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Synthesis of novel chiral bis-*N*-substituted-hydrazinecarboxamide receptors and probing their solution-phase recognition to chiral carboxylic guests by ESI-TOF/MS and tandem ESI-MS

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ABSTRACT

Seven novel bis-*N*-substituted-hydrazinecarboxamide receptors were synthesized in good to excellent yields by reacting chiral dicarbohydrazides, obtained from commercially available tartaric acid, with substituted aromatic isocyanates. The newly synthesized hydrazinecarboxamides formed structurally unique supramolecular aggregates, which have been confirmed by ESI-TOF/MS and tandem ESI-MS. They also showed molecular recognition to a selection of chiral carboxylic guests and oligopeptides, which mimic the backbone structure of the bacterial cell wall. The structures of the novel compounds were verified by various spectroscopic techniques including FTIR, ^{1}H NMR, ^{13}C NMR, ESI-TOF/MS, tandem ESI-MS, 2D ROESY NMR, and CD spectroscopy.

1. Introduction

Over the past decades, molecular self-assembly (MSA) has emerged as a stupendous field of endeavors in supramolecular chemistry.[1] MSA has a wide range of applications in biology, nanochemistry, and material science.[2] In order for molecules to undergo self-organization, they must possess functionalities, which aid formation of complementary structures.[3] Noncovalent interactions, such as hydrogen bonds and π–π-stacking play a prominent role in holding and thus stabilizing the assembled associations.[4] In most cases, the self-assembled structures can possess attractive and distinct properties, which differ entirely from that of the non-assembled precursors.[5] An example from nature, which demonstrates the concept of MSA is the self-assembly of the tobacco mosaic virus (TMV).[6] The helical structure of TMV forms by self-assembly of a defined number of protein subunits around a single strand of ribonucleic acid (RNA). Another common example is the Watson–Crick base pairing model in deoxyribonucleic acid (DNA), in which the building blocks assemble together to form a precise and extremely well ordered double helix strand of encoded genetic information. Peptide amphiphiles (PAs), which were firstly reported by Stupp and co-workers, spontaneously formed high molecular weight cylindrically nanofibers.[7] Both the hydrophobicity and hydrogen bonds participate cooperatively in the formation of the self-assembled aggregates.[7]

Mass spectrometry (MS) has been extensively used in studying noncovalent interactions.[8] The detection of biological macromolecules, host/guest (H/G) complexes or self-assembled associations became possible with the development of soft-ionization MS techniques, such as electrospray ionization (ESI). An important feature of ESI-MS is that the solution-phase information can be retained into the gas phase. However, there are some limitations and obstacles associated with detecting high ordered self-assembled structures. These obstacles usually include low peak intensities of the complexes or decomposition of the intact assembled associations before reaching the detector.

Recently, we reported on the synthesis of a new class of chiral cyclophane-*type* macrocycles (**A**) and (**B**) in almost quantitative yields (Fig. 1).[9] We showed that the macrocycles could be obtained in both enantiomeric forms (*R*) or (*S*) by reacting chiral dicarbohydrazides, obtained from commercially available diethyl tartrate, with aromatic dialdehydes and diisocyanates in [2+2]

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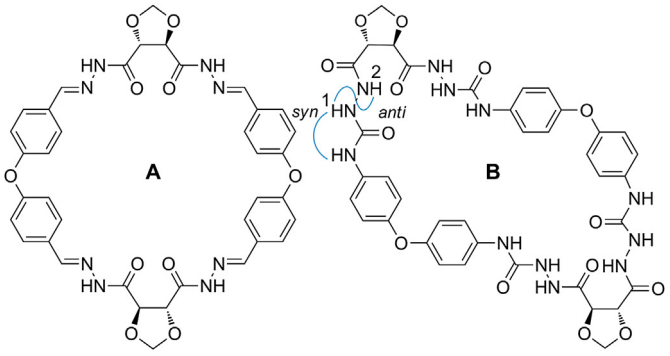

Fig. 1. Tetra-(carbohydrazide) cyclophane (**A**) and tetra-(hydrazinecarboxamide) cyclophane (**B**).

macrocyclization reactions. In this contribution, we report on the synthesis of new bis-*N*-substituted-hydrazinecarboxamides with hydrazido urea functionalities and assessment of their solution-phase recognition to a selection of chiral carboxylic guests by using electrospray ionization time-of-flight mass spectrometry (ESI-TOF/MS) and tandem ESI-MS. Parallel to our work with cyclophanes (**A**) and (**B**), Gawroński and co-workers reported on the synthesis of a tetra-(carbohydrazide) cyclophane macrocycle from (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarbohydrazide and terephthaldehyde.[10] Macrocycle (**A**) possesses four acylhydrazone moieties, making it suitable for different applications in dynamic combinatorial chemistry (DCC), while macrocycle (**B**) possesses more functionalities and has a higher degree of flexibility.[9,11] Similar to the case of trianglimine chemistry, macrocycles (**A**) and (**B**) were formed under the conformational bias of the dicarbohydrazide precursor.[12]

2. Results and discussion

2.1. Synthesis and conformational analysis

In continuation to our work with cyclophane macrocycles (**A**) and (**B**), we report on the synthesis of a new class of two-armed receptors (**7**–**13**), which mimic the backbone structure of macrocycle (**B**). The receptors of this kind were expected to show a high degree of flexibility. The new receptors (**7**–**13**) were obtained from the reactions of chiral dicarbohydrazides (**1**–**3**) with substituted aromatic isocyanate (**4**–**6**) in anhydrous THF (Fig. 2). The structures of compounds (**7**–**13**) were verified by various spectroscopic techniques including FTIR, ^{1}H NMR, ^{13}C NMR, 2D ROESY, circular dichroism (CD) spectroscopy, ESI-TOF/MS, and tandem MS. The ^{1}H NMR spectrum of (**7**) showed three broad signals at δ 10.05, 8.54, and 8.04 ppm corresponding to the six amidic N*H* protons.

The FTIR spectrum showed a strong absorption band at ν 1689 cm^{-1}, corresponding to the stretching vibration of the C=O moieties. The ESI-TOF/MS, in the negative ion mode, showed the expected molecular ion peak at *m*/*z* 487.1588 as [M−H]$^-$. The high resolution mass spectrometry (HRMS) data for the new receptors are shown in Table 1.

The 2D ROESY spectrum of receptor (**7**) (Fig. 3) showed through space interactions between H^c–H^d and H^d–H^e, which suggested a *syn*/*syn* conformation of the N*H* moieties. Unlike in the case of receptor (**7**), the N*H* moieties in macrocycle (**B**) assume a *syn*/*anti* conformation.[9c] It is worth noting that the *syn*/*syn* conformer of macrocycle (**B**) has more energy than the *syn*/*anti* or the *anti*/*anti* conformers due to the electrostatic repulsion between the C=O moieties (6)-(9), (21)-(24), (27)-(30), and (3)-(42).[9c] In order to further understand the reasons for the preferential formation of the

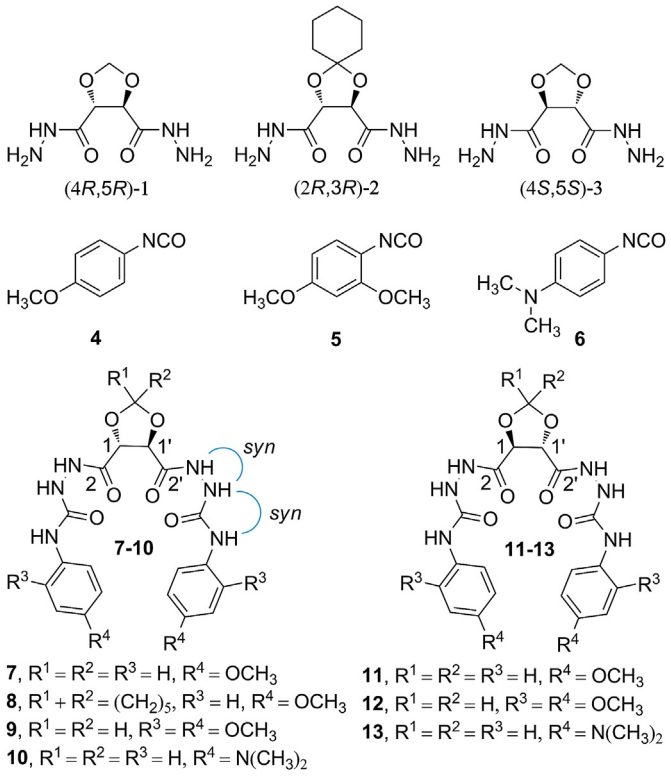

Fig. 2. Two-armed receptors (**7**–**13**) obtained through addition of chiral dicarbohydrazides (**1**–**3**) to substituted aromatic isocyanates (**4**–**6**) in THF.

Table 1
ESI-TOF/MS data and yields of receptors (**7**–**13**)

Product	Molecular formula	Calcd *m*/*z*	[a]Found *m*/*z*	Error [ppm]	Yield %
7	$C_{21}H_{24}N_6O_8$	487.1583	487.1588	−1.0	78
8	$C_{26}H_{32}N_6O_8$	555.2209	555.2224	−2.8	74
9	$C_{23}H_{28}N_6O_{10}$	547.1794	547.1782	2.2	93
10	$C_{23}H_{30}N_8O_6$	513.2216	513.2240	−4.8	89
11	$C_{21}H_{24}N_6O_8$	487.1583	487.1570	2.7	96
12	$C_{23}H_{28}N_6O_{10}$	547.1794	547.1799	−1.0	99
13	$C_{23}H_{30}N_8O_6$	513.2216	513.2233	−3.5	93

[a] Products detected as [M−H]$^-$ ions.

syn/*syn* conformer over the *syn*/*anti* or the *anti*/*anti* conformers for receptor (**7**), we performed molecular modeling studies at the Austin Model 1 (AM1) level using HyperChem software (Release 8.0.6).[13] Data from the 2D ROESY NMR were used for subsequent structure modeling calculations. Molecular modeling suggested a spiral-*like* structure for (**7**), in which the N*H* moieties are *syn*/*syn* oriented with possibility of formation of two intramolecular hydrogen bonds between (N*H*···O=C) (3)-(5′) and (3′)-(5). These interactions stabilize the structure of (**7**) and reduce the electrostatic repulsion between the C=O moieties (2)-(5) and (2′)-(5′) (Fig. 4).

2.2. Probing solution-phase recognition of receptors (7–13) to chiral carboxylic guests (14–20) by using ESI-TOF/MS

ESI-MS has been widely used as a versatile soft ionization method in studying weak noncovalent interactions.[8,14] The ability of the technique to provide precise mass values, high resolution, and little or almost no fragmentations, makes it an indispensable tool in supramolecular analysis. Recently, we reported on the use of ESI-TOF/MS in probing the mechanism of trianglimine formation in real-time and studying the dynamic reversibility and molecular recognition of the tetra-(carbohydrazide) cyclophane macrocycles