Tetrahedron Letters,Vol.27,No.24,pp 2721-2724,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

CYCLOPIPERAZINES: A NEW APPROACH TO CHIRAL MACROCYCLIC RECEPTORS[1]

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Abstract: The synthesis and preliminary substrate binding properties of a series of piperazine-containing macrocycles are described.

Cyclodextrin-based receptors have been central to the development of host-guest chemistry over the past few years.[2] Three key features of the cyclic oligosaccharide structure which account for this interest are 1) a well defined and variable cavity capable of including a substrate, 2) a number of chiral groups flanking the cavity, 3) reactive or potentially-functionalized groups positioned on the receptor to interact with a bound substrate.[2] Our interest in the construction of multitopic receptors and catalysts[3] and the synthetic limitations of the naturally - derived cyclodextrins prompted us to develop synthetic receptors[4] with the same features of cavity, chirality and potential functionality. Our approach was to use substituted piperazines as building blocks to the receptors. In particular, 2,5-disubstituted piperazines are structurally analogous to the D-glucose components of cyclodextrin (figure 1) and are readily available in optically pure form from α-amino acids. The ring substituent provides a chiral and potentially functionalized group which can be changed by varying the starting amino acid. In this paper we report the synthesis and preliminary binding properties of the first of these macrocycles containing piperazine and 2,5-dimethyl piperazine derivatives.

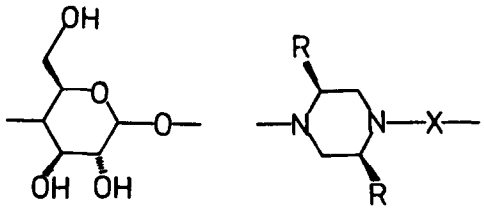
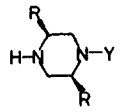


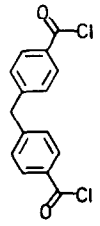
Figure 1

Two types of macrocycle have been prepared. The first of type (1) is similar in size to α-cyclodextrin and was prepared in 5 steps from piperazine. Monoprotection of piperazine with benzyl chloroformate (1 equiv., CH_2Cl_2,Et_3N)

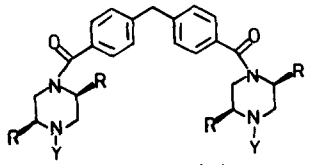
gave (2a) (59% yield) which was then reacted with 4,4'-bis-(chlorocarbonyl)-diphenylmethane (3) to form diamide (4) (85% yield).[5] Deprotection of (4) (H_2, Pd-C) to (5)[5] followed by reaction with a second equivalent of (3) under high dilution conditions (CH_2Cl_2,Et_3N) gave tetraamide (6) (49% yield). Target macrocycle (1)[6] was prepared from (6) in 63% yield by diborane reduction (BH_3·THF, reflux) and acid work up (MeOH, HCl). The key cyclic tetraamide



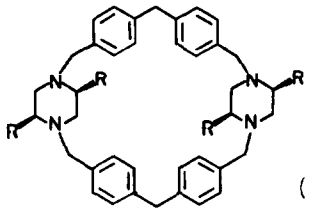
(2)a;R=H,Y=Cbz
b;R=CH_3,Y=Cbz
c;R=H,Y=H
d;R=CH_3,Y=H



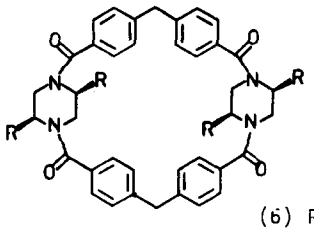
(3)



(4) R=H,Y=Cbz
(5) R=H,Y=H

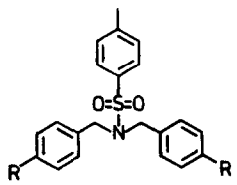


(1) R=H

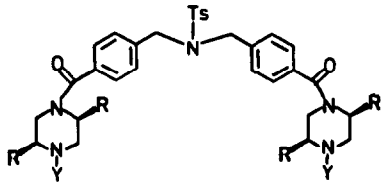


(6) R=H

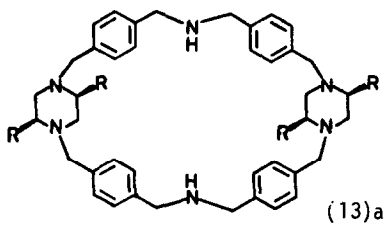
(6) could also be prepared in 35% yield by the direct high dilution reaction of (3) and piperazine. Despite the presence of a suitable cavity, (1) did not show inclusion properties with a range of hydrophobic substrates. This was due to the poor solubility of (1) in aqueous



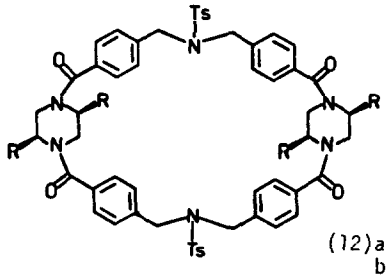
(7) R=CN
(8) R=COOH
(9) R=COCl



(10)a;R=H
Y=Cbz
b;R=CH_3
Y=Cbz
(11)a;R=H
Y=H
b;R=CH_3
Y=H



(13)a;R=H
b;R=CH_3



(12)a;R=H
b;R=CH_3

acid and the need for an organic cosolvent (DMSO) to bring it into solution.

The water solubility of the receptors was improved by increasing the size of the cavity and the number of hydrophilic groups in the ring. Alkylation of p-toluenesulfonamide with two equivalents of p-cyanobenzyl bromide (aq. NaOH, 80°C) gave dinitrile (7) which was hydrolyzed (NaOH, EtOH) to (8) and converted ($SOCl_2$, CH_2Cl_2) to diacid chloride (9) in good overall yield. Reaction of (9) with (2a) (2 equiv., CH_2Cl_2,Et_3N) and deprotection (H_2, Pd-C) of resulting diamide (10a) gave (11a) which was coupled under high dilution conditions with (9) to form cyclic tetraamide (12a) in 34% yield. Both detosylation and reduction were achieved in a single step with $LiAlH_4$ (THF, reflux 18 hrs.) to provide (13a).[7] Once again, cyclic tetraamide (12a) could be formed directly by the reaction of (9) and (2c) in 28% yield. Analogous sequences using (2b), derived from L-alanine,[8] in place of (2a) provided chiral piperazine macrocycle (13b)[11], $[\alpha]_D^{25}$ = +92.9 (c = 1, $CHCl_3$), in similar overall yields.

Both (13a) and (13b) were soluble in water below pH 2 and caused a strong enhancement in the fluorescence intensity of added 1-anilinonaphthalene-8-sulfonate (1,8-ANS). This suggests a hydrophobic association between (13a) and (13b) and the guest. In each case a Benesi-Hildebrand plot[12] of fluorescence intensity gave a straight line (indicating a 1:1 complex) from which association constant values (K_{ass}) could be determined (Table 1).[13] The K_{ass} value for (13a) and (13b) with 1,8-ANS are reasonably comparable to those of other paracyclophane-based receptors[4] and are 160 and 41 times larger than that for β-cyclodextrin.[14] The smaller K_{ass} for (13b) presumably reflects increased steric crowding by the methyl groups at the cavity opening. In contrast to these results, acyclic analog (14) caused no fluorescence enhancement with 1,8-ANS.[15]

We are currently investigating further the substrate binding properties of (13a) and (13b) with particular regard to enantioselective complexation. We are also extending the synthetic approach to chiral cyclopiperazine receptors containing functional groups (e.g. hydroxymethyl, from serine).

Table 1[13] Association constant values (K_{ass}) for receptor-1,8-ANS complexes

Receptor	K_{ass}
(13a)(R = H)[a]	$9.1 \times 10^3 M^{-1}$
(13b)(R = CH_3)[a]	$2.4 \times 10^3 M^{-1}$
β-cyclodextrin[14]	$5.8 \times 10^1 M^{-1}$
ref. 4b	$3.8 \times 10^2 M^{-1}$
ref. 4g	$6.3 \times 10^3 M^{-1}$
ref. 4d	$3.2 \times 10^6 M^{-1}$

(a) Protonated form at pH 1.4.

Acknowledgements: We thank the National Institute of Health for partial support of this work and Sophie Wilkinson for preliminary studies on piperazine synthesis.

References

1. Presented in part at the National ACS meeting, Philadelphia, September 1984.
2. See "Cyclodextrin Chemistry", M.L. Bender and M. Komiyama, Eds., Springer-Verlag, Berlin, 1978.
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4. A number of synthetic cyclophane-based macrocyclic receptors have been reported a) K. Odashima and K. Koga in "Cyclophanes"; P.M. Keene, S.M. Rosenfeld, Eds.; Academic Press, Vol. II, p 629 (1984) and references therein b) I. Tabushi, Y. Kuroda, and Y. Kimura, Tetrahedron Lett. 3327 (1976). c) F. Vögtle and W.M. Müller, Angew. Chem. Int. Ed. Eng., 23, 713 (1984), d) F. Diederich and K. Dick, J. Am. Chem. Soc. 106, 8024 (1984). e) S.P. Adams and H.W. Whitlock, J. Am. Chem. Soc. 104, 1602 (1982). f) Y. Murakami, in "Cyclophanes II", F. Vögtle, Ed. "Topics in Current Chemistry", Springer, Berlin, 1983, pp 107. g) K. Odashima, A. Itai, Y. Litaka, and K. Koga, J. Am. Chem. Soc. 102, 2504 (1980).
5. All new compounds gave satisfactory nmr, uv-vis, ir and combustion or high resolution mass spectral data.
6. (1) ^{1}H NMR ($CDCl_3$) 7.17 (AB quart, J = 7.9 Hz, 16 H, ArH), 3.90 (s, 4 H, $ArCH_2Ar$), 3.44 (s, 8 H, $ArCH_2N$), 2.43 (m, 16 H, NCH_2CH_2N).
7. (13a) ^{1}H NMR ($CDCl_3$) 7.18 (s, 16 H, ArH), 3.72 (s, 8 H, $ArCH_2NH$), 3.50 (s, 8 H, $ArCH_2N$), 2.41 (m, 16 H, NCH_2CH_2N). Mass spec. M^+ = 614.4084 $C_{40}H_{50}N_6$ requires 614.4071.
8. The diketopiperazine of L-alanine was prepared by cyclization of the methyl ester[9] or deprotection (H_2/Pd-C) and cyclization of dipeptide Z-Ala-Ala-OMe, $[\alpha]_D^{25}$ = -58.62 (c = 1, DMSO).[10] Diborane reduction (THF, reflux) and acid work up (MeOH/HCl) gave (2d), $[\alpha]_D^{25}$ = +3.75 (c = 1, $CHCl_3$).
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11. (13b) ^{1}H NMR ($CDCl_3$) 7.26 (s, 16 H, ArH), 3.82, 3.40 (AB quart, J = 13.2 Hz, 8 H, CH_2N), 3.80 (s, 8 H, CH_2NH), 2.51 (m, 4 H, CH_2CH), 2.42 (m, 8 H, CH_2CH), 1.60 (br s, 2 H, NH), 1.08 (d, J = 6.0 Hz, 12 H, CH_3). Mass spec. M^+ + H = 671.4805, $C_{44}H_{59}N_6$ requires 671.4801.
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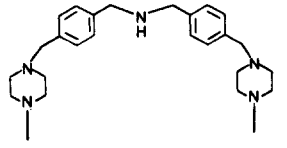
13. Fluorescence studies were done in KCl-HCl buffer (pH 1.4); excitation wavelength 375 nm; measured at 538 nm (13a), 490 nm (13b); concentration ranges 1.0 x 10^{-5} - 5.0 x 10^{-4} M (13a), 2.1 x 10^{-4} - 3.2 x 10^{-3} M (13b), 3.6 x 10^{-6} M 1,8 ANS.
14. I. Tabushi, K. Shimokawa, N. Shimizu, H. Shirakata and K. Fujita, J. Am. Chem. Soc. 98, 7855 (1976).
15. (14) prepared by the reaction of (9) and 1-methylpiperazine followed by $LiAlH_4$ reduction.



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(Received in USA 31 December 1985)