3-Dihydroxydicarbohydrazide (5)

Hydrazine monohydrate (3.1 mL, 116.8 mmol) was added to a stirred solution of (+)-diethyl L-tartrate (5 mL, 29.2 mmol) in ethanol (40 mL). The mixture was refluxed for 7 h. The precipitate was filtered off, washed with methanol, diethyl ether and dried to give the title compound (**5**) as a white solid (4.61 g, 88%); mp 208–209 °C; IR ν_{max}/cm^{-1} 3408, 3354, 3309 and 3286 (OH and NH), 1661 (C═O); ^1H NMR (400 MHz, DMSO-d_6) δ_H 8.75 (2H, brs, N*H*), 5.34 (2H, brs, C*H*), 4.21 (6H, brs, NH_2 and O*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 171.0, 72.7; MS (ESI-MS, H_2O, HCTultra) *m*/*z* (Calcd 178.1; exp. 200.7, M + Na^+, 100%), (HRMS, ESI-TOF, H_2O) *m*/*z* (Calcd 379.1296; meas. 379.1285, 2M + Na^+).

(2*S*,3*S*)-2,3-Dihydroxydicarbohydrazide (6)

Hydrazine monohydrate (3.1 mL, 116.8 mmol) was added to a stirred solution of (−)-diethyl D-tartrate (5 mL, 29.2 mmol) in ethanol (40 mL). The mixture was refluxed for 7 h. The precipitate was filtered off, washed with methanol, diethyl ether and dried to give the title compound (**6**) as a white solid (3.64 g, 70%); mp 208–209 °C; IR ν_{max}/cm^{-1} 3408, 3354, 3309 and 3286 (OH and NH), 1659 (C═O); ^1H NMR (400 MHz, D_2O) δ_H 4.64 and 4.46 (2H, brs, C*H*); ^{13}C NMR (100 MHz, D_2O) δ_C 171.8, 71.9; MS (ESI-MS, H_2O, HCTultra) *m*/*z* (Calcd 178.1; exp. 200.7, M + Na^+, 100%), (HRMS, ESI-TOF, H_2O) *m*/*z* (Calcd 379.1296; meas. 379.1281, 2M + Na^+).

General procedure for the synthesis of tetra-carbohydrazide macrocycles (7–18)

Dicarbohydrazide (**2**), (**4**), (**5**) or (**6**) (1.2 mmol) and the corresponding dialdehyde (1 mmol) were mixed in MeOH (<0.05 M) and two drops of catalytic AcOH were added. The reaction mixture was refluxed for 7 h. The precipitate which form was filtered off, washed with water, chloroform and dried to give the corresponding macrocycle in a quantitative yield.

(3*R*,4*R*,16*R*,17*R*)-Tetra-carbohydrazide cyclophane (7)

Prepared from (4*R*,5*R*)-1,3-dioxolane-4,5-dicarbohydrazide (**2**) and isophthaldehyde as a white solid precipitate (99%); mp > 315 °C (decomp.); IR ν_{max}/cm^{-1} 3218 (NH), 1681 (C═O, C═N); ^1H NMR (400 MHz, DMSO-d_6) δ_H 11.78 (4H, brs, N*H*), 8.40–8.19 (2H, m, C*H*═N), 8.08–7.96 (2H, m, C*H*═N), 7.88–7.12 (8H, m, Ar*H*), 5.45 (2H, brs, C*H*), 5.23–5.08 (4H, m, CH_2), 4.78 (1H, brs, C*H*), 4.52 (1H, brs, C*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 170.4, 165.8, 148.9, 144.5, 134.7, 129.7, 97.2, 77.5; MS (ESI-MS, DMF and ACN, HCTultra) *m*/*z* (Calcd 576.2; exp. 599.1, M + Na^+, 100%), (HRMS, APCI-TOF, DMSO) *m*/*z* (Calcd 599.1609; meas. 599.1596, M + Na^+).

(3*R*,4*R*,17*R*,18*R*)-Tetra-carbohydrazide cyclophane (8)

Prepared from (4*R*,5*R*)-1,3-dioxolane-4,5-dicarbohydrazide (**2**) and terephthaldehyde as a pale yellow solid precipitate (99%); mp > 345 °C (decomp.); IR ν_{max}/cm^{-1} 3206 (NH), 1672 (C═O,

C═N); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H 11.77 (4H, brs, N*H*), 8.35 (1H, brs, C*H*═N), 7.95–7.87 (2H, m, C*H*═N), 7.74–7.11 (9H, m, C*H*═N and Ar*H*), 5.38 (2H, brs, C*H*), 5.20–4.99 (4H, m, CH_2), 4.76 (1H, brs, C*H*), 4.49 (1H, brs, C*H*); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_C 170.5, 165.7, 148.9, 144.4, 134.3, 128.0, 97.5, 77.3; MS (ESI-MS, DMF and ACN, HCTultra) *m*/*z* (Calcd 576.2; exp. 577.1, M + H$^+$, 100%), (HRMS, APCI-TOF, DMSO) *m*/*z* (Calcd 577.1790; meas. 577.1782, M + H$^+$).

(3*R*,4*R*,21*R*,22*R*)-Tetra-carbohydrazide cyclophane (9)

Prepared from (4*R*,5*R*)-1,3-dioxolane-4,5-dicarbohydrazide (**2**) and 4,4′-diformylbiphenyl as a yellow solid precipitate (98%); mp > 340 °C (decomp.); IR ν_{max}/cm^{-1} 3211 (NH), 1672 (C═O, C═N); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H 11.72 (4H, brs, N*H*), 7.94 (2H, brs, C*H*═N), 7.79–7.05 (18H, m, C*H*═N and Ar*H*), 5.38–5.02 (6H, m, C*H* and CH_2), 4.48 (1H, brs, C*H*), 4.33 (1H, brs, C*H*); MS (ESI-MS, DMSO, HCTultra) *m*/*z* (Calcd 728.2; exp. 729.2, M + H$^+$, APCI-MS^2, 100%), (HRMS, APCI-TOF, DMSO) *m*/*z* (Calcd 729.2475; meas. 729.2508, M + H$^+$).

(3*S*,4*S*,16*S*,17*S*)-Tetra-carbohydrazide cyclophane (10)

Prepared from (4*S*,5*S*)-1,3-dioxolane-4,5-dicarbohydrazide (**4**) and isophthaldehyde as a white solid precipitate (99%); mp > 323 °C (decomp.); IR ν_{max}/cm^{-1} 3223 (NH), 1680 (C═O, C═N); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H 11.78 (4H, brs, N*H*), 8.40 (1H, brs, C*H*═N), 8.07–7.96 (2H, m, C*H*═N), 7.88–7.14 (9H, m, C*H*═N and Ar*H*), 5.46–5.40 (2H, m, C*H*), 5.23–5.08 (4H, m, CH_2), 4.86–4.79 (1H, brs, C*H*), 4.52 (1H, brs, C*H*); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_C 170.4, 165.8, 148.9, 144.5, 134.4, 129.7, 97.3, 77.5; MS (ESI-MS, DMF and ACN, HCTultra) *m*/*z* (Calcd 576.2; exp. 599.1, M + Na$^+$, 100%), (HRMS, APCI-TOF, DMSO) *m*/*z* (Calcd 599.1609; meas. 599.1599, M + Na$^+$).

(3*S*,4*S*,17*S*,18*S*)-Tetra-carbohydrazide cyclophane (11)

Prepared from (4*S*,5*S*)-1,3-dioxolane-4,5-dicarbohydrazide (**4**) and terephthaldehyde as a pale yellow solid precipitate (99%); mp > 346 °C (decomp.); IR ν_{max}/cm^{-1} 3206 (NH), 1671 (C═O, C═N); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H 11.77 (2H, brs, N*H*), 11.62 (2H, brs, N*H*), 8.36 (1H, brs, C*H*═N), 7.92–7.87 (2H, m, C*H*═N), 7.80–7.18 (9H, m, C*H*═N and Ar*H*), 5.37–5.00 (6H, m, C*H* and CH_2), 4.76 (1H, brs, C*H*), 4.22 (1H, brs, C*H*); ^{13}C NMR (100 MHz, DMSO-d$_6$) δ_C 170.7, 165.4, 146.1, 144.2, 135.3, 128.0, 97.0, 77.8; MS (ESI-MS, DMF and ACN, HCTultra) *m*/*z* (Calcd 576.2; exp. 577.1, M + H$^+$, 100%), (HRMS, APCI-TOF, DMSO) *m*/*z* (Calcd 577.1429; meas. 577.1450, M + H$^+$).

(3*S*,4*S*,21*S*,22*S*)-Tetra-carbohydrazide cyclophane (12)

Prepared from (4*S*,5*S*)-1,3-dioxolane-4,5-dicarbohydrazide (**4**) and 4,4′-diformylbiphenyl as a yellow solid precipitate (97%); mp > 340 °C (decomp.); IR ν_{max}/cm^{-1} 3210 (NH), 1673 (C═O, C═N); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H 11.72 (4H, brs, N*H*), 8.39 (1H, brs, C*H*═N), 7.94 (2H, brs, C*H*═N), 7.79–7.04 (17H, m, C*H*═N and Ar*H*), 5.38 (2H, brs, C*H*), 5.19–5.02 (4H, m, CH_2), 4.75–4.32 (2H, m, C*H*); MS (APCI-MS^2, DMSO, HCTultra) *m*/*z* (Calcd 728.2; exp. 729.2, M + H$^+$, 100%), (Calcd 728.2; exp. 727.2, M − H$^+$, 100%).

(3*R*,4*R*,22*R*,23*R*)-Tetra-carbohydrazide cyclophane (13)

Prepared from (4*R*,5*R*)-1,3-dioxolane-4,5-dicarbohydrazide (**2**) and 4-(4-formylphenoxy)benzaldehyde as a white solid precipitate (99%); mp > 315 °C (decomp.); IR ν_{max}/cm^{-1} 3220 (NH), 1681 (C═O, C═N); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H 11.66 (4H, brs, N*H*), 8.34 (1H, brs, C*H*═N), 8.06 (1H, brs, C*H*═N), 7.93 (1H, brs, C*H*═N), 7.71–7.43 (9H, m, C*H*═N and Ar*H*), 7.09–6.65 (8H, m, Ar*H*), 5.42 (2H, brs, C*H*), 5.42–5.10 (4H, brs, CH_2), 4.75 (1H, brs, C*H*), 4.54 (1H, brs, C*H*); ^{1}H NMR (400 MHz, DMF-d$_7$) δ_H 11.70 (2H, brs, N*H*), 11.54 (2H, brs, N*H*), 8.51 (1H, brs, C*H*═N), 8.28 (1H, brs, C*H*═N), 8.12 (1H, brs, C*H*═N), 8.00–7.94 (1H, m, C*H*═N), 7.76 (7H, m, Ar*H*), 7.57 (1H, brs, Ar*H*), 7.14–6.83 (8H, m, Ar*H*), 5.65 (1H, brs, C*H*), 5.59 (1H, brs, C*H*), 5.35–5.23 (4H, m, CH_2), 4.90 (1H, brs, C*H*), 4.78 (1H, brs, C*H*); ^{13}C NMR (100 MHz, DMSO-d$_6$) 170.3, 165.6, 157.7, 148.8, 144.4, 129.7, 119.5, 97.2, 77.5; ^{13}C NMR (100 MHz, DMF-d$_7$) 170.2, 165.7, 158.4, 148.6, 144.2, 129.4, 119.2, 97.4, 78.0; MS (ESI-MS, DMF and ACN, HCTultra) *m*/*z* (Calcd 760.2; exp. 761.3, M + H$^+$, 100%), (HRMS, APCI-TOF, DMSO) *m*/*z* (Calcd 761.2314; meas. 761.2292, M + H$^+$).

(3*R*,4*R*,22*R*,23*R*)-Tetra-carbohydrazide cyclophane (14)

Prepared from (4*R*,5*R*)-1,3-dioxolane-4,5-dicarbohydrazide (**2**) and 4,4′-diformyltriphenylamine as a yellow solid precipitate (99%); mp > 224 °C (decomp.); IR ν_{max}/cm^{-1} 3214 (NH), 1681 (C═O, C═N); ^{1}H NMR (400 MHz, DMF-d$_7$) δ_H 11.38 (2H, brs, N*H*), 11.22 (2H, brs, N*H*), 8.20 (1H, brs, C*H*═N), 7.92 (1H, brs, C*H*═N), 7.80 (1H, brs, C*H*═N), 7.74 (1H, brs, C*H*═N), 7.49–7.22 (6H, m, Ar*H*), 7.22–6.98 (6H, m, Ar*H*), 6.91–6.77 (6H, m, Ar*H*), 6.77–6.49 (8H, m, Ar*H*); 5.32 (2H, brs, C*H*), 5.06–4.94 (4H, m, CH_2), 4.62 (1H, brs, C*H*), 4.46 (1H, brs, C*H*); ^{13}C NMR (100 MHz, DMSO-d$_6$) 170.3, 165.4, 148.3, 146.3, 144.4, 130.4, 129.1, 126.0, 125.2, 123.5, 97.1, 77.5; MS (ESI-MS, DMF and ACN, HCTultra) *m*/*z* (Calcd 910.3; exp. 911.5, M + H$^+$, 100%), (HRMS, APCI-TOF, DMSO) *m*/*z* (Calcd 933.3079 ; meas. 933.3048, M + Na$^+$).

(3*S*,4*S*,22*S*,23*S*)-Tetra-carbohydrazide cyclophane (15)

Prepared from (4*S*,5*S*)-1,3-dioxolane-4,5-dicarbohydrazide (**4**) and 4-(4-formylphenoxy)benzaldehyde as a white solid precipitate (98%); mp > 305 °C (decomp.); IR ν_{max}/cm^{-1} 3219 (NH), 1681 (C═O, C═N); ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H 11.65 (4H, brs, N*H*), 8.35 (1H, brs, C*H*═N), 8.07 (1H, brs, C*H*═N), 7.93 (1H, brs, C*H*═N), 7.71–7.52 (8H, m, C*H*═N and Ar*H*), 7.43 (1H, brs, Ar*H*) 7.10–6.66 (8H, m, Ar*H*), 5.42 (2H, brs, C*H*), 5.22–5.05 (4H, brs, CH_2), 4.75 (1H, brs, C*H*), 4.54 (1H, brs, C*H*); ^{13}C NMR (100 MHz, DMSO-d$_6$) 170.3, 165.6, 157.7,

148.8, 144.4, 129.7, 119.5, 97.2, 77.5; MS (ESI-MS, DMF and ACN, HCTultra) *m/z* (Calcd 760.2; exp. 761.3, M + H^+, 100%), (HRMS, APCI-TOF, DMSO) *m/z* (Calcd 783.2134; meas. 783.2113, M + Na^+).

(3*S*,4*S*,22*S*,23*S*)-Tetra-carbohydrazide cyclophane (16)

Prepared from (4*S*,5*S*)-1,3-dioxolane-4,5-dicarbohydrazide (**4**) and 4,4′-diformyltriphenylamine as a yellow solid precipitate (99%); mp > 220 °C (decomp.); IR ν_{max}/cm^{-1} 3214 (NH), 1681 (C═O, C═N); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 11.59 (4H, brs, N*H*), 8.28 (1H, brs, C*H*═N), 7.96 (1H, brs, C*H*═N), 7.85 (1H, brs, C*H*═N), 7.67–7.57 (2H, m, C*H*═N, Ar*H*), 7.46–7.28 (7H, m, Ar*H*), 7.22–6.96 (8H, m, Ar*H*), 6.94–6.56 (10H, m, Ar*H*), 5.35 (2H, brs, C*H*), 5.19–5.05 (4H, m, CH_2), 4.71 (1H, brs, C*H*), 4.45 (1H, brs, C*H*); ^{13}C NMR (100 MHz, DMSO-d_6) 170.3, 165.4, 148.3, 146.3, 144.3, 130.4, 129.1, 126.1, 125.1, 123.5, 97.1, 77.5; MS (ESI-MS, DMF and ACN, HCTultra) *m/z* (Calcd 910.3; exp. 911.5, M + H^+, 100%), (HRMS, APCI-TOF, DMSO) *m/z* (Calcd 911.3260; meas. 911.3292, M + H^+).

(3*R*,4*R*,17*R*,18*R*)-Tetra-carbohydrazide cyclophane (17)

Prepared from (2*R*,3*R*)-2,3-dihydroxy dicarbohydrazide (**5**) and terephthaldehyde as a white solid precipitate, (99%); mp > 295 °C (decomp.); IR ν_{max}/cm^{-1} 3268 (broad absorption band, OH and NH), 1668 (C═O, C═N); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 11.27 (4H, brs, N*H*), 8.44 (4H, brs, C*H*═N), 7.70 (8H, brs, Ar*H*) 5.91 (4H, brs, O*H*), 4.49 (4H, brs, C*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 168.9, 147.6, 136.2, 127.9, 73.4; MS (APCI-MS^2, DMSO, HCTultra) *m/z* (Calcd 552.2; exp. 553.0, M + H^+, 100%), (Calcd 552.2; exp. 551, M − H^+, 100%), (HRMS, APCI-TOF, DMSO) *m/z* (Calcd 553.1844; meas. 553.1816, M + H^+).

(3*S*,4*S*,17*S*,18*S*)-Tetra-carbohydrazide cyclophane (18)

Prepared from (2*S*,3*S*)-2,3-dihydroxy dicarbohydrazide (**6**) and terephthaldehyde as a pale yellow solid precipitate, (99%); mp > 295 °C (decomp.); IR ν_{max}/cm^{-1} 3263 (broad absorption band, OH and NH), 1667 (C═O, C═N); ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 11.27 (4H, brs, N*H*), 8.43 (4H, brs, C*H*═N), 7.70 (8H, brs, Ar*H*) 5.94 (4H, brs, O*H*), 4.49 (4H, brs, C*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C 169.0, 147.7, 136.2, 127.9, 73.4; MS (APCI-MS^2, DMSO, HCTultra) *m/z* (Calcd 552.2; exp. 553.0, M + H^+, 100%), (Calcd 552.2; exp. 550.9, M − H^+, 100%), (HRMS, APCI-TOF, DMSO) *m/z* (Calcd 553.1941; meas. 553.1954, M + H^+).

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