Cyclohexane-based 1,3-Dipodands: Complexation and Conformational Biasing

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Cyclohexane-based cis-1,3-dipodand (1) undergoes ring inversion to a diaxial conformation upon Na+ complexation, while related diaxially biased dipodand (2) is a better host.

Neutral acyclic ligands (podands) are of current interest owing to their wide applicability as alkali metal ion-complexing hosts and as models for ionophoric antibiotics.[1] Podands are generally better solvated and less conformationally preorganized for complexation than the related crown[2] and cryptand[3] hosts and this is reflected in lower complex (podate) stability. In order to understand more clearly conformational aspects of host–guest binding[4] we are investigating oligopodands (multi-'arm' podands)[5] designed to undergo large but relatively well-defined conformational changes upon complexation with metal ions. We report here the complexation-induced conformational biasing of cyclohexane-based cis-1,3-dipodand (1) and the relative Na+ complexing abilities of (1) and anancomeric model dipodand (2).[6] Others have reported stereochemical investigations of complexation of cyclohexyl crown ethers[7] and related trans-1,2-dipodands.[8]
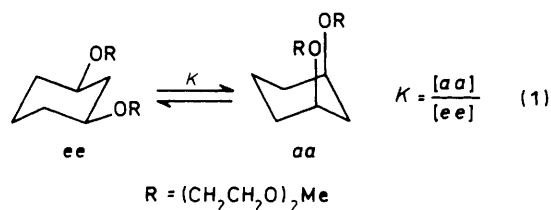
Podands (1) and (2)† were synthesized by alkylation of the corresponding cis-diols (Scheme 1A). cis-Cyclohexane-1,3-diol was isolated from a cis/trans mixture by a literature method.[9] The diol precursor to (2) was prepared as shown in Scheme 1B.

On the basis of available data for methoxy-substituted cyclohexanes,[12] free (1) is expected to exist as a conformational mixture biased toward diequatorial (ee) conformers [equation (1)]. Molecular mechanics calculations (MM2)[13] on model cis-1,3-dimethoxycyclohexane give a steric energy difference, $\Delta E_s(aa - ee)$, $(aa = $ diaxial) of 1.34 kcal mol^{-1} (1 cal = 4.184 J). Hexadentate metal ion binding, however,

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† Satisfactory C and H analyses were obtained; n.m.r., i.r., and mass spectra are consistent with reported structures.
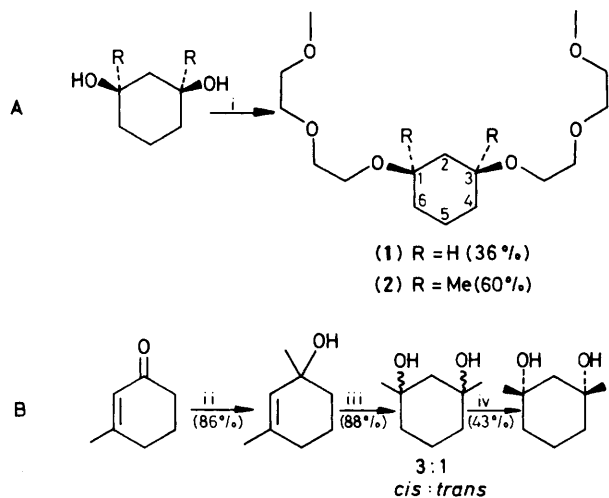
Scheme 1. i, NaH, DMF; MeOCH₂CH₂OCH₂CH₂OTs, DMF. ii, MeLi, Et₂O; aq. NH₄Cl (ref. 10). iii, Hg(OAc)₂, H₂O; NaBH₄, NaOH. iv, 20% aq. H₂SO₄ (ref. 11). Ts = p-MeC₆H₄SO₂; DMF = dimethylformamide.

$$K = \frac{[aa]}{[ee]} \qquad (1)$$

R = (CH₂CH₂O)₂Me

Figure 1

Table 1. Selected ¹³C chemical shifts of ligands (1) and (2) and their NaBPh₄ complexes (δ_c, CDCl₃).

Podand	Carbons	δ_c Free	δ_c Complexed	$\Delta\delta_c$[a]
(1)	1,3	77.1	75.1	−2.0
	2	38.9	36.4	−2.5
	4,6	31.8	27.6	−4.2
	5	20.8	13.7	−7.1
(2)	1,3	74.8	76.0	1.2
	2	44.9	50.7	5.8
	4,6	36.1	32.6	−3.5
	5	18.0	16.7	−1.3
	C–CH₃	26.2	26.5	0.3

[a] δ_c Complexed − δ_c free.

requires a diaxial (aa) conformation of (1). This is in complete accord with our n.m.r. spectroscopic results. Although CDCl₃ does not measurably dissolve NaBPh₄ (¹H n.m.r.), a CDCl₃ solution of (1) dissolves 0.99(3) equiv. (¹H n.m.r. integration), indicative of 1:1 complex formation. The ¹H n.m.r. spectra and the relative ¹³C chemical shifts of free and complexed (1) (Table 1) provide evidence of podand ring inversion to an aa conformation upon complexation.‡ ¹³C N.m.r. shifts are known to be a sensitive stereochemical probe but less sensitive for the detection of polyether complexation in the absence of conformational change.[4] We suggest distorted ag⁻aag⁺aag⁺g⁻aag⁻aag⁺a (Figure 1) as a reasonable conformation for the complex cation, noting that it is expected to be ion-paired with BPh₄⁻ in chloroform.

Anancomeric dipodand (2) is a model for the aa conformations of (1). (MM2 calculations show that cis-1,3-dimethoxy-1,3-dimethylcyclohexane is strongly biased toward axial-methoxy conformations: $\Delta E_s = -3.4$ kcal mol⁻¹.) Like (1), (2) dissolves one equiv. [1.02(1)] of NaBPh₄ in CDCl₃. As

‡ 360 MHz ¹H N.m.r. signals that are conformationally diagnostic of the ring inversion are: free (1) (CDCl₃) δ 1.19 [q, 1H, ²J ~ ³J ~ 11.3 Hz, H-2(ax)], 2.44 [dm, 1H, ²J 11.5 Hz and m breadth (20 Hz) inconsistent with app ³J, H-2(eq)], 3.24 [37 Hz br. m, 2H, H-1,3(ax)]; Complexed (1) (CDCl₃) δ 1.69 [dt, 1H, ²J 15.6 and ³J 4.2 Hz, H-2(ax)], 1.81 [dp, 1H, ²J 15.6 Hz and ³J 2.4 Hz, H-2(eq)], H-1,3 resonance obscured by arm-CH₂ resonances. The 7.1 p.p.m. upfield shift of the C(5) carbon resonance (Table 1) results from the two additional gauche interactions experienced by this carbon upon ring inversion. The complexation-induced shifts of C(2), C(4),(6), and C(1),(3) resonances are consistent with known β-oxygen and α-oxygen effects in six-membered rings but are also influenced by changes in the arm conformations.
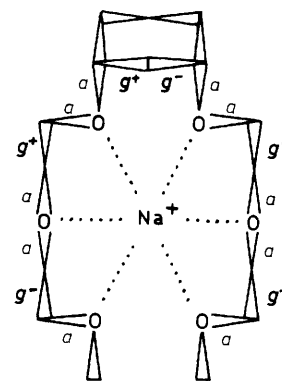
expected, the n.m.r. results show that (2) does not ring-invert upon complexation.§ A 1:1:1 [(1):(2):NaBPh₄] competition experiment, monitored by ¹³C n.m.r. spectroscopy, gave K_{obs} (2)/K_{obs} (1) of 6.8(1). Thus, biasing of podand toward the complexing conformation(s) increases the complex stability constant. The conformational equilibrium constant K [equation (1)] can be formulated in terms of the stability constant for (1) [K_{obs}, equation (2)] and the hypothetical stability constant for aa-(1) [K_{aa}, equation (3)] as shown in equation (4). If K_{obs} (2) is used as an approximation of K_{aa} (1) (which assumes similar distributions of 'arm' conformers for the diaxial free ligands), then application of equation (4) to the results of the competition experiment leads to K(1) of 0.17 and ΔG°_{298} (aa − ee) = 1.1 kcal mol⁻¹. This value is not unreasonable and agrees well with the model MM2 results (vide supra) considering that the latter take no account of differential entropy and solvation effects.

$$K_{obs} = [ML^+]/([L][M^+]) \qquad (2)$$

where [L] = [aa] + [ee]
ML⁺ = complex

$$K_{aa} = [ML^+]/([aa][M^+]) \qquad (3)$$

$$K = 1/[(K_{aa}/K_{obs}) - 1] \qquad (4)$$

§ The ¹H C–CH₃ resonance does not shift from δ 1.1 upon complexation and the corresponding methyl ¹³C resonance shifts downfield by only 0.3 p.p.m. [The observed downfield shifts of C(2) and C(4),(6) can be explained largely in terms of changes in arm conformations upon complexation, as will be addressed in a full paper.]

The results suggest that semiquantitative host–guest stability constants may be obtained for a series of related hosts with the aid of conformational energy calculations if complexation data for a suitable anancomeric model are available.

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