

Design and Synthesis of a New Class of Nonmacrocyclic Alkali Metal Host Compounds

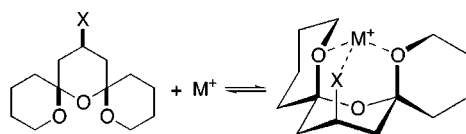
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ABSTRACT



A new class of nonmacrocyclic metal ion hosts has been examined that features a polyspirocyclic framework that offers a 1,3,5-triaxial presentation of ligating centers. These compounds are easily synthesized and exploit stereoelectronic influences to preorganize the metal ion binding site. While compounds bearing oxygen substituents ($X = \text{OH}$, OMe) failed to show appreciable binding of alkali metals, the aminated host ($X = \text{NHbn}$) exhibited strong binding with association constants (K_a) greater than 10^7 – 10^8 as measured by picrate extraction analysis.

The rational creation of new metal ion hosts continues to be an alluring endeavor.¹ In the search for nonmacrocyclic alternatives to the coronand and cryptand hosts, the critical importance of preorganization of the ligating centers for effective coordination has been recognized.² This feature is especially noteworthy in natural³ and synthetic acyclic

podands.⁴ Another novel class of nonmacrocyclic host molecules has emerged that is based upon a 1,3,5-triaxially substituted cyclohexane template. In particular, Angyal has examined the metal-binding characteristics of carbohydrates and inositols (**1**, Figure 1),⁵ while Hegtschweiler has studied

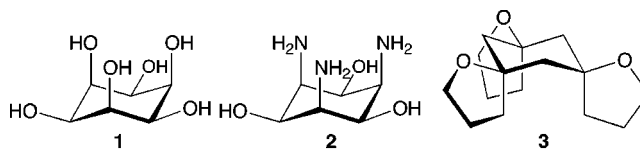


Figure 1. Nonmacrocyclic hosts based upon cyclohexane templates.

the coordinating properties of various triamino cyclohexanetriols (**2**).⁶ The polyspirocyclic tetrahydrofurans (**3**) recently reported by Paquette and co-workers exhibit impressive metal binding characteristics and serve to illustrate the importance of prior organization of the ligating sites.⁷

Toward an objective of developing new asymmetric metal ion host molecules, we have examined *trans*-15-substituted-

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(1) For reviews, see: (a) Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D., Vogtle, F., Gokel, G. W., Eds. *Comprehensive Supramolecular Chemistry*, Vol. 1; Pergamon: Oxford, 1996. (b) Izatt, R. M.; Pawluk, G. W.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1995**, *95*, 2529. (c) Gokel, G., *Crown Ethers and Cryptands*; The Royal Society of Chemistry: Cambridge, UK, 1991.

(2) For a recent review, see: Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2055, and relevant references therein.

(3) Westley, J. W., *Polyether Antibiotics: Naturally Occurring Acid Ionophores*, Vols. 1 and 2; Marcel Dekker: New York, 1983.

(4) For particularly pertinent examples, see: (a) Li, G.; Still, W. C. *Tetrahedron Lett.* **1993**, *34*, 919. (b) Erickson, S. D.; Still, W. C. *Tetrahedron Lett.* **1990**, *31*, 4253. (c) Imori, T.; Still, W. C.; Rheingold, A. L.; Staley, D. L. *J. Am. Chem. Soc.* **1989**, *111*, 3439.

(5) Angyal, S. J. *Adv. C. Carbohydr. Chem. Biochem.* **1989**, *47*, 1.

(6) Hegetschweiler, K. *Chem. Soc. Rev.* **1999**, *28*, 239.

(7) (a) Negri, J. T.; Rogers, R. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 5073. (b) Paquette, L. A.; Tae, J.; Hinkey, E. R.; Rogers, R. D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1409. (c) Tae, J.; Rogers, R. D.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 138. (d) Paquette, L. A.; Tae, J.; Gallucci, J. C. *Org. Lett.* **2000**, *2*, 143. (NOTE: Compound **3** is depicted in its most stable, uncomplexed conformation.)

1,7,9-trioxadipiro[5.1.5.3]hexadecanes of the type **4** as attractive candidates by several criteria (Figure 2).⁸ As

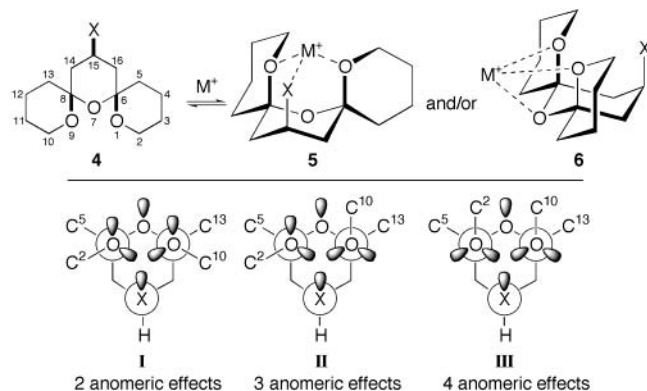


Figure 2. Metal ion binding with substituted polyspiroketal.

indicated, two possible modes of metal binding can be envisioned, through either triaxial (**5**) or equatorial/diaxial (**6**) coordination with a metal ion. Assuming a chair conformation for the central ring, three staggered conformations of the outer two rings may be considered (**I**, **II**, **III**). While all three conformations present converging lone pairs to allow binding of type **5**, only conformation **I** would allow for the alternative binding mode **6**. Consideration of stereoelectronic effects suggests that conformation **I** may be the least favorable form as it offers the fewest potential anomeric, or gauche, effects.⁹ Consequently, it was anticipated that the desired mode of binding (**5**) would be favored through stereoelectronic preorganization of the ligating centers.

Adding to the appeal of this type of binding array is its synthetic availability through thermodynamically driven spiroketalization of readily available diketo diol precursors (such as **7**, Figure 3). As indicated, spiroketalization may

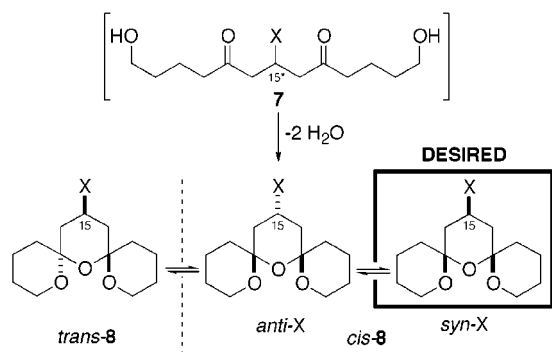


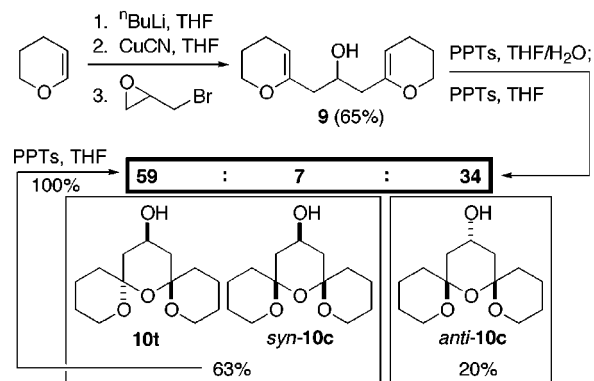
Figure 3. Stereochemical issues in polyspiroketalization.

proceed to afford either *trans* or *cis* relationships about the spirocyclic centers (*trans*- and *cis*-**8**). To access triaxial arrays of type **5**, a *pro*-C15 substituent (15*) may be installed in

precursor **7**. This introduces two possible *cis*-spiroketals (*anti*- and *syn*-isomers) of which the *syn-cis* isomer is desired (*syn-cis*-**8**). It could be anticipated that stereoelectronic effects would strongly influence the steric course of this spirocyclization reaction. Previous studies in these laboratories examined the spiroketalization of the parent diketo diol **7** (X = H) to find that a 68:32 mixture of *trans*:*cis* bis-spiroketal was obtained.^{8b} This result was interpreted to be the consequence of dipole repulsion favoring the *anti* disposition of the spirocyclic oxygens that was augmented by a twist-boat conformation of the central ring that accommodates a geometry enabling four imperfect stabilizing anomeric effects.

The spirocyclization of a C15*-substituted precursor, **7**, was examined in order to gain access to triaxial structures suitable for metal binding. As shown in Scheme 1, epi-

Scheme 1. Thermodynamically Driven Polyspiroketal Synthesis



bromohydrin was treated with the vinylcuprate¹⁰ derived from dihydropyran to assemble the intact bis-spiroketal precursor **9** in good yield. Acid-catalyzed hydration of vinyl ethers affords **7** (X = OH) which may be subsequently dehydratively spirocyclized to a 59:7:34 mixture of **10t**:*syn*-**10c**:*anti*-**10c** in 83% yield. It is noteworthy that the C15 hydroxyl group exerts a noticeable directing effect in favor of the desired *cis*-spiro isomer, improving the *trans*:*cis* ratio relative to the unsubstituted example (59:41 versus 68:32). While experiments to determine the origin of this directing effect have yet to be carried out, it may be the result of destabilization of the twist-boat conformation of the central ring that favors the *trans*-isomer in the parent compound.

Of practical value in the present study, *anti*-**10c** may be conveniently isolated by simple flash chromatography while the remaining inseparable mixture of **10t** and *syn*-**10c** can be quantitatively recycled through acid-catalyzed isomer-

(8) (a) McGarvey, G. J.; Stepanian, M. W. *Tetrahedron Lett.* **1996**, *31*, 5461. (b) McGarvey, G. J.; Stepanian, M. W.; Bressette, A. R.; Ellena, J. F. *Tetrahedron Lett.* **1996**, *37*, 5465.

(9) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: Oxford, 1983. (b) *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R., Ed.; ACS Symp. Series 539; American Chemical Society: Washington, DC, 1993.

(10) Lithiation of dihydropyran: Amouroux, R. *Heterocycl.* **1984**, *22*, 1489. Cuprate formation: Kozlowski, J. A.; Lipshutz, B. H.; Wilhelm, R. S. *Tetrahedron* **1984**, *24*, 5005.

To calibrate our binding measurements, the association constants for dicyclohexano-18-crown-6 were obtained for comparison with previous studies (entry 1).¹⁹ Examination of the parent *cis*-spiroketal (*cis*-**8**, entry 3) allowed direct assessment of the contribution of diaxial/equatorial binding of type **5** (Figure 2). No appreciable binding of this type is observed as evidenced by the low association constants observed. Entries 4 and 5, however, offer the possibility of triaxial metal binding with the inclusion of a *syn*-C15 oxygen substituent. Poor metal ion association was also observed for these compounds, comparable to that found in the unsubstituted parent compound. While intramolecular hydrogen bonding could be expected to compete with metal binding in alcohol *syn*-**10c** (entry 4), it was surprising that methyl ether *syn*-**12** (entry 5) was equally ineffective as a host.²⁰

In contrast, replacement of the oxygen substituent with benzylamine (**14**, entry 6) resulted in remarkably strong binding with all the metal ions investigated. A revealing comparison is found with crown ether which bears six ligating centers (entry 1). Host **14** respectively binds sodium and lithium ions greater than 2 and 3 orders of magnitude

(18) Cram, D. J.; Kaneda, T.; Koenig, K. E.; Lein, G. M.; Stuckler, L.P. *J. Am. Chem. Soc.* **1979**, *101*, 3553.

(19) The association constants obtained were in good agreement with those reported in other studies. See refs 4c and 18.

(20) It is noteworthy that Paquette and co-workers observed similarly poor host characteristics with a *triaxial* 1,3,5-trimethoxycyclohexane derivative. See ref 4c.

more tightly while associating with the potassium ion only slightly less tightly despite bearing only three centers for coordination. Another useful comparison may be made with Paquette's spirocyclic host (**3**, entry 2) which exhibits binding constants 1, 2, and 3 orders of magnitude less than **14** for potassium, sodium, and lithium, respectively.

The impressive metal binding of **14** validates the supposition that small nonmacrocylic arrays may be effective hosts if appropriate preorganization of the ligating centers is imposed. It is noteworthy that the preorganization in the present host does not come at a high synthetic cost as thermodynamic controlling features, including stereoelectronic effects, are exploited to enforce the desirable geometry. It is anticipated that this bis-spiroketal motif may be profitably exploited to create useful chiral environments about select metal ions for subsequent utilization in asymmetric recognition and in the mediation of asymmetric transformations.

Acknowledgment. Support for this research from the University of Virginia is gratefully acknowledged.

Supporting Information Available: Experimental procedures for Schemes 1, 2, and 3, full characterization for compounds **9**, **10t**, *syn*-**10c**, *anti*-**10c**, *syn*-**12**, *anti*-**12**, **11**, **13**, and **14** and X-ray crystallographic data for *anti*-**12**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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