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New Conformationally Constrained Polyaza Macrocycles Prepared via the Bis(chloroacetamide) Method

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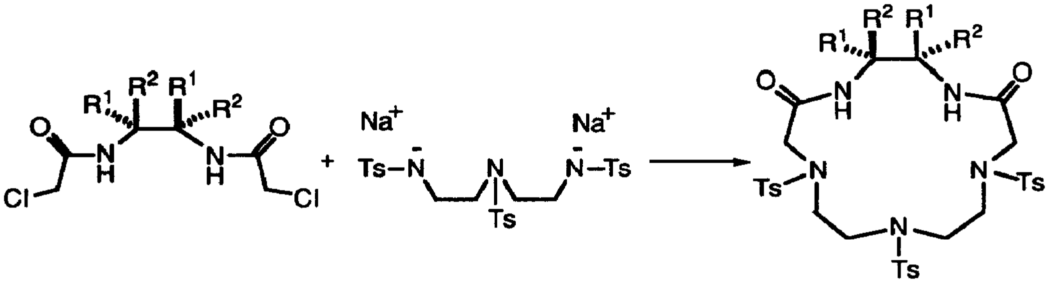
Abstract. The synthesis of two new series of conformationally constrained polyazamacrocycles featuring polysubstitution at macrocycle ring carbons is described.

We report here the designed syntheses of two novel series of regio- and stereo-specifically substituted pentaazamacrocycles with conformationally constraining substituents on macrocycle carbons. This method features the rapid, convergent synthesis of relatively complex carbon substitution patterns leaving all of the macrocycle nitrogens as secondary amines. We have been studying the syntheses of 1,4,7,10,13-pentaazacyclopentadecane ([15]aneN_5) macrocycles with well defined polysubstitution at the macrocycle ring carbons, such as **10 - 13**, for use as ligands in manganese based superoxide dismutase mimics.[1] Of greatest utility for this application are macrocycles in which all of the ring nitrogens are secondary amines. Stereo- and regio-defined substitution at macrocyclic ring carbons offers extensive opportunities for controlling the conformational properties of the macrocycle.[2,3]

A series of methyl, allyl, and fused cyclohexano substituted [15]aneN_5 macrocycles were chosen as targets. In particular, the use of vicinal diequatorial or geminal substituents on the macrocyclic ring should help to rigidify the chelate ring on which they reside, and to stabilize to some extent, the adjacent and remote chelate rings. Initially, we wanted to prepare macrocycles, which, when complexed to a metal, would have substituents on a single chelate ring. The success of these syntheses and subsequent metal chelation studies prompted the design and synthesis of macrocycles containing substituents on two chelate rings which exercise even greater control over the macrocycle conformation.

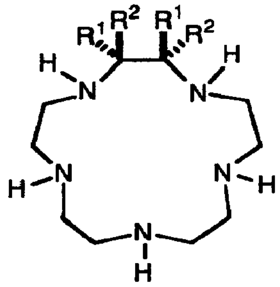
For the synthesis of less substituted (unsubstituted and some monosubstituted) [15]aneN_5 macrocycles, the method of Richman and Atkins[4] works well. As substitution becomes more complex and sterically congested, yields decrease and detosylations eventually fail.[5] Bradshaw and coworkers have demonstrated that bis(chloroacetamides) of vicinal diamines can be cyclized with triamines to give [15]aneN_5 macrocycles, with some[6] or all[7] of the macrocycle nitrogens becoming tertiary amines in the reduced product. In order to test the applicability of this cyclization method toward making the desired macrocycles containing substituents at macrocycle carbons, the bis(chloroacetamides) **1-4** were prepared according to standard procedure.[8] The dianion of tris(N-tosyl)diethylenetriamine[9] was used instead of the triamine in these cyclizations so as to eliminate any unwanted reactions at the middle nitrogen of the triamine and also to take advantage of any decreased internal entropy due to the p-toluenesulfonyl substituents.[10] Reactions of **1**, **2**, and **3** with **5** gave macrocycles **6**, **7** and **8**, respectively in isolated yields of 46%, 61%, and 38%. The bis(chloroacetamide) of 2,3-diamino-2,3-dimethylbutane **4** underwent cyclization with **5** to give macrocycle **9** in the remarkably high yield of 72 %. Reduction of macrocycles **6**, **7**, **8**, and **9** using lithium aluminum hydride[11] gave the saturated, detosylated macrocycles **10**, **11**, **12**, and **13**.



1 $R^1 = CH_3$; $R^2 = H$
2 $R^1 = CH_2CH{=}CH_2$; $R^2 = H$
3a $R^1 = (CH_2)_4$; $R^2 = H$
4 $R^1, R^2 = CH_3$

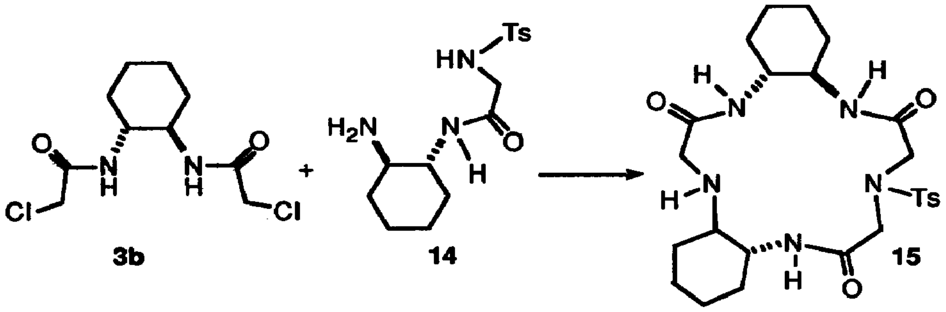
5

6 $R^1 = CH_3$; $R^2 = H$
7 $R^1 = CH_2CH{=}CH_2$; $R^2 = H$
8 $R^1 = (CH_2)_4$; $R^2 = H$
9 $R^1, R^2 = CH_3$

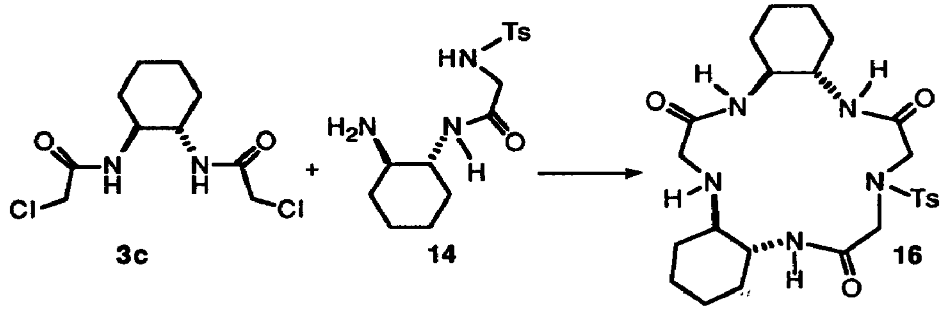


10 $R^1 = CH_3$; $R^2 = H$
11 $R^1 = CH_2CH{=}CH_2$; $R^2 = H$
12 $R^1 = (CH_2)_4$; $R^2 = H$
13 $R^1, R^2 = CH_3$

All of these di- and tetra-substituted macrocycles are symmetrical and substituted at only one chelate ring, i.e., the substituents are between two adjacent nitrogens of the macrocycle. In **10** - **12** the substituents are *trans*. The use of two fused cyclohexanes as substituents would be expected to confer greater control over macrocycle conformation. Although racemic *trans*-1,2-diaminocyclohexane was used to prepare macrocycles **8** and **12**, the enantiomers (both commercially available) were required for the bis(cyclohexano) macrocycles. Thus, the bis(chloroacetamides) of 1R, 2R-diaminocyclohexane, **3b**, and 1S, 2S-diaminocyclohexane, **3c**, were separately prepared and reacted with the monoadduct of N-tosylglycine and 1R, 2R-diaminocyclohexane **14** in the presence of base in N, N-dimethylacetamide to give macrocycles **15** and **16** in yields of 50 and 44%, respectively. The monoadduct **14** can be prepared in modest yield by reaction of excess diaminocyclohexane and N-tosyl glycine under standard coupling conditions at -10 °C. Alternatively, a monosilylation step with t-butyldiphenylsilyl chloride followed by coupling, then acid cleavage of the silyl group proved useful.

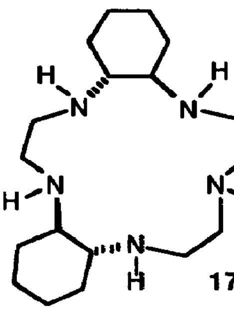


3b **14** **15**



3c **14** **16**

Reduction of macrocycles **15** and **16** gave the saturated macrocycles **17** and **18**. These isomeric compounds feature two *trans* cyclohexane rings fused to the macrocyclic ring.



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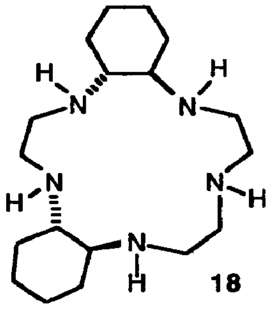

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Several examples of polymethyl substitution at carbons of macrocycles of other ring sizes, such as [14]aneN$_4$ macrocycles have been reported.[12] The bis(gem dimethyl) segment (2,3-diamino-2,3-dimethylbutane) has been previously incorporated into other size macrocycles, as has *trans* fused 1,2-diaminocyclohexane.[3] It is likely that our method could be used for other ring sizes and substitution patterns, to augment the supply of polysubstituted polyazamacrocycles.

In summary, we have demonstrated the facile preparation[13] of two new series of [15]aneN$_5$ macrocycles with conformationally constraining substituents on macrocycle carbons via bis(chloroacetamide) cyclizations. The preparation, chemistry, and biological activity of the metal complexes prepared with these ligands will be reported in due course.

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13. Typical procedures for (a) Cyclization. D,L-5,6-dimethyl-1,10,13-tris(N-p-toluenesulfonyl)-1,4,7,10,13-pentaazacyclopentadecane-3,8-dione: To a stirred solution of 1,4,7-tris(N-p-toluenesulfonyl)-1,4,7-triazaheptane-1,7-disodium salt (27.6 g, 43.7 mmol) in anhydrous DMF (1.50 l) was added a solution of D,L-N,N´-bis(chloroacetyl)-2,3-diaminobutane (10.5 g, 43.7 mmol) in anhydrous DMF (1.00 l) dropwise over 2.5 h under Ar, and the resulting cloudy mixture was stirred for 14 h. The solvent was then removed *in vacuo* and the residue was dissolved in a mixture of $CHCl_3$ (1.5 l) and H_2O (1.0 l). The layers were separated and the $CHCl_3$ layer washed with H_2O (2 x 1 l), saturated NaCl solution (0.5 l), and was dried ($MgSO_4$). The solution was then concentrated to a volume of 200 ml at which point the product began to crystallize. Addition of CH_3OH gave 14.6 g (45.6% yield) of the product as colorless needles: mp 240-242°C; ^1H NMR ($CDCl_3$) ∂ 1.20 (d, J = 7.0 Hz, 6H), 2.44 (s, 9H), 3.20 (m, 4H), 3.38 (m, 2H), 3.46 (d, J = 16 Hz, 2H), 3.53 (m, 2H), 3.87 (m, 2H), 3.90 (d, J = 16 Hz, 2H), 6.51 (d, J = 7.2 Hz, 2H), 7.34 (m, 6H), 7.71 (m, 6H); ^{13}C NMR ($CDCl_3$) ∂ 18.51, 21.59, 49.92, 50.72, 51.58, 54.53, 127.55, 127.69, 129.98, 130.10, 133.95, 134.32, 143.97, 144.48, 169.20; FAB mass spectrum (NBA-Li) m/z (relative intensity) 740.2[$(M+Li)^+$, 100].
    (b) Reduction. Synthesis of D,L-2,3-dimethyl-1,4,7,10,13-pentaazacyclopentadecane: To a stirred slurry of D,L-5,6-dimethyl-1,10,13-tris(N-p-toluenesulfonyl)-1,4,7,10,13-pentaazacyclopentadecane-3,8-dione (7.34 g, 10.0 mmol) in anhydrous THF (250 ml) was added a solution of $LiAlH_4$ in THF (1.0 M, 250 ml, 250 mmol) and the mixture was refluxed for 48 h. The reaction mixture was then cooled to 0 °C and H_2O (7.78 ml) was cautiously added dropwise. After stirring for 5 minutes, aqueous 15% NaOH (7.78 ml) was added, followed by H_2O (23.3 ml). The resulting slurry was stirred for 1 h, THF (500 ml) was added and the mixture was filtered. The solid was washed with hot THF (2 x 500 ml) and the filtrate and washings were combined. Removal of the solvent *in vacuo* gave 2.86 g of a pale yellow solid. Crystallization from hexanes gave 903 mg (37.1% yield) of the product as colorless needles: mp 70-2 °C; ^1H NMR ($CDCl_3$) ∂ 1.05 (m, 6H), 1.90 (br s, 5H), 2.23 (m, 2H), 2.50 (m, 2H), 2.76 (several m, 12H), 2.96 (m, 2H); ^{13}C NMR ($CDCl_3$) ∂ 17.25, 47.05, 48.08, 48.51, 49.02, 59.46; FAB MS (GT-HCl) m/z (relative intensity) 244 [$(M+H)^+$, 60], 158 [$(M-86)^+$, 100]; High resolution mass spectrum calculated for $C_{12}H_{29}N_5$: 244.2501, found: 244.2451.

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