Tetrahedron Letters, Vol. 33, No. 40, pp. 5925-5928, 1992
Printed in Great Britain

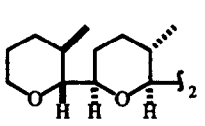
0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Enhancing the Binding Properties of a Conformationally Rigid Podand Ionophore

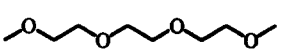
Shawn D. Erickson, Michael H. J. Ohlmeyer and W. Clark Still
Department of Chemistry, Columbia University, New York, NY 10027

Abstract: Stereospecific functionalization of a conformationally rigid podand yields new ionophores having binding properties comparable to those of the macrocyclic crown ethers.

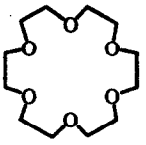
Nonmacrocyclic host molecules (podands) are generally regarded as poor receptors because their acyclic molecular components typically have many conformations and only few of these may be suitable for substrate binding. However, the naturally occurring polyethers and a series of tetrahydropyranoid ionophores (e.g. **1**) developed in these laboratories are podands which form stable complexes with ions[1]. The enhanced binding properties of these systems relative to simple podands result from a stereochemically enforced restriction of the number of the low energy conformations of the podand. This preorganization[2] enhances binding both entropically and enthalpically. The methylated podand **1** pushes host preorganization to the limit. According to molecular mechanics, **1** has only one conformation which is significantly populated and capable of polydentate ion-binding. This conformation has been found in numerous x-ray crystal structures of its complexes[3] and its backbone is qualitatively the same as the x-ray conformation of 18-C-6/potassium. Relative to the flexible triglyme dimethyl ether, the conformationally restricted podand **1** is >20-fold more ionophoric for potassium.



1

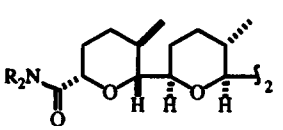


Triglyme dimethyl ether



18-C-6

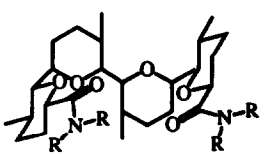
To enhance the ionophoric properties of **1**, we have added conformationally fixed ligating groups to its binding site. In this communication we report the synthesis and binding properties of such podands **2**, the dialkyl carboxamide substituted analogs of **1**. The diequatorial isomer of **2** should exist in a conformation having its amide carbonyls directed in toward the binding site and thus resembling the ligating array of 18-C-6. As expected, cations bind to these hosts with enhanced association constants which we find to be 100-500-fold larger than with either **1** or **3**. With potassium, the magnitude of the binding observed with **2** approaches that found for 18-C-6.

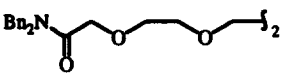


equatorial-equatorial

R = Me, 2a; R = Bn, 2b

=

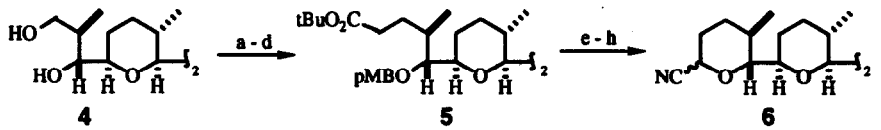




3

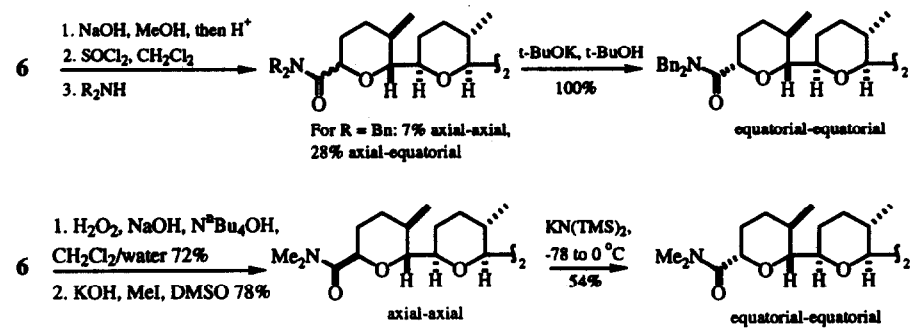
The synthesis of **2** is outlined in Scheme 1. The hydroxyl groups of dipyran **4**[3] were differentiated by selective DIBAL reduction of the corresponding *para*-methoxybenzylidene acetal. Two-carbon homologation of the free hydroxy terminus was accomplished by standard means to give the *bis*-*t*-butyl ester **5**. Subsequent deprotection and cyclization gave a *bis*-lactone which was reduced and converted to the corresponding lactol methyl ether. The nitrile function was introduced with trimethylsilylcyanide using Lewis acid catalysis to give the key *bis*-cyanohydrin ether **6**, which was formed primarily as the diaxial isomer.

Scheme 1. Synthesis of Podand 3.



a. p-Methoxybenzaldehyde, PPTS, benzene reflux, 83%; b. DIBAL, -78 °C to 0 °C, 93%; c. I_2, PPh_3, imidazole, 0°C, dichloromethane, 84%; d. $KN(TMS)_2$, $CH_3CO_2{}^tBu$, -78 °C, THF,75%; e. DDQ, wet dichloromethane, 25 °C, f. benzene ,reflux, cat CSA, 83% over steps e and f; g. DIBAL, dichloromethane, -78 °C, then methanol/toluene, cat. CSA, 70%; h. TMSCN, BF_3OEt_2, dichloromethane, 25 °C, 94%.

Conversion to the dimethyl or dibenzyl amides could be achieved by complete hydrolysis of the nitrile under basic conditions to give the *bis*-acid which was subsequently activated as an acyl chloride and treated with dimethyl or dibenzyl amine. Unfortunately, this procedure gave somewhat erratic results and yielded mainly the non-C_2 axial-equatorial amide. A more reproducable alternative involved partial hydrolysis to the diaxial primary amide in a two-phase system with phase transfer catalysis[4]. This amide was then alkylated[5] in a subsequent step to give the diaxial dialkylamide reproducably which was epimerized under basic conditions to the more stable diequatorial isomer.



The stereochemistry of the carboxamide substituents followed from the ^1H nmr coupling constants of their adjacent hydrogens (diaxial br d, J = 5.2 Hz; diequatorial t, J = 2.7, 11.5 Hz).

The linear podand **3** was prepared by Jones oxidation of pentaethylene glycol to the *bis*-acid followed by conversion to the *bis*-acyl chloride ($SOCl_2$) and amide ($BnNH_2$).

The association constants between the amide-substituted podands and alkali metal cations were measured using the $D_2O/CDCl_3$ picrate extraction method developed by Cram[6,8], and the results are shown in Table 1. As expected, the binding constants of the diequatorial isomer of the functionalized and preorganized podand **2** (eq-eq) are substantially larger than those of the corresponding system **3** which lacks any conformational restraint. Thus, preorganization in these molecules contributes an apparent 2-4 kcal/mol to the binding energy. The association constants of the diequatorial amides with potassium are strikingly large: with eq-eq **2a**, the constant of $4x10^7$ is very close to that observed with macrocyclic crown ethers having the same number of ligating oxgens (18-C-6 = $2.3x10^8$ and dicyclohexyl-18-C-6 = $2.0x10^8$)[7,8]. Changing the podand stereochemistry at one of the positions α to the carboxamide to give the non-C_2 eq-ax epimer causes a drop in the association constant with potassium of approximately one order of magnitude. A second epimerization yielding the ax-ax amide causes a further order of magnitude drop in the association constant. These diaxial carboxamides have the association energies which are approximately the same as observed with the simple podand **1** which is preorganized, but unfunctionalized. This, together with the rather regular drop in association constant along the series of functionalized podands suggests that each additional amide ligand *in the correct orientation* contributes about 1 kcal/mol in binding energy with the potassium ion. The binding constants of the diequatorial epimers with lithium and sodium ions are approximately equal and about one order of magnitude smaller than that with potassium. The decrease in binding energy on moving from the eq-eq to the eq-ax isomer is also less pronounced with lithium and sodium. This result implies that the smaller ions fill the binding cavity only partially and interact strongly with only one of the amide ligands at a time.

Table 1. Association Constants for Alkali Metal Picrates (ΔG kcal/mol)

	Li^+	Na^+	K^+
2a eq-eq	$1.2x10^6$ (-8.3)	$1.9x10^6$ (-8.6)	$4.2x10^7$ (-10.4)
2b eq-eq	$1.3x10^6$ (-8.3)	$1.1x10^6$ (-8.2)	$2.7x10^7$ (-10.1)
2a eq-ax	$8.2x10^5$ (-8.1)	$1.3x10^6$ (-8.3)	$8.2x10^5$ (-8.1)
2b eq-ax	$9.3x10^5$ (-8.1)	$9.5x10^5$ (-8.1)	$5.0x10^6$ (-9.1)
2a ax-ax	$7.3x10^3$ (-5.3)	$6.6x10^3$ (-5.2)	$2.0x10^4$ (-5.9)
2b ax-ax	-	-	$2.4x10^5$ (-7.3)
1	$1.3x10^4$ (-5.6)	$3.0x10^4$ (-6.1)	$9.1x10^4$ (-6.8)
3	$1.5x10^4$ (-5.7)	$4.9x10^4$ (-6.4)	$7.2x10^4$ (-6.6)
Cy_2-18-C-6	$1.9x10^5$ (-7.2)	$2.3x10^6$ (-8.7)	$2.0x10^8$ (-11.3)

While preorganization of ligating functional groups in molecular receptors is most commonly achieved through the formation of *macrocycles*, a large ring structure is not a requirement for effective ionophores. Preorganization can be obtained alternatively by incorporating acyclic structures which produce conformational locking mechanisms such as the array of chiral centers and methyl substituents in **1**.[9] Functionalization of a conformationally homogeneous podand by additional ligating groups which converge on a cation site binding site can give new, nonmacrocyclic ionophores whose association constants with alkali metal cations are comparable with those of crown ethers.[10]

References and Notes

1. a. T. Iimori, W.C. Still, A.L. Rheingold and D.L. Staley, *J. Am. Chem. Soc.*, **111**, 3439 (1989); b. T. Iimori, S.D. Erickson, A.L. Rheingold and W.C. Still, *Tetrahedron Lett.*, **30**, 6947 (1989); c. S.D. Erickson and W.C. Still, *Tetrahedron Lett.*, **31**, 4253 (1990).

2. D.J. Cram, *Angew. Chem. Int. Ed. Engl.*, **27**, 1009 (1988).

3. X. Wang, S.D. Erickson, T. Iimori and W.C. Still, *J. Am. Chem. Soc.*, in press.

4. S. Cacchi, D. Misti and F. La Torre, *Synthesis* , 243 (1980)

5. R.A.W. Johnstone and M.E. Rose, *Tetrahedron* , **35**, 2169 (1979)

6. R.C. Helgeson, G.R. Weisman, J.L. Toner, T.L. Tarnowski, Y. Chao, J.M. Mayer and D.J. Cram, *J. Am. Chem. Soc,*. **101**, 4928 (1979).

7. While a value of $>10^{11}$ has been reported (G.D. Beresford and J.F. Stoddart, *Tetrahedron Lett.*, **21**, 867 (1980)), we find the extraction coefficient of potassium picrate with 18-crown-6 and dicyclohexyl-18-crown-6 to be nearly the same under the identical conditions. The value we measured for dicyclohexyl-18-crown-6 was 2.6×10^8, in good agreement with the literature value[8].

8. K.E. Koenig, G.M. Lein, P. Stuckler and D.J. Cram, *J. Am. Chem. Soc,*. **101**, 3553 (1979).

9. For an elegant example of a conformationally inflexible, synthetic nonmacrocyclic host see: J. Rebek, B. Askew, N. Islam, M. Killoran, D. Nemeth and R. Wolak, *J. Am. Chem. Soc.*, **107**, 6735 (1985).

10. This work is supported by NIH Grant HL25634.

(Received in USA 1 June 1992; accepted 14 July 1992)