ORGANIC LETTERS

2003
Vol. 5, No. 9
1431−1433

Bowl-Shaped C_3-Symmetric Receptor with Concave Phosphine Oxide with a Remarkable Selectivity for Asparagine Derivatives

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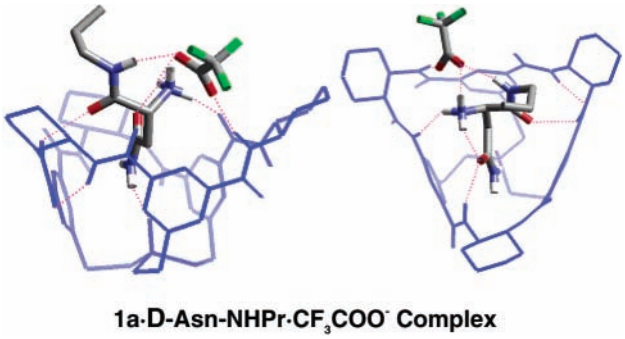
Received January 30, 2003

ABSTRACT



A bowl-shaped C_3-symmetric receptor (1a) that has a phophine oxide functionality in the interior of a "molecular bowl" shows remarkable selectivity for Asn derivatives.

Construction of host molecules possessing a rigidly defined cavity with a concave functionality is of great interest.[1,2] Incorporation of an inwardly pointing functionality into the cavity of a bowl-shaped receptor[3] is reminiscent of the active site of enzymes. If a functional group is embedded in an appropriately sized cavity-shaped molecular host with a rigid framework, the cavity will function as a reaction site or binding site with unique properties.

A previous C_3-symmetric receptor synthesized in our group had a hydrophobic binding cavity with a potential preference for binding lipophilic residues.[4] We expected that introduction of a H-bonding polar functionality within the binding cavity would alter the binding affinity and selectivity toward H-bonding guests compared to hosts without a polar group within the cavity.[5] To introduce a concave functionality into

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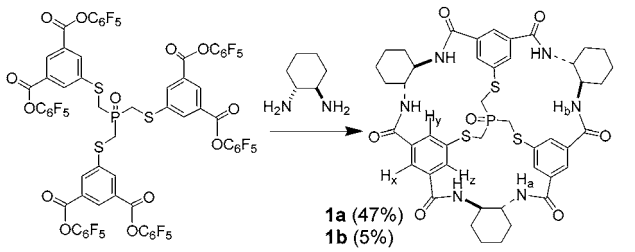
10.1021/ol034168b CCC: $25.00
Published on Web 04/02/2003

the cavity, we designed a C_3-symmetric receptor (**1a**,**b**) with a phosphine oxide moiety at the bottom of the bowl. A CPK model of the designed receptor indicates that P═O is directed either inside or outside the cavity. Composed of a binding cavity with a H-bonding functionality, and H-bond donor and acceptor functionalities on the periphery of the surrounding wall of the bowl-shaped host, **1a** (or **1b**) is expected to show enantioselectivity and residue selectivity in the binding of amino acid derivatives and small peptides. Herein we report a remarkable residue selectivity for Asn alkyl amide against Gln, Glu, and Asp derivatives with quite similar H-bond donor/acceptor geometries in polar media.

Scheme 1



The syntheses of **1a** and **1b** began with trialkylation of tris(chloromethyl)phosphine oxide[6] with dimethyl 5-mercaptoisophthalate. An intermolecular macrolactamization between hexakis(pentafluorophenyl ester) and (1*R*,2*R*)-diaminocyclohexane provided **1a** and **1b** in 47 and 5% yields, respectively.

^{31}P NMR spectroscopy was used in order to show the direction of phosphine oxide at the bottom of receptors. Compounds **1a** and **1b** were shown to have P═O inside the cavity and outside the cavity, respectively, which was elucidated through the changes of the complexation-induced ^{31}P chemical shift between **1a** (or **1b**) and NH_4^+, Ph_2SnCl_2, and tBuNH$_3^+$. Ph_2SnCl_2 and tBuNH$_3^+$ are expected to act as bulky Lewis acids[7] and thus form 1:1 complex with phosphine oxide outside the cavity. Addition of excess tBuNH$_3^+$ to a ~10:1 mixture of **1a** and **1b** resulted in a large downfield shift ($\Delta\delta$ = 5.5 ppm) of ^{31}P resonance for **1b** and a small downfield shift ($\Delta\delta$ = 0.5 ppm) for **1a**. Addition of excess Ph_2SnCl_2 to **1a** in 10:1 (v/v) $CDCl_3/CD_3OD$ caused a small downfield shift of the ^{31}P NMR signal. Successive addition of an NH_4^+ solution to the mixture of **1a** and Ph_2SnCl_2 gave rise to a large downfield shift ($\Delta\delta$ = 4.2 ppm) of the ^{31}P NMR signal. Therefore, the result implies that the major product **1a** has the P═O moiety within the cavity. Furthermore, **1a** showed a less polar character on the TLC (R_f = 0.4, CH_2Cl_2/MeOH, 10:1, v/v, compared to R_f = 0.3 of **1b**), indicating that the P═O inside the cavity of **1a** is more shielded from the solvent environment. The lowest-energy structure of the macrotricyclic compound also reveals that P═O is pointing into the cavity.[8]

NMR titration experiments of **1a** (or **1b**) with various *N*-dodecylamide amino acid derivatives were performed in $CDCl_3/CD_3OD$ (10:1, v/v) solution (Table 1). With Boc-protected, *N*-alkylamide amino acid derivatives, no complexation was detected (entry 4), which means that the ammonium group is crucial for the binding through the charged H-bonding interaction. *N*-Alkylamide amino acid derivatives with a lipophilic side chain show weaker binding affinity compared to those with a hydrophilic side chain (entries 1 and 2 vs 3 and 5−11). In particular, Asp, Asn, Glu, and Gln derivatives with stronger side chain H-bond donors exhibited better binding affinity compared to those with a weaker H-bond donor in the side chain (entries 6−11). It turns out that the D-isomer always binds preferentially. Compound **1b** shows more than a 20-fold decrease in binding affinity to D-Asn-NHR, which clearly indicates that outwardly directed P═O of **1b** cannot be involved in H-bond interaction with the guest. Job analysis for the complex between **1a** and D-Asn-NHR confirmed a 1:1 stoichiometry. ^{31}P resonance of **1a** moves downfield upon addition of Asn-NHR. The saturation binding curve from the ^{31}P NMR titration of **1a** with Asn-NHR implies that P═O in the cavity of **1a** interacts with one of the H-bond donors of the guest. The highest affinity was found for Asn derivatives (entry 6). In comparison, Gln derivatives with the same H-bond donor and acceptor geometry except for an additional methylene on the side chain showed far reduced binding affinity to **1a** (entry 10). Surprisingly, Asp derivatives with a stronger H-bond donor (carboxylic acid group) in place of the amide group of Asn showed a dramatic decrease in binding constants (entry 9). This is remarkable in that subtle

Table 1. Binding Constants of **1a** and **1b** with Various Ammonium Guests[a]

	guest[b]	H	K_a (M^{-1})	es[c]
1	D,L-Val-NHR[d]	**1a**	400 (D), 80 (L)	83:17
2	D,L-Phe-NHR	**1a**	1000 (D), 170 (L)	85:15
3	D,L-Ser-NHR	**1a**	1800 (D), 1500 (L)	55:45
4	*N*-Boc-D-Val-NHR	**1a**	nc[e]	
5	D,L-Thr-NHR	**1a**	2250 (D), 1050 (L)	68:32
6	D,L-Asn-NHR	**1a**	45000 (D), 12000 (L)	79:21
7	D,L-Asn-(β-NHMe)-NHR	**1a**	3100 (D), 2000 (L)	61:39
8	D,L-Asn-NHR	**1b**	2050 (D), 1650 (L)	55:45
9	D,L-Asp-NHR	**1a**	5000 (D), 1600 (L)	76:24
10	D,L-Gln-NHR	**1a**	3000 (D), 2000 (L)	60:40
11	D,L-Glu-NHR	**1a**	5200 (D), 700 (L)	88:12

[a] Measured by ^{1}H NMR titration in $CDCl_3/CD_3OD$ (10:1, v/v) at 25 °C. [b] Guests were used as their trifluoroacetate salts. [c] Es (enantioselectivity) = K_a(D)/K_a(L). [d] R = docecyl. [e] No complexation detected.

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changes in H-bond functionalities and lengths of the side chain of the guest caused dramatic effects on the binding affinity. We were particularly interested in which part of the Asn guest points into the cavity to interact with P═O. ^{1}H NMR titration of the Asn guest with **1a** in 10% CD_3OH in $CDCl_3$ revealed that the primary amide proton resonances on the side chain of Asn moved upfield (L-Asn, $\Delta\delta$ of the syn amide proton = −0.73 ppm and $\Delta\delta$ of the anti amide proton = −0.51 ppm; D-Asn, $\Delta\delta$ of the syn amide proton = −0.47 ppm and $\Delta\delta$ of the anti amide proton = −0.43 ppm, upon addition of 3 equiv of **1a** to the guest), which suggests that the primary amide group is located near the shielding faces of three aromatics (Figure 1).

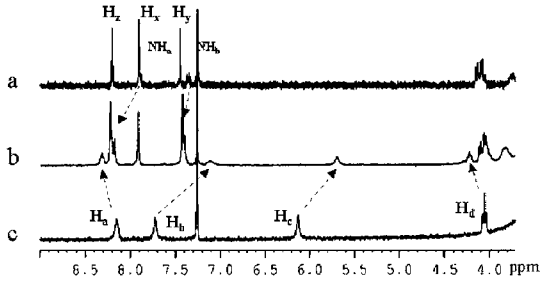

Figure 1. ^{1}H NMR spectra of (a) **1a**, (b) complex upon addition of 3 equiv of **1a** to L-Asn-NHR, and (c) L-Asn-NHR in 10% CD_3OH in $CDCl_3$ (H_a, α-amide proton; H_b, β-syn amide proton; H_c, β-anti amide proton; H_d, chiral methine proton). R = dodecyl.

Since the primary amide proton resonances experience an upfield shift, we believe that it participates in an H-bond with P═O inside the cavity. Indeed, Asn-(β-NHMe)-NHR shows much weaker affinity, indicating the absence of an H-bonding interaction of the β-amide proton of the guest with P═O of **1a** (entry 7). Other amide protons of **1a** and the Asn guest display downfield shifts, indicating intermolecular H-bonding interaction outside the cavity upon complexation. Additional support comes from intermolecular NOE experiments that indicate contacts between the primary amide protons of Asn and the three aromatic protons of **1a**. The sensitivity of binding to steric and electronic effects of the side chain of the guest is compatible with a complex in which H-bond donors in the side chain are buried within the binding cavity to interact with P═O.

Although we do not know the exact structural origin of the chiral discrimination between **1a**/D-Asn-NHR and **1a**/L-Asn-NHR, van't Hoff plots between **1a** and D- or L-Asn-NHR in $CD_3OD/CDCl_3$ (1:4, v/v) provided thermodynamic parameters controlling the enantioselective complexation process: the complexation process is driven by favorable enthalpy changes with a negative contribution by entropy changes (L-Asn-NHR, $\Delta H° = -14.8$ kcal/mol and $\Delta S° = -37.4$ cal mol^{-1} degree^{-1}; D-Asn-NHR, $\Delta H° = -9.6$ kcal/mol and $\Delta S° = -19.7$ cal mol^{-1} degree^{-1}). The fact that binding to D-Asn-NHR is enthalpically less favorable and entropically more favorable compared to L-Asn-NHR suggests that the structural changes in **1a** and D-Asn-NHR are less pronounced in the process of complexation in comparison with those in **1a** and L-Asn-NHR.

We need to answer why Asp derivatives with a stronger H-bond donor in the side chain show much weaker binding affinity compared to Asn guests. The energy-minimized structures of D-Asn-NHPr$^+$CF$_3$COO$^-$ and D-Asp-NHPr$^+$CF$_3$COO$^-$ revealed exactly the same H-bonding patterns and H-bond donor/acceptor geometries (Figure 2).[8] The only

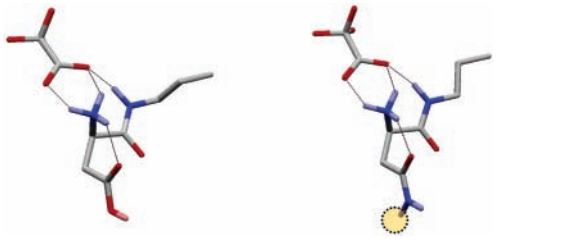

Figure 2. Lowest-energy structures for D-Asp-NHPr$^+$CF$_3$COO$^-$ (left) and D-Asn-NHPr$^+$CF$_3$COO$^-$ (right). H-bonds are shown as dotted lines. Dotted circle in yellow indicates the β-anti amide proton participating in the H-bond with P═O of **1a**.

difference comes from the side chain geometry. As shown in the energy-minimized structures of the complexes, the anti amide proton in the side chain of Asn participates in a H-bond with P═O (Supporting Information). However, in the case of Asp derivatives, a β carboxylic acid proton should be syn to the carboxyl oxygen and therefore hardly involved in the H-bond with P═O. We believe this is the main reason for the reduced affinity of the Asp guest to **1a**.

In conclusion, we have developed a bowl-shaped C_3-symmetric receptor (**1a**) that has a phophine oxide functionality in the interior of a molecular bowl. Remarkable selectivity for Asn derivatives turns out to be due to the participation of P═O in cooperative H-bonding with the guest inside the cavity of **1a** and subtle differences in the intermolecular H-bond mode within the cavity.

Acknowledgment. Support of this work by the KOSEF (Grant R02-2002-000-00137-0) is gratefully acknowledged.

Supporting Information Available: Synthetic, spectral, NMR titration, Job plot, van't Hoff plot, and computational modeling details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034168B