Tetrahedron Letters,Vol.27,No.18,pp 1987-1990,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

AN ARTIFICIAL MOLECULAR RECEPTOR MOLECULE FOR DITOPIC ANIONS

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The synthetic strategy to connect two macrotricyclic ammonium salts of different sizes (1, 2) to give the ditopic receptor 9 is described. A host-guest complexation analysis reveals that the binding of 13 in contrast to the analogues 10 - 12 involves interactions with either tetrahedral subsite of 9. The ditopic receptor 9 discriminates between 12 and 13 by a factor of 3 relative to the monotopic host 2.

Enzymatic substrate specificity is brought about by virtue of a precise arrangement of anchor groups in the protein which recognise and bind different moieties of the substrate. Thus an optimal alignment of the guest with respect to catalytically active functions of the macromolecular host is guaranteed. An approach to adapt this enzymic mode for creating substrate specificty is the construction of multisite receptors composed of individual artificial anchor groups which are interconnected by covalent bonds [1].

The moderate substrate specificity of monotopic macrotricyclic quaternary ammonium anion hosts 1 and 2 [2] prompted me to design a ditopic host molecule 9 consisting of two independent anion binding units 1 and 2 which are linked by a p-xylene bridge. Biologically relevant molecules like sugar bisphosphates or nucleotides may be expected to bind selectively to host 9. Here I report on the synthesis of 9 and on an attempt to quantify the selectivity advantage of its design as a ditopic receptor molecule.

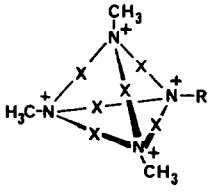
An intermediate 4 in the synthesis of 3, an artificial receptor for zwitter ionic prim. aminocarboxylates [3] initiated the synthesis of 9. The reduction of 4 to the corresponding benzylic alkohol 5 presented severe problems because of the insolubility of the ammonium salt 4 in aprotic solvents generally required for hydride reductions. This conversion finally could be accomplished in high yield using a major excess of borane dimethylsulfide complex in nitromethane/trimethylborate as solvent in which the BF_4^- salt of 4 is readily soluble [4]. Product 5 [5] was transformed into the benzylic bromide 6 (conc. aq. HBr) which was received as a crystalline BF_4^- salt in 88% yield (2 steps). Alkylation of the parent macrotricyclic tertiary amine 8 with 6 in equimolar amounts yielded a mixture of alkylation products with the desired compound 7 predominating. The mixture could be

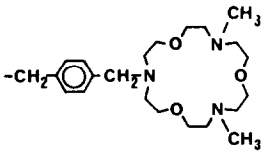
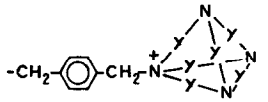
separated by aqueous size exclusion chromatography furnishing 7 in 44% yield. The yield could be improved considerably (80%) if the tertiary amine was used in tenfold excess. Methylation of 7 to give the target compound 9 was less straight forward than expected: Under the usual reaction conditions (excess CH_3I, CH_3CN, 25° over night) two compounds were obtained, which coeluted on gelfiltration and displayed identical pH titration curves. However, HPLC and NMR spectroscopy revealed the differences: Whereas the major component of the mixture gave one sharp singlet integrating for 6 methyl groups the minor one showed two methyl resonances in an 1 : 5 peak area ratio. Based on this finding in conjunction with the chromatographic behaviour which evidenced a more hydrophobic character for the latter component and the failure to interconvert these compounds it is believed that these methylation products represent a pair of in-out isomers [6]. One $N-CH_3$ group on the bigger macrotricycle unlike all the others may point towards the center of the tetrahedron thus filling in part the central cavity. The ratio of these isomers varied with the reaction conditions, higher temperatures favoring the "all out" isomer. The methylation products were isolated by prep. HPLC and crystallized readily as the BF_4^- salts.

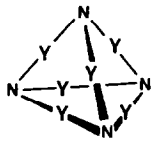
The addition of the monotopic anion I^- to an aqueous solution of 9 (as the fluoride salt) shifts the broad $N-CH_2$ NMR signal progressively to lower field. Plotting these shift changes versus guest/host ratio a monotonous smooth curve is obtained, which indicates a host/guest complexation of 1 : 2 stoichiometry. Obviously both tetrahedral subsites in 9 are fully functional in anion complexation and bind iodide with similar association constants. There is no indication that a third guest anion can be bound even if extreme concentration relations (guest/host $\approx$13) are applied. This could have been a possibility if the two tetrahedrons cooperate to form a third molecular cavity between them by adopting an eclipsed conformation across the p-xylene bridge. The absence of a 1 : 3 host-guest complex suggests that 9 rather acquires an extended staggered conformation which of course could as well be infered from pure electrostatic considerations.

In order to prove the greater selectivity of the ditopic host 9 in comparison to its monotopic analogue 2 and to demonstrate its origin in the cooperativity of the binding subsites a trend analysis of the binding constants of a series of structurally related ditopic guest molecules 10 - 13 was undertaken. These substrates differ only in the distance between two anionic functions, a carboxylate and an o-nitrophenolate moiety. Initial investigations with 1 and 2 had shown that the latter anionic group exclusively binds to the bigger tetrahedral macrotricycle, thereby experiencing a bathochromic shift of its UV-VIS absorption band. A Benesi-Hildebrand treatment [7] confirmed clean 1 : 1 stoichiometry of the host-guest complexation of compounds 10 - 13 with either 2 or 9 and furnished the association constants. Thus selectivity factors Q could be calculated and these are depicted in Fig. 1.

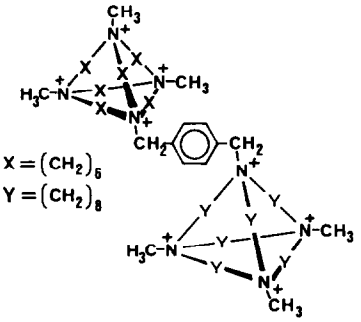
Host 9 is a better receptor than 2 for any of the substrates 10 - 12 by a factor of Q$\sim$4. This may simply be a reflection of the higher positive charge of 9 and consequently of the more favorable electrostatic interactions with the anionic substrates. The spacing between the anionic sites seems of no importance. But lengthening the distance by another E-



	R
1	$-CH_3$ $X = (CH_2)_6$
2	$-CH_3$ $X = (CH_2)_8$
3	
4	$-CH_2-C_6H_4-COOH$
5	$-CH_2-C_6H_4-CH_2OH$
6	$-CH_2-C_6H_4-CH_2Br$
7	 $X = (CH_2)_6$ $Y = (CH_2)_8$

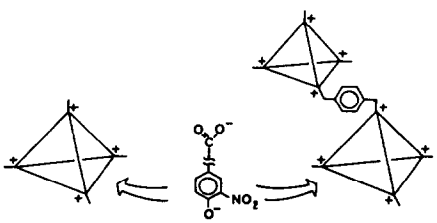


8 $Y = (CH_2)_8$



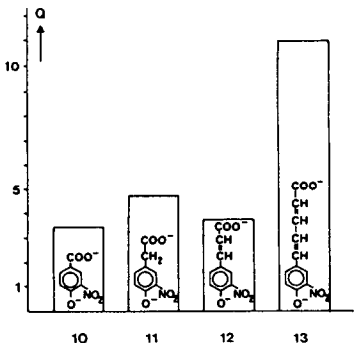
9 $X = (CH_2)_6$ $Y = (CH_2)_8$

Figure 1



2 guest 10-13 9

$$Q = \frac{K_{ass}(\text{guest} \subset 9)}{K_{ass}(\text{guest} \subset 2)}$$



double bond (≙ ~2.8 Å) i.e. replacing 12 for 13 as a guest the selectivity factor rises to 11. The sudden increase in selectivity by a factor of ~3 by mere stretching the distance between the anionic functions must be taken as an indication that 13 but not the shorter guests 10 - 12 can span the gap between the two tetrahedral anion binding sites. Only 13 is capable of interacting with both anchor groups of the ditopic receptor 9. This represents another example for the notion [3] that connecting two individual binding subsites by only one rotatable bridge leads to a selectivity enhancement for appropriate guests by a factor of 3 - 4.

Acknowledgement: This work was supported by Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie.

1) For recent examples see: A.D. Hamilton and P. Kazanjian, Tetrahedron Lett., 5735 (1985); I.Willner and Z.Goren, J.Chem.Soc.Chem.Commun. 1983, 1469; Ch.-F. Lai, K. Odashima and K. Koga, Tetrahedron Lett., 5179 (1985); cf. Ref. 3).

2) F.P. Schmidtchen, Chem.Ber. 114, 597 (1981); ibid. 117, 1287 (1984).

3) F.P. Schmidtchen, Tetrahedron Lett., 4361 (1984).

4) The success of any step in this synthesis depended on fast and reliable HPLC methods to separate highly charged organic polycations, see: H.Oswald and F.P. Schmidtchen, J.Liqu.Chrom., in press.

5) The analytical data (^{1}H NMR, ^{13}C NMR, IR, elemental analysis) of the new compounds are in full agreement of the structures assigned.

6) H.E. Simmons and C.H. Park, J.Am.Chem.Soc. 90, 2428, 2429 (1968); F.Vögtle and J.Franke, Angew.Chem.Int. Ed.Engl. 24, 219 (1985).

7) H.A. Benesi and J.H. Hildebrand, J.Am.Chem.Soc. 71, 2703 (1949); R.J.Bergeron and W.P. Roberts, Anal.Biochem. 90, 844 (1978).

(Received in Germany 23 January 1986)