Tetrahedron Letters,Vol.27,No.48,pp 5869-5872,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ANION COORDINATION CHEMISTRY - SYNTHESIS AND ANION BINDING FEATURES OF CYCLOPHANE TYPE MACROBICYCLIC ANION RECEPTOR MOLECULES

*Dennis Heyer and Jean-Marie Lehn**

Institut Le Bel, UA 422 CNRS, 4 rue Blaise Pascal, 67000 Strasbourg, France.

Abstract. Three triply bridged cyclophane type, macrobicyclic polyamines 1-3 *have been synthesized; in their hexa-protonated form they strongly bind a variety of anionic substrates, thus acting as anion receptor molecules.*

Anion coordination chemistry, the complexation of anionic species by organic receptor molecules is being studied more and more actively, establishing itself as a new field of coordination chemistry[1,2]. In order to define the basic structural, thermodynamic and reactional features of anion complexes, suitable ligands capable of effecting strong and selective anion binding must be developped.

In earlier work we have described several classes of anion complexing agents of acyclic, macrocyclic or macropolycyclic type containing ammonium and guanidinium groups as binding sites ([1,3] and references therein). In a continuing exploration of ligand geometries, we now report the synthesis of three new macropolycyclic ligands. Two of them, 1 and 2 are of cylindrical structure A and belong to the macrobicyclic triply bridged (1,3,5)-cyclophane type; the third one 3 has dome shape B and combines two different tripodal binding subunits[5], one of 1,3,5-trisubstituted benzene type and one of tren, $N(CH_2CH_2CH_2)_3$, type. Compound 3 is a hybrid between 1 and 2 one one hand, and, on the other hand, the "Bis-Tren" macrobicyclic receptor which was shown earlier to strongly and selectively bind anions in a structurally well defined coordination geometry[3].

Synthesis of the Macrobicyclic Polyamines 1-3.

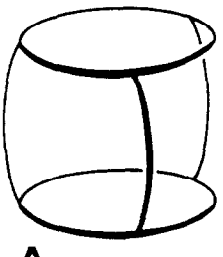
The synthesis of compounds 1-3 was based on the tripode-tripode coupling strategy[6] for constructing the macrobicyclic structure.

The tris-tosylamide 5 was obtained by treatment of the tribromide 4 with sodium azide, reduction of the resulting triazide with $LiAlH_4$ and reaction of the triamine obtained with tosylchloride (75% overall yield). Condensation of tribromide 4 with excess $TsHNCH_2CH_2CH_2O(THP)$[7] (K_2CO_3, CH_3CN, 80°, 24h) gave 6 (79%) which by deprotection (MeOH, pTsOH catalytic, r.t., 1h) to 7 (90%) and mesylation (MsCl, Et_3N, CH_2Cl_2, -78°C → 25°C, 2h) yielded 8 (98%). Reaction of 5 with $ClCH_2CH_2OCH_2CH_2O(THP)$[6] ($K_2CO_3$, DMF, 80°C, 18-36h) gave 10 (60%) which by deprotection and mesylation afforded successively 11 (96%) and 12 (98%) (same conditions as with 6 and 7 respectively).

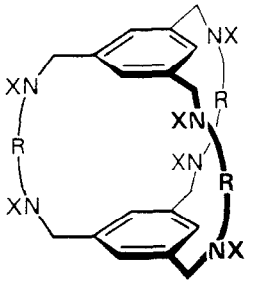
Dedicated to Professor Guy Ourisson on the occasion of his 60th birthday.

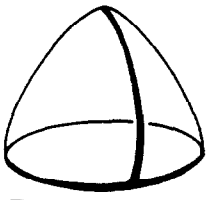
The triple coupling reaction between 5 and 8 was conducted in conditions similar to those described earlier[6], dropwise addition of 8 to 5 in DMF over 7h, in presence of Cs_2CO_3 at 80°C. The triply bridged hexatosylamide 9 was isolated by chromatography of the crude condensation product on alumina and crystallized with 0.5 $CHCl_3$ from $CHCl_3$/EtOH in 65% yield. Reaction of 5 with 12 followed by purification in similar conditions afforded the cyclophane hexatosylamide 13 (white powder) in 35% yield. Finally, applying the same condensation and purification procedures to the reaction of 5 with 14 (prepared as previously described[6]), gave the macrobicyclic hexatosylamide 15 (white powder) in 48% yield.

The final step, the removal of the tosyl groups, was performed by treating the hexatosylamides 9, 13 and 15 with 33% HBr/AcOH in presence of a large excess of phenol at 40°C for 24h. Use of a lower temperature and longer reaction time than in previous work[6], markedly improved the yields in the present cases. Conducting the reactions at room temperature might lead to further improvement. The crude hydrobromide salts obtained were passed over an ion exchange resin in its basic form to give the free amines, which were isolated by crystallization from isopropanol as the hexatosylate salts of 1, 2 and 3 in 48%, 22% and 40% yield respectively. Finally, another compound of type B, possessing shorter bridges than 3, was prepared by condensing $N(CH_2CH_2CH_2NHTos)_3$[6] with 4, to give the tritosylamide 16 (56%) which was converted into the tetramine 17 (48%) by procedures similar to those described above.

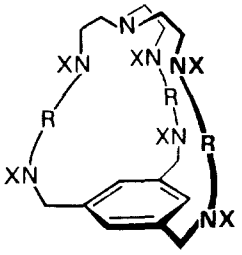


A





B



1 X = H R = $-(CH_2)_3-$

2 X = H; R = $-CH_2CH_2OCH_2CH_2-$

9 X = Ts R = $-(CH_2)_3-$

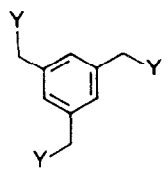
13 X = Ts; R = $-CH_2CH_2OCH_2CH_2-$

3 X = H; R = $-CH_2CH_2OCH_2CH_2-$

15 X = Ts; R = $-CH_2CH_2OCH_2CH_2-$

16 $-(CH_2)_3-TsNCH_2-$ bridges

17 $-(CH_2)_3-NHCH_2-$ bridges



4 Y = Br

5 Y = NHTs

6 Y = TsN(CH2)3OTHP

7 Y = TsN(CH2)3OH

8 Y = TsN(CH2)3OMs

10 Y = TsN(CH2)2O(CH2)2OTHP

11 Y = TsN(CH2)2O(CH2)2OH

12 Y = TsN(CH2)2O(CH2)2OMs

14 N(CH2CH2N(Ts)CH2CH2O(CH2)2OMs)3

All new compounds described had microanalytical and spectral (^{1}H-NMR, ^{13}C-NMR, mass) data in agreement with the assigned structures. The structure of 1 was confirmed by determination of the crystal structures of the hexatosylate and hexanitrate salts of 1-6H^{+} [8].

Anion Binding by Receptor Molecules 1-3.

Protonation of the six secondary amine groups of compounds 1-3 yields macrobicyclic hexa-ammonium ions which may function as anion receptor molecules, their ammonium groups serving as interaction sites for binding the anionic substrates. Extensive NMR and pH-metric studies of anion binding were performed. Only a few results will be described here.

Anion complexation by the hexaprotonated forms of 1-3 was detected by the chemical shifts changes occuring in the 200 MHz proton NMR spectra of the ligands on addition of a given salt[9]. Whereas only small shifts were observed with 2-6H^{+} and 3-6H^{+}, 1-6H^{+} gave large shifts especially with the NO_3^-, SO_4^{2-} and Cl^- anions ($\Delta\delta$ = 135, 60 and 30 Hz respectively for the $CH_2CH_2CH_2$ signal). NMR titration experiments indicated the formation of 1:1 complexes by 1-6H^{+} with NO_3^-, Cl^- and oxalate. Also a 1:1 complex between 2-6H^{+} and dithionate $^{-}O_3S\text{-}SO_3^-$ was isolated. pH-Metric studies[10] indicated that 1-6H^{+}, 2-6H^{+} and 3-6H^{+} form stable complexes with a number of anions. The stability constants log K_s lie in the range 2.5-4.0 for the monovalent ions Cl^-, NO_3^-, N_3^-; for dianions like SO_4^{2-}, $S_2O_6^{2-}$ and oxalate they reach values of 5.0-6.5. The proton NMR spectrum (at 25°C) of 1-6H^{+} (hexatriflate or hexatosylate) in the presence of about 0.5 eq. nitrate (in CD_3NO_3) or oxalate (in CD_3OD) contained the signals of both the complex and the free ligand, indicating that anion exchange was slow.

The structure of the complexes may be either: i) of **inclusion type**, the anion being located in the cavity of the macropolycyclic receptor, as in **anion cryptates** described earlier[1-3]; ii) of **exclusive type**, with the anion outside the cavity and hydrogen bonded to the NH_2^+ sites on a face of the macropolycycle. The receptors 2 and 3, which possess relatively large cavities, should in principle be able to form inclusion complexes as well as exclusive ones with most anions studied; only the former can allow bonding of a single substrate to all NH_2^+ sites; the 1/1 complex of $S_2O_6^{2-}$ with 2-6H^{+} may be of this type. The smaller receptor 1 could form inclusion complexes with the smaller anions, but binding of the larger ones (like SO_4^{2-}, $S_2O_6^{2-}$, tosylate) is expected to be of exclusive type, as found for the tosylate anions in the crystal structure of 1-6H^{+}, 6 TsO^- [8].

The large NMR shifts observed for 1-6H^{+} with certain anions, in particular with NO_3^-, may indicate that a conformational change occured on binding. Indeed, in the crystal structure of 1-6H^{+}, 6NO_3^- the macropolycycle has similar shape and the six anions are located outside the cavity as in the structure of the hexatosylate[8], so that no large difference in NMR chemical shifts would be expected for these two salts. On the other hand, the 1/1 stoichiometry, the much higher stability compared to tosylate[10] as well as numerous NMR data (shifts, ^{14}N and ^{15}N NMR, relaxation times[11]) agree with an inclusive, cryptate structure for the nitrate complex in solution. This may indicate the occurence of an exclusive ⟶ inclusive conversion when the anions are sufficiently well solvated by the medium to relax their hydrogen bonding to the NH_2^+ sites; as a result, internal binding of a single NO_3^- could take place together with a conformational change turning the NH_2^+ sites towards the inside of the cavity. Similar processes might occur with the other anions

which form highly stable complexes and give large NMR shifts. Solvation dependent interconversion between exclusive and inclusive cesium cryptates has been described[12]. Further studies are under way in order to investigate the inclusive/exclusive cryptate nature of the anion complexes formed by hexaprotonated 1-3, the occurence of conversion from external to internal binding, as well as the thermodynamic and kinetic properties of these complexes.

In conclusion, the polyammonium macrobicycles 1-$6H^+$, 2-$6H^+$ and 3-$6H^+$ are novel receptor molecules yielding stable complexes with a variety of anions. They also provide study cases for the formation of exclusive and inclusive anion cryptate complexes.

Acknowledgement. D.H. thanks the CNRS-NSF exchange program and the Ministère de la Recherche et de la Technologie for research fellowships.

References and Notes

1. J.M. Lehn, Pure Appl. Chem. 50, 871 (1978); Accounts Chem. Res. 11, 49 (1978); Science 227, 849 (1985); E. Graf and J.M. Lehn, J. Am. Chem. Soc. 98, 6403 (1976).
2. J.L. Pierre and P. Baret, Bull. Soc. Chim. France 1983, II-367; F. Vögtle, H. Sieger and M. Müller, Topics Current Chem. 98, 107 (1981); E. Kimura, ibid. 128, 113 (1985).
3. J.M. Lehn, E. Sonveaux and A.K. Willard, J. Am. Chem. Soc. 100, 4914 (1978); B. Dietrich, J. Guilhem, J.M. Lehn, C. Pascard and E. Sonveaux, Helv. Chim. Acta 67, 91 (1984).
4. For cyclophanes of this type, see for instance F. Vögtle and G. Hohner, Topics Current Chem. 74, 1 (1978) and references therein.
5. For trithia-macrobicycles of this type see, A. Ricci, R. Danieli and S. Rossini, J. Chem. Soc. Perkin I 1976, 1691.
6. B. Dietrich, M.W. Hosseini, J.M. Lehn and R.B. Sessions, Helv. Chim. Acta 68, 289 (1985).
7. Obtained in 65% yield from 3-aminopropanol by tosylation followed by treatment with 3,4-dihydropyran (pTsOH.H_2O, CH_2Cl_2, r.t., 5h; see also ref. 6); THP: tetrahydropyranyl.
8. J. Guilhem, D. Heyer, J.M. Lehn and C. Pascard, unpublished results.
9. Anion binding experiments were performed with the hexatosylates of 1-3, since these large anions are expected to bind more weakly and to have less tendency to form an inclusion complex than the other anions studied. The six secondary ammonium groups of 1-3, all have pK_a's above 5.8[10].
10. Titration with 0.1N NaOH of aqueous solutions containing 1mM ligand hexatosylate, 1mM pTsOH, 15mM monovalent anion or 5mM divalent anion and 0.1M NaOTs at 25°, under argon. Since the anions studied are in competition with a large excess of tosylate, the stability constants are apparent, lower limits of the intrinsic ones which would obtain in absence of any complexing species. More detailed account and discussion of the stability constants will be given in another report.
11. J.P. Kintzinger, A. Zahidi, D. Heyer and J.M. Lehn, unpublished results.
12. E. Kauffmann, J.L. Dye, J.M. Lehn and A.I. Popov, J. Am. Chem. Soc. 102, 2274 (1980).

(Received in France 10 October 1986)