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SYNTHESIS OF AN OPTICALLY ACTIVE SPERMINE MACROCYCLE, (S)-6-(HYDROXYMETHYL)-1,5,10,14-TETRAAZACYCLOOCTADECANE, AND ITS COMPLEXATION TO ATP

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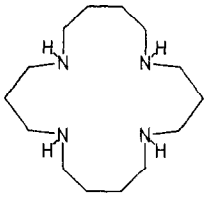
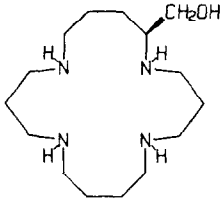
Abstract: The title compound was prepared in high yield from L-ornithine via a Richman-Atkins type macrocyclization. ^{31}P-NMR binding studies indicate formation of a 1:1 complex of the protonated macrocycle with ATP.

Macrocyclic polyamines have been widely investigated in the coordination chemistry of transition metal cations.[1] Recently, 12 to 36-membered ring protonated polyamines have been shown to form complexes with a variety of anions, including halides,[2,3] carboxylates,[4] phosphates,[5,6] and other polyoxoanions.[7] The structural features defining the selectivity and geometry of anion binding are important in the design of biomimetic complexing agents and catalysts. The introduction of functionalized side chains of defined stereochemistry onto the macrocyclic binding site provides a means of tailoring both the structure of the complex and the function of the receptor for transport, catalysis or other processes.[8]

Few of the known anion-binding polyamines possess substituent groups; none is optically active. Here, we report the synthesis of a new macrocyclic spermine analog, (6), which is both optically active and suitably functionalized for elaboration of the appended side chain. The synthetic route is outlined in Scheme I beginning with L-ornithine. Other diamino acids may also be used; thus a family of macrocyclic polyamines of varying ring size can be generated.[9]



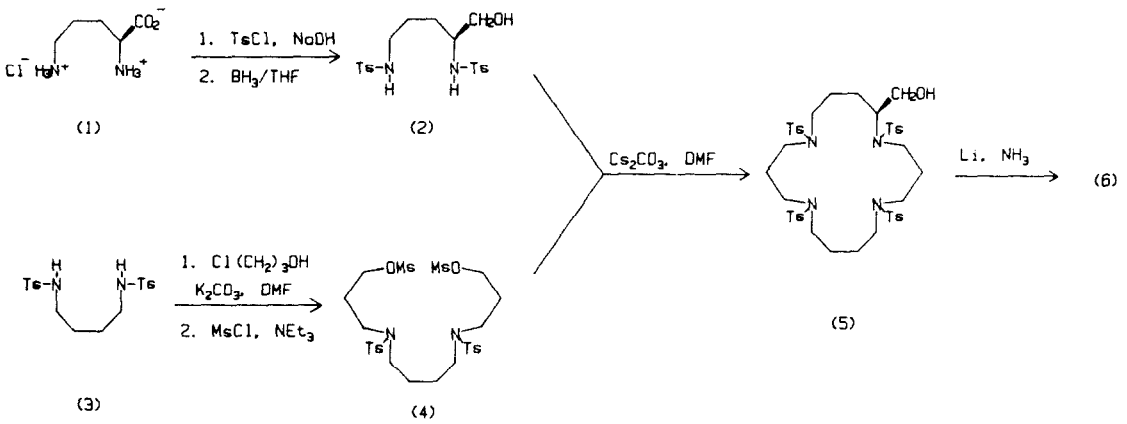
[18] ane-N_4



(6)

L-Ornithine hydrochloride (1) was treated with p-toluenesulfonyl chloride in an aqueous pH 12-13 solution to yield the N,N'-ditosylamide. Reduction with borane/THF (24 hr., 20° C) produced the corresponding alcohol, (2), contaminated with about 25% of a cyclized product identified as N,N'-ditosyl-3-aminopiperidine. The two products were readily separated (silica, 6% MeOH/$CHCl_3$) to give the crystalline alcohol (2) in 58% yield. The enantiomeric purity of (2) was checked by the method of Feringa[10] and found to be >95% ee.

SCHEME I



The other partner for the macrocyclization reaction was prepared by bis-N-alkylation of 1,4-diaminobutane-N,N'-ditosylamide (3)[11] with 3-chloropropanol (K_2CO_3, DMF, 95°C, 48 hr.) in 45% yield after chromatography (silica, 6% MeOH/$CHCl_3$) followed by nearly quantitative conversion to the dimesylate (4) (methanesulfonyl chloride, CH_2Cl_2, 20°C). The macrocyclic coupling of (2) and (4) was achieved by use of Cs_2CO_3, a modification by Kellogg and coworkers[12] of the Richman-Atkins method[13] of macrocyclic polyamine synthesis. In this case, separate solutions of (2) and (4) were added dropwise to a suspension of 4 equiv. Cs_2CO_3 in DMF at 80°C, and heating was continued overnight. Macrocycle (5) was isolated in 55% yield after silica gel chromatography (2.5:1 EtOAc/hexanes). Removal of the tosyl groups (Li, NH_3/THF, 4 equiv. MeOH) gave the desired tetraamine (6) as a colorless oil. The tetrahydrochloride of (6) was recrystallized from EtOH/H_2O to yield analytically pure material[14] (65% from (5)).

Macrocycle (6) as the free amine displayed the anticipated spectral characteristics including two doublets of doublets in the proton NMR spectrum ($CDCl_3$, δ 3.33, J=5.2, 10.6 Hz; δ 3.61, J=4.2, 10.6 Hz) for the hydroxymethylene group and a broad infrared absorption at 3300 cm^{-1}. Further structural evidence came from the fact that macrocyclization of the t-butyldimethylsilyl derivative of (2) with (4) and subsequent deprotection produced a compound identical with (5) in all respects. Thus, the alcohol side chain did not participate in the macrocyclization reaction. In addition, macrocycle (6) was optically active: $[\alpha]_D^{20}$=6.4°, (c=4, $CHCl_3$).[15]

One biological function of polyamines is coordination to anions. In particular, tetraprotonated spermine is often associated with the phosphate backbone of DNA and RNA and plays a role in cell replication and differentiation.[16] The parent [18]ane-N_4 has shown the highest stability constants for complexation of AMP, ADP, and ATP of any of the linear or cyclic tetra- or pentaamines.[6a] This can be rationalized by considering two factors: (1) separation of the amine nitrogens by 3 or 4 methylene groups yields pK_a's in the range of 7 and above, so that the polyamine may be fully protonated near neutral pH; (2) a larger number of protonated nitrogens in a small ring will give a higher positive charge density. Thus, [18]ane-N_4 is an ideal size for strong association with monotopic anions.

As a confirmation of the phosphate-binding ability of the new spermine analog (6) we

studied nucleotide binding by ^{31}P-NMR. Unfortunately, only the γ phosphorus of ATP (and to some extent the β) was sufficiently sensitive to polyamine binding. AMP showed very little change in chemical shift although it is quite likely that it forms strong complexes to (6).[6a] The results of binding studies with ATP are shown in Figure 1. Solutions were prepared by addition of solid (6)·4HCl to a 0.020 M. solution of $(NMe_4)_2ATP\cdot H_2O$[17] in 20% D_2O/H_2O and adjustment of the pH to 6.8 with NMe_4OH. From a plot of the change in γ ^{31}P chemical shift with added polyamine it is clear that ATP binds strongly to (6). This is in accord with related work that has shown 1:1 binding constants of spermine with ATP of 10^3 to 10^4 depending on pH,[18] and studies by Kimura[6a] of the [18]ane-N_4/ATP binding in which log K_s=6.6. Since pK_{a4} of ATP and pK_{a1} of the protonated polyamine[3] are approximately the same, 6.8, macrocycle (6) should exist in its tri- and tetra-protonated forms while ATP is a mixture of tri- and tetraanionic species under the experimental conditions. It seems plausible that the stoichiometry of the present complex is 1:1; indeed, the data are most consistent with this interpretation. Determination of the stability constants of complexation to ATP and a series of deoxyribonucleotides awaits more accurate potentiometric measurements and is currently underway.

Figure 1

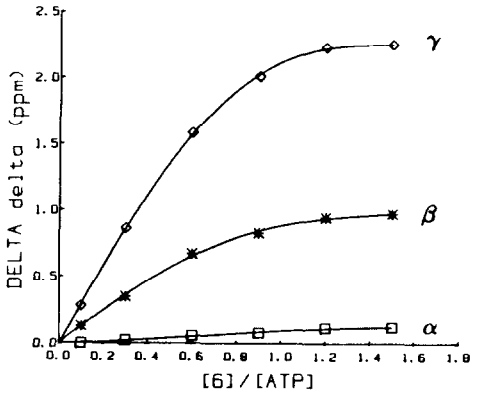


Figure 1. Downfield shift in ^{31}P-NMR resonances of α, β, and γ phosphorus atoms of ATP as a function of added (6). Conditions: 0.020 M. ATP, 20% D_2O/H_2O, pH 6.8, 21 C., 121.5 MHz.

In summary, we have shown that a diamino acid such as ornithine may be incorporated into a macrocyclic polyamine framework after conversion to an N,N'-ditosylamide. Reduction of the carboxylic acid moiety provides a more soluble compound less prone to epimerization while retaining a hydroxy functional group suitable for further elaboration of the side chain. Manipulation of the carboxylate group prior to tosylation led to cyclization to a lactam in most cases. The present procedure minimizes such side reactions.

Macrocycle (5) is easily derivatized to yield new anion receptors with pendant groups; results of these studies will be presented in due course. In light of recent interest in anion transport with lipophilic polyamines[19] and catalysis of ATP hydrolysis with macrocyclic hexaamines,[20] macrocycles of this type should find numerous applications.

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14. $C_{15}H_{38}N_4OCl_4 \cdot 2H_2O$, calc. C 38.47%, H 9.04%, N 11.96%; found C 38.37%, H 9.16%, N 11.72%; m.p. 300-301°C (dec.), $[\alpha]_D^{20}=9.6°$ (c=5, H_2O); ^{1}H-NMR (D_2O, 300MHz) δ 1.77 (m, 8H), 2.08 (br m, 4H), 3.1-3.35 (m, 15H), 3.61 (dd, J=6.0, 12.5 Hz, 1H), 3.77 (dd, J=3.5, 12.5 Hz, 1H).

15. Although the enantiomeric excess has not yet been determined, the stereogenic carbon is unlikely to epimerize under the reaction conditions from (2) to (6).

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