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Two new chiral macrocyclic ligands containing the pyrimidine subcyclic unit (Figure 1) have been prepared. Chiral dimethyl-substituted pyrimidino-crown 1 was prepared from 4-methoxy-5-methyl-2,6-pyrimidinedimethyl ditosylate 3 and chiral dimethyl-substituted tetraethylene glycol. Treatment of dimethyl 4-methoxy-5-methyl-2,6-pyrimidinedicarboxylate 4 with the diamine derivative of chiral dibenzyl-substituted tetraethylene glycol gave the chiral dibenzyl-substituted pyrimidino-crown diamide 2. Starting 4-methoxy-5-methyl-2,6-pyrimidinedimethanol 11 was prepared by a six step process from acetamide hydrochloride and diethyl oxalpropionate.

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New Chiral Pyrimidino-Crown Ether Ligands

by

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NEW CHIRAL PYRIMIDINO-CROWN ETHER LIGANDS

J. Ty Redd, Jerald S. Bradshaw, Peter Huszthy
and Reed M. Izatt

Abstract

Two new chiral macrocyclic ligands containing the pyrimidine subcyclic unit (Figure 1) have been prepared. Chiral dimethyl-substituted pyrimidino-crown **1** was prepared from 4-methoxy-5-methyl-2,6-pyrimidinedimethyl ditosylate **3** and chiral dimethyl-substituted tetraethylene glycol. Treatment of dimethyl 4-methoxy-5-methyl-2,6-pyrimidinedicarboxylate **4** with the diamine derivative of chiral dibenzyl-substituted tetraethylene glycol gave the chiral dibenzyl-substituted pyrimidino-crown diamide **2**. Starting 4-methoxy-5-methyl-2,6-pyrimidinedimethanol **11** was prepared by a six step process from acetamidine hydrochloride and diethyl oxalpropionate.

Introduction.

The synthesis and unique complexing characteristics of cyclic polyethers were first reported by Pedersen [2] about a quarter of a century ago. Since that landmark paper, a large variety and number of macrocyclic compounds have been prepared and their complexation properties have been studied [3,4]. As originally postulated [2] and later confirmed [5,6], there is a qualitative relationship between complex stability and the ratio of cation diameter to ligand cavity diameter. However, it is also evident that complex stability in these macrocyclic complexes depends on many other cation, ligand and ion/ligand parameters.

For the past three decades, work in this laboratory has been directed toward the systematic determination of the parameters that affect complex stability, and to understand that stability in terms of thermodynamic and kinetic data for complex formation [3,7-11]. In our studies, various structural changes have been made to the basic crown ether structure in an attempt to enhance the selectivity of these ligands and the stability of complexes formed with both metal and organic cations. Some of these modifications involve the substitution of ligand polyether oxygen donor atoms by sulfur and/or nitrogen atoms. Other substitutions have involved the insertion of aromatic and/or heterocyclic ring systems into the macroring.

Enantiomeric recognition of organic amines and ammonium salts by chiral macrocycles is an area of molecular recognition that is receiving considerable attention at the present time [12-15]. Our interest in enantiomeric recognition has focused on the interaction of chiral pyridino-crown ligands with chiral organic ammonium salts [15]. In certain cases, these chiral pyridine-containing crowns have demonstrated appreciable enantiomeric recognition. These systems afford the possibility of systematically investigating how enantiomeric recognition varies with changes to the chiral host and chiral guest.

In view of the success of the pyridine-derived crowns in the above mentioned studies, we now report the synthesis of chiral pyrimidine-containing crown ethers **1** and **2** (Figure 1). We are currently converting these pyrimidino-crowns to the proton-ionizable pyrimidono-crowns by treatment with strong base. The new proton-ionizable crowns, as well as the results of a study of their use in complexing primary organic amines and ammonium salts, will be reported when that work is finished.

Results and Discussion.

The new chiral pyrimidino-crown ethers were prepared as shown in Scheme I. 4-Methoxy-5-methyl-2,6-pyrimidinedimethyl ditosylate (**3**) was treated with a chiral dimethyl-substituted diol to give chiral dimethyl-substituted pyrimidino-crown **1** in a 29% yield (Scheme I). Chiral dibenzyl-substituted pyrimidino-crown diamide **2** was prepared in a 19% yield from dimethyl 4-methoxy-5-methyl-2,6-pyrimidinedicarboxylate (**4**) and the diamine derivative of chiral dibenzyl-substituted tetraethylene glycol (Scheme I). The structures proposed for these new macrocyclic compounds are consistent with data obtained from their ir, ¹H nmr and mass spectra, and combustion analyses.

Starting pyrimidine-containing dimethanol **11**, ditosylate **3** and diester **4** were prepared as shown in Scheme II. Compounds **7-9** were prepared as reported [16] except in the case of compound **7**. When equimolar amounts of acetamide hydrochloride (**5**) and diethyl oxalpropionate (**6**) were refluxed in ethanolic sodium ethoxide, ethyl 2,5-dimethyl-4-oxopyrimidine-6-carboxylate (**7**) separated in a 52% yield when the reaction mixture was cooled.

Selective bromination of **7** proceeded readily (92%) using a bromine-acetic acid-sodium acetate solution as reported by Hagmann and coworkers [16]. Treatment of tribromomethylpyrimidine **8** with 3 equivalents of aqueous silver nitrate in methanol and ethyl acetate gave the mixed diester derivative **9** as a solid in yields of about 90%.

Refluxing **9** in phosphorous oxychloride gave ethyl 2-(carbomethoxy)-4-chloro-5-methylpyrimidine-6-carboxylate (**10**) (82%) as a white solid. When **10** was added to a solution of sodium methoxide in methanol at 4°, dimethyl 4-methoxy-5-methyl-2,6-pyrimidinedicarboxylate (**4**) was isolated in a 93% yield. Compound **4** was used to prepare chiral diamido-crown **2** shown in Scheme I. Attempts to prepare compound **4** by treating mixed diester derivative **9** with thionyl chloride in methanol were unsuccessful.

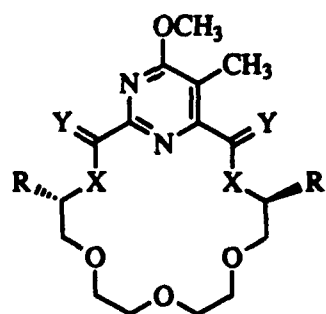
Diester **4** was reduced quantitatively by sodium borohydride in methanol. Starting diester **4** was insoluble in methanol at 4° but the reaction mixture became clear when **4** was reduced to the desired 2,6-pyrimidinedimethanol (**11**). Diol **11** was isolated as a solid. Diol **11** was also treated with tosyl chloride and potassium hydroxide in tetrahydrofuran to produce the ditosylated derivative **3**. Ditosylate **3** was then used to prepare chiral crown **1** as shown in Scheme I.

REFERENCES AND NOTES

- [1] Presented at the 205th National Meeting of the American Chemical Society, Denver, Colorado, March 28, 1993.
- [2] C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 7017 (1967).
- [3a] R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb, J. J. Christensen and D. Sen, *Chem. Rev.*, **85**, 271 (1985); [b] R. M. Izatt, K. Pawlak, J. S. Bradshaw and R. L. Bruening, *Chem. Rev.* **91**, 1721 (1991); [c] L. F. Lindoy, *The Chemistry of Macrocyclic Ligand Complexes*, Cambridge University Press, Cambridge, 1989.
- [4a] G. W. Gokel and S. H. Korzeniowski, *Macrocyclic Polyether Syntheses*, Springer-Verlag, Berlin, 1980; [b] G. W. Gokel, *Crown Ethers and Cryptands*, in *Series Monographs in Supramolecular Chemistry*, J. F. Stoddart, ed., vol 3, 1991; [c] R. M. Izatt and J. J. Christensen, *Synthesis of Macrocycles - the Design of Selective Complexing Agents*, Wiley-Interscience, New York, 1987; [d] J. D. Lamb, R. M. Izatt, J. S. Bradshaw and J. J. Christensen, *Organic Macrocycles in Encyclopedia of Physical Science and Technology*, Academic Press, Inc., 1987; [e] J. S. Bradshaw, K. E. Krakowiak and R. M. Izatt, *Aza-crown Macrocycles in Heterocyclic Compounds*, Vol 51, E.C. Taylor, ed., John Wiley and Sons, Inc., New York, 1993; [f] S. R. Cooper, *Crown Compounds: Toward Future Application*, VCH Publishers, Inc., New York, Cambridge, 1992.
- [5] R. M. Izatt, D. J. Eatough and J. J. Christensen, *Struct. Bonding*, **16**, 161 (1973).
- [6] J. J. Christensen, D. J. Eatough and R. M. Izatt, *Chem. Rev.*, **74**, 351 (1974).
- [7] J. J. Christensen, J. Ruckman, D. J. Eatough and R. M. Izatt, *Thermochim. Acta*, **3**, 203 (1972).
- [8] D. J. Eatough, J. J. Christensen and R. M. Izatt, *Thermochim. Acta*, **3**, 219 (1972).

- [9] R. M. Izatt, J. D. Lamb, N. E. Izatt, B. E. Rossiter, J. J. Christensen and B. H. Haymore, *J. Am. Chem. Soc.*, **101**, 6273 (1979).
- [10] C.-Y. Zhu, J. S. Bradshaw, J. L. Oscarson and R. M. Izatt, *J. Incl. Phenom.*, **12**, 275 (1992)
- [11] S. L. Baxter and J. S. Bradshaw, *J. Heterocyclic Chem.*, **18**, 233 (1981).
- [12] S. P. Artz, M. P. deGrandpre and D. J. Cram, *J. Org. Chem.*, **50**, 1486 (1985).
- [13] P. G. Potvin and J. M. Lehn, Design of Cation and Anion Receptors, Catalysts and Carriers, in Synthesis of Macrocycles: The Design of Selective Complexing Agents, R. M. Izatt and J. J. Christensen, eds., Wiley-Interscience, New York, pp 167-239 (1987).
- [14] J. F. Stoddart, Chiral Crown Ethers, in Topics in Stereochemistry, vol. 17, E. L. Eliel and S. H. Wilen, eds., Wiley-Interscience, New York, pp 207-288 (1988).
- [15] J. S. Bradshaw, P. Huszthy, C. W. McDaniel, M. Oue, C. Y. Zhu and R. M. Izatt, *J. Coord. Chem.*, **27**, 105 (1992).
- [16] W. K. Hagmann, F.Z. Basha, M. Hashimoto, R. B. Frye, S. Kojo and S. M. Hecht, *J. Org. Chem.*, **46**, 1413 (1981).

Figure 1. Macrocyclic Ligands



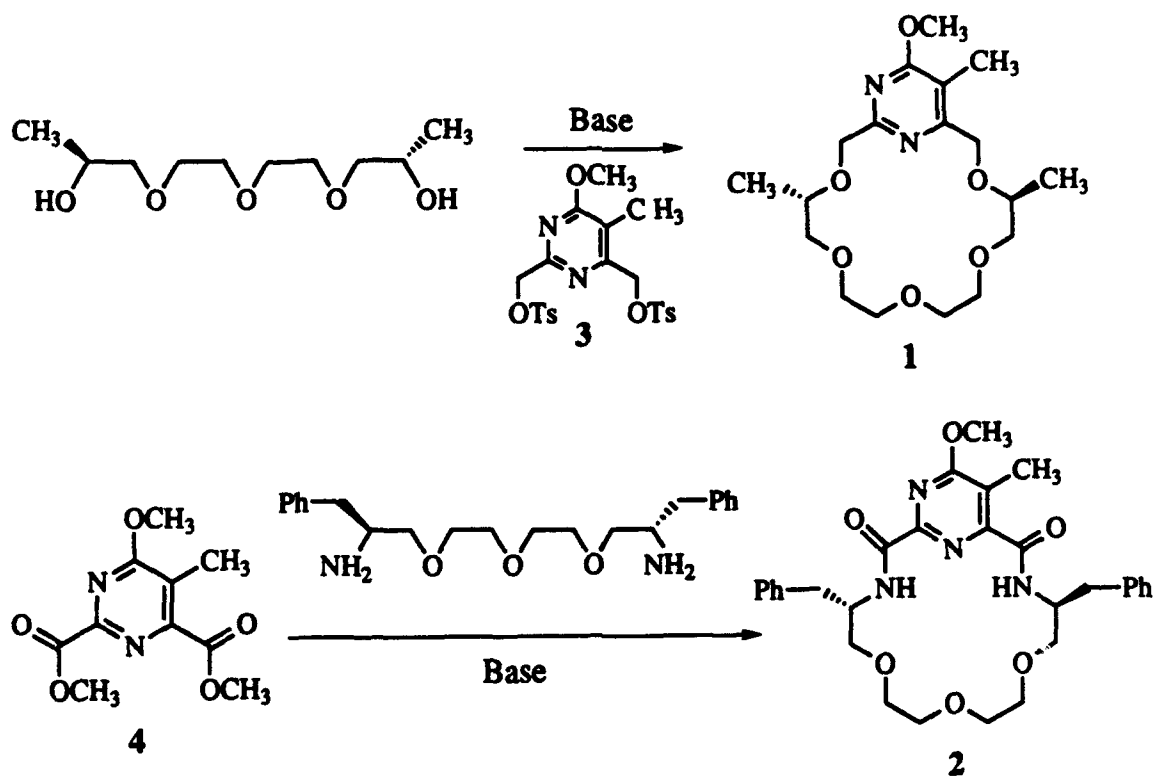
X = O

1, Y = H₂; R = CH₃

X = NH

2, Y = O; R = CH₂C₆H₅

Scheme I. Preparation of Pyrimidino-crown Ethers



Scheme II. Preparation of Starting Pyrimidines 3, 4 and 11

